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University of Durham

Improving the Management of Large Colorectal Polyps

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**A thesis submitted to the University of Durham in fulfilment of the
regulations for the degree of Doctor of Medicine**

2015

Abstract

NAME: Dr Amit Chattree

TITLE OF THESIS: Improving the Management of Large Colorectal Polyps

HIGHER DEGREE FOR WHICH SUBMITTED: Doctor of Medicine (MD)

YEAR OF SUBMISSION: 2015

This thesis is focused on identifying current practices in the management of large non pedunculated colorectal polyps (LNPCPs) and the development of a structured management framework to improve outcomes. The methodology used includes a systematic review to ascertain current knowledge and retrospective quantitative analysis to identify current LNPCP management outcomes. The English Bowel Cancer Screening Programme (BCSP) which has a high volume of recorded LNPCP data was used to facilitate the latter process. In addition, qualitative analysis using consensus methodology to create best practice guidelines, key performance indicators (KPIs) to audit LNPCP outcomes and a complex polyp multidisciplinary team process was undertaken.

The main outcomes of this thesis were:

1. Confirmation of variation in LNPCP management practices leading to variable outcomes
2. Formulation of evidence based and expert consensus LNPCP management guidelines
3. Identification of KPIs to allow audit of LNPCP management and outcomes
4. Identification of pertinent research questions to improve evidence LNPCP base
5. Development and pilot of regional complex polyp multidisciplinary team meeting

Dedications

To my beautiful wife Sandy, Krishna, Arjun, Mum and Dad

Acknowledgements

I would like to express my unreserved gratitude to my supervisors, Professor Matt Rutter and Professor Pali Hungin for their support with all the work undertaken in fulfilment of this thesis including study design and implementation, recruitment of collaborating clinicians and organisations, access to relevant data sources and their continued advice. I would also like to thank Dr Sachin Gupta for his continued support and advice throughout my research work. I am also very grateful to Dr Jamie Barbour and Dr Sunil Dolwani for their assistance with developing and implementing the complex polyp multidisciplinary team meeting and Professor Douglas Wilson for his considerable assistance with the statistical analysis undertaken in this thesis. I would also like to thank the clinical directors of the North East England Bowel Cancer Screening centres (Dr David Nylander, Dr John Painter and Dr John Silcock) for facilitating access to relevant BCSP data in addition to lead BCSP specialist screening nurses Helen Savage and Mary Ritchie.

Finally I would like to thank the members of the large polyp working group not already mentioned (Professor Brian Saunders, Professor Pradeep Bhandari, Dr Bjorn Rembacken, Dr Siwan Thomas-Gibson, Mr Gethin Lewis, Mr Rupert Pullen, Mr William Garrett, Dr Maurice Loughrey, Dr John Anderson, Dr Andrew Veitch) and the British Society of Gastroenterology for their valuable contribution with the consensus methodology.

Authorship Note

The contribution of Professor Douglas Wilson, who helped to perform the statistical analysis undertaken in chapter 6, is formally acknowledged. Ethical approval was granted by the University of Durham ethics committee for all work undertaken in this thesis. I confirm that no part of the material offered has previously been submitted by me for a degree in this or any other university. All material from the work of others has been referenced accordingly with no copyright infringements.

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List of abbreviations

ACPGBI: Association of Coloproctology of Great Britain and Ireland

AP: Abdominoperineal

APC: Argon plasma coagulation

ASGE: American Society for Gastrointestinal Endoscopy

BCSP: Bowel Cancer Screening Programme

BSG: British Society of Gastroenterology

CEM: Confocal endomicroscopy

CO₂: Carbon dioxide

CRC: Colorectal cancer

CT: Computerised tomography

EMR: Endoscopic mucosal resection

EMR-C: Cap assisted endoscopic mucosal resection

ERCP: Endoscopic retrograde cholangiopancreatography

ESGE: European Society for Gastrointestinal Endoscopy

ESD: Endoscopic submucosal dissection

FICE: Flexible spectral imaging colour enhancement

FOBT: Faecal occult blood testing

GA: General anaesthetic

GS: Succinated gelatin

HR: Hazard ratio

KPI: Key performance indicator

LAEP: Laparoscopic assisted endoscopic polypectomy

LNM: Lymph node metastases

LNPCP: Large non-pedunculated colorectal polyp

LS: Laparoscopic surgery

LST: Laterally spreading tumour

LST-G: Laterally spreading tumour-Granulated type

LST-NG: Laterally spreading tumour-Non-granulated type

MDM: Multidisciplinary team meeting

MDT: Multidisciplinary team

MRI: Magnetic resonance imaging

NBI: Narrow band imaging

NHS: National Health Service
NICE: National Institute for Clinical Excellence
NPCP: Non-pedunculated polyp
NPV: Negative predictive value
NS: Normal saline
NSAIDS: Non-steroidal anti-inflammatory drugs
OR: Odds ratio
OS: Open surgery
PPS: Post polypectomy syndrome
PPV: Positive predictive value
RCT: Randomised controlled trial
RR: Relative risk
SH: Sodium hyaluronate
SIR: Standardised incidence ratio
SMSA: Size, morphology, size, access
SQR: Sydney Quotient Ratio
TEMS: Transanal endoscopic microsurgery
TAMIS: Transanal minimally invasive surgery
UEMR: Underwater endoscopic mucosal resection
USD: US dollars
95% CI: 95% confidence interval

Contents:

Abstract	2
Dedications	3
Acknowledgements	4
Authorship note	5
Introduction	12
Chapter 1: A Review of the Literature	17
1.1) Colorectal Polyps: An Overview.....	17
1.1.1) Polyp Morphology.....	18
1.1.2) Polyps and Risk of Malignancy.....	18
1.1.3) Malignant Polyps.....	19
1.2) The NHS Bowel Cancer Screening Programme.....	22
1.2.1) Predicted outcomes of bowel cancer screening.....	22
1.2.2) Colonoscopy and polypectomy in the Bowel Cancer Screening Programme.....	23
1.2.3) The management of large colorectal polyps in the Bowel Cancer Screening Programme.....	24
1.2.4) New developments in the Bowel Cancer Screening Programme.....	24
1.3) The Removal of Colonic Polyps	25
1.3.1) Optimising service delivery for large colorectal polyps.....	27
1.3.2) Pre-Removal Assessment.....	36
1.3.3) Lesion Assessment and Identification.....	37
1.3.4) Considerations with anti-thrombotic medication.....	43
1.3.5) Peri-procedural management.....	46
1.3.6) Polyp Assessment.....	46
1.4) To Resect or Refer?	50
1.5) Endoscopic Resection Principles.....	52
1.6) Equipment.....	57
1.6.1) Snares.....	57
1.6.2) Diathermy and coagulation.....	57
1.7) Post Resection.....	60
1.7.1) Complications.....	63
1.7.2) Follow-up Arrangements.....	65
1.7.3) Recurrence and Residual Tissue.....	65
1.8) Other therapeutic modalities.....	69
1.8.1) Endoscopic Submucosal Dissection.....	69
1.8.2) Cap assisted EMR.....	71
1.8.3) Underwater EMR.....	72
1.8.4) Surgical Therapy.....	73
1.9) Histological and Radiological Considerations.....	78
1.9.1) Histopathology.....	78
1.9.2) Radiological Investigations.....	79
Chapter 2: Consensus Methodology	80
2.1) Consensus Methodology: An Introduction and Background.....	80
2.1.1) Delphi technique.....	80
2.1.2) Nominal Group Technique.....	82
2.1.3) National Institutes of Health (NIH) Conference Approach.....	82
2.2) The use of consensus methodology in endoscopic research	83
2.2.1) The Use of Consensus Methodology for the Management of Large Colorectal Polyps.....	83
2.3) Aims and Methods.....	84
2.3.1) Consensus Methodology Use.....	86
Chapter 3: British Society of Gastroenterology/Association of Coloproctology of Great Britain and Ireland Large Non Pedunculated Colorectal Polyps Guideline Development	91
3.1) Introduction.....	91
3.2) Methodology.....	91
3.3) Results.....	94
3.3.1) Summary of Key Recommendations.....	95

3.4) Agreed Statements and Voting Summary.....	100
3.4.1) Definitions and Terminology.....	100
3.4.2) Service Provision and Management Principles.....	102
3.4.3) Lesion assessment.....	104
3.4.4) Endoscopic Management: Pre-procedure.....	106
3.4.5) Endoscopic Management: Peri-procedure.....	108
3.4.6) Endoscopic Management: Post-procedure.....	112
3.4.7) Surgical Management.....	113
3.5) Discussion.....	114
3.5.1) Definitions.....	118
3.5.2) Service Provision and Management Principles.....	119
3.5.3) Lesion Assessment.....	124
3.5.4) Endoscopic management: Pre-procedure.....	124
3.5.5) Endoscopic Management: Peri-procedure.....	126
3.5.6) Post procedure.....	131
3.5.7) Surgical Management of LNPCPs.....	134
3.6) External Consultation Process	136
Chapter 4: Development of Key Performance Indicators for the Management of Large Non-Pedunculated Colorectal Polyps.....	142
4.1) Measures of Quality in Healthcare.....	142
4.2) Key Performance Indicators.....	144
4.2.1) Definitions and Data quality.....	147
4.2.2) Service user profile.....	147
4.2.3) Data availability.....	147
4.2.4) Local application of KPIs.....	148
4.3) KPI development process.....	149
4.3.1) Consultation with key stakeholders and advisory groups.....	150
4.3.2) Defining the audience and purpose of a KPI.....	150
4.3.3) Choosing an area to measure.....	150
4.3.4) Achieving a balance in measurement.....	150
4.3.5) Determine selection criteria.....	152
4.3.6) Data Collection and Handling.....	152
4.3.7) Defining Targets.....	152
4.3.8) Results Reporting to stakeholders and pilot testing KPIs.....	153
4.3.9) Implementation.....	153
4.4) Why are LNPCPs suitable for KPIs?	153
4.4.1) Is the problem important?	153
4.4.2) Are there public safety concerns?	154
4.4.3) Is there evidence to suggest practice is suboptimal?	154
4.4.4) Is there evidence to suggest practice can be improved?.....	154
4.4.5) Can management become more cost effective?	154
4.5) Methodology.....	155
4.6) Results.....	158
4.6A) Voting Summary.....	159
4.6.1) Optimal decision making.....	159
4.6.2) Endoscopic skill.....	160
4.6.3) Safety.....	161
4.6.4) Timeliness.....	163
4.6.5) Volume of Procedures.....	164
4.7) Discussion.....	164
4.7.1) Optimal Decision Making.....	166
4.7.2) Endoscopic Skill.....	167
4.7.3) Safety.....	168
4.7.4) Timeliness.....	169
4.7.5) Volume of Procedures.....	170
4.8) External Consultation.....	171
Chapter 5: Retrospective Analysis of BCSP 2011-12 Large Non-Pedunculated Colorectal Polyp Outcomes.....	173
5.1) Introduction.....	173
5.1.1) Null hypothesis.....	174
5.2) Methodology.....	174

5.2.1) Relevant information retrieved from BCSP database for each lesion \geq 2cm.....	176
5.3) Results.....	178
5.3.1) Summary of Results.....	178
5.4) Whole group analysis.....	179
5.4.1) Polyp Size.....	179
5.4.2) Polyp Morphology	182
5.4.3) Lesion Location.....	185
5.4.4) Argon Plasma Coagulation Use.....	186
5.4.5) Endoscopist Procedure Volume.....	187
5.5) Intercentre Comparison.....	189
5.5.1) Diagnosis of Malignancy: Assessment of decision making.....	189
5.5.2) Use of Primary Endotherapy: Assessment of decision making.....	190
5.5.3) 3 Month Recurrence: Assessment of completeness of resection.....	191
5.5.4) 12 Month Recurrence: Assessment of curative resection.....	192
5.5.5) Use of Secondary Surgery: Assessment of ineffective therapy.....	193
5.5.6) Endotherapy within 8 weeks of diagnosis: Assessment of timeliness of management.....	194
5.5.7) Endotherapy attempted of malignant lesions: Assessment of decision making.....	195
5.5.8) Use of Primary Surgery: Assessment of decision making.....	196
5.6) Multivariable analysis	197
5.7) Complications.....	198
5.8) Screening Centre Outcomes Applied to Key Performance Indicators.....	199
5.9) Discussion.....	199
5.9.1) Whole Group Analysis.....	200
5.9.2) Argon Plasma Coagulation in relation to Residual/Recurrent tissue.....	204
5.9.3) Intercentre Analysis.....	204
5.9.4) Application of Key Performance Indicators to North East of England Outcomes	208
5.9A) Summary.....	210
Chapter 6: Establishment of a Multidisciplinary Network for the Management of Large Non Pedunculated Colorectal Polyps.....	212
6.1) Introduction.....	212
6.1.1) Null hypothesis.....	215
6.2) Methodology.....	215
6.2.1) Initial Planning.....	215
6.2.2) Consensus methodology use.....	216
6.3) Organisation and Implementation of regional complex polyp Multidisciplinary Meeting.....	217
6.3.1) Logistical Issues and Solutions.....	217
6.4) Results.....	222
6.4.1) Identification of Parameters for Inclusion in MDT Minimum Dataset Proforma.....	222
6.4.2) Final Complex Polyp Minimum Dataset Sheet.....	224
6.4.3) Cases Discussed.....	225
6.4.4) A Summary of Participation by North East of England BCSP Centres.....	241
6.5) Discussion.....	242
6.5.1) Initial Concerns.....	243
6.5.2) Overcoming Logistical Issues.....	244
6.5.3) Comprehensive Follow-of Cases.....	245
6.5.4) Feedback.....	246
6.5.5) Imaging.....	249
6.5.6) Refinement of Meeting Format.....	250
6.5.7) Refinement of Meeting Format.....	251
6.6) MDM Role in Decision Making- Application of Optimal Decision Making Key Performance Indicator.....	252
6.7) Conclusions.....	253
Chapter 7: Discussion and Overall Conclusions.....	254
7.1) Findings and achievements.....	254
7.2) Implications of this research.....	255
7.3) Limitations	257
7.4) Inability to create guidelines for advanced polypectomy training and accreditation.....	261
7.5) Reflections from undertaking thesis.....	262
7.6) Further Work.....	265
7.6.1) Alternative options in the development of LNPCP decision-making processes.....	267
7.7) Conclusions.....	268

References.....	269
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List of Tables and Figures

Tables

Table 1. A comparison of outcomes from trials of endoscopic management of LNCPs.....	27
Table 2. Schonberg Scoring System.....	35
Table 3. Schonberg Score with corresponding estimated 5 year mortality risk.....	36
Table 4. SMSA Scoring system to assess polyp difficulty.....	43
Table 5. SMSA scores with corresponding difficulty levels.....	43
Table 6. Areas of LNCP management with conflicting evidence base.....	84
Table 7. An overview of the GRADE system.....	90
Table 8. WHO criteria used to assess rigidity of KPIs.....	151
Table 9. Summary of agreed domains and KPIs for LNCP.....	158
Table 10: Information sought from individual case analysis and rationale.....	175
Table 11: List of variables and outcomes.....	177
Table 12. Summary of North East BCSP LNCP Complications.....	198
Table 13. KPIs applied to North East BCSP Outcomes.....	199
Table 14. Comparison of NE BCSP LNCP Outcomes with International Series.....	211
Table 15. Factors suggestive of MDM suitability in LNCP management.....	214
Table 16. Summary of Complex Polyp MDM Cases Discussed.....	240
Table 17: Summary of cases not referred during first 3 months of MDM pilot.....	241
Table 18: Perceived advantages and disadvantages of MDM.....	249

Figures

Figure 1. Poor prognostic histological features.....	21
Figure 2. Anatomic landmarks of pedunculated and sessile malignant polyps with respect to Haggitt level.....	21
Figure 3. Depth of submucosal invasion in sessile malignant polyps.....	22
Figure 4. Adenoma surveillance guidelines.....	24
Figure 5. Illustration showing subtype of polyps using Paris classification method.....	48
Figure 6. Kudo Pit Pattern Subtypes.....	50
Figure 7. Large sessile polyp identified.....	61
Figure 8. Submucosal injections made to lift lesion.....	61
Figure 9. Sessile adenoma with submucosal lift.....	62
Figure 10. Snare passed around adenoma.....	62
Figure 11. Post polypectomy site with clear base.....	62
Figure 12. Major Histopathological Considerations in the Management of LNCPs.....	79
Figure 13. A Summary of statements used/discarded at each round.....	94
Figure 14. Quality Assurance Triangle Model.....	144
Figure 15. Factors associated with KPI development.....	147
Figure 16. A Summary of Results and Follow-up of cases.....	178
Figure 17. Mandatory referral criteria for LNCPs identified within BCSP.....	219
Figure 18. Final Complex Polyp Minimum Dataset Sheet.....	224
Figure 19. Summary of cases referred by centre.....	241

Introduction

Theme:

Improving clinical practice towards better outcomes

Hypothesis

The current management of large colonic polyps is subjective and variable. The development of an evidence based, coordinated framework will result in improved outcomes.

Introduction:

Colorectal cancer (CRC) remains one of the world's most common forms of cancer and is the second most common cause of cancer death in the UK, with a significant financial burden in terms of hospital stay and oncological, endoscopic and surgical treatments. The importance of CRC is such that it is one of only three types of cancer along with breast and cervical cancer to have a national screening programme in the UK (1). Its incidence has continued to increase, in part due to increased detection in the Bowel Cancer Screening Programme (BCSP) (2).

Although the development of CRC is multi-factorial, approximately 90% of cases are understood to result from the malignant transformation of benign growths (polyps) in the lining of the bowel wall into adenocarcinoma over time. These growths are known as adenomas or adenomatous polyps and the process is known as the 'adenoma to carcinoma sequence' (3).

The most effective established modality of colorectal cancer prevention is the removal of adenomatous polyps in the symptomatic population and in the asymptomatic population via the BCSP (4).

Large colonic adenomas confer a significantly higher risk of malignant progression than smaller polyps and a significant proportion of this group may already harbour malignancy (5). Their removal is vital but also more complicated than standard polyp removal in colonoscopy (polypectomy), in terms of being able to achieve successful clearance and in the prevention of complications such as heavy bleeding and a perforation of the bowel wall. As such, they have traditionally been managed surgically (5, 6).

However, newer advanced endoscopic techniques, such as endoscopic mucosal resection (EMR) that uses a submucosal fluid injection and snare resection, have increased in use. EMR is now widely used for the management of large colonic polyps in the UK and internationally, not just in high volume tertiary referral centres but increasingly in smaller district general hospitals and is now considered first line management (7, 8).

In the appropriate circumstances, EMR is efficacious in the safe removal of large colonic adenomas, thus preventing adenocarcinoma via the adenoma-carcinoma sequence (5, 9). In addition, it has significant benefits as it is associated with reduced procedural cost, length of hospital stay and co-morbidity than surgical methods (10, 11). However, it should be considered that it is an advanced, technically difficult procedure and is associated with a potentially high rate of potentially life-threatening complications such as bowel perforation and severe bleeding. In addition, unsuccessful EMR with residual or recurrent tissue growth can result in more complicated management, often secondary surgical management, and the development of colorectal cancer (12).

Although surgical management of large colonic polyps has reduced greatly, it still accounts for up to 10% of all colonic polyps managed. Less invasive forms of surgery such as laparoscopic (keyhole) surgery have largely replaced open surgery, but whilst shown to be as effective, have similar morbidity rates to open surgery (11, 13). Endoscopic management may not be appropriate in certain circumstances. These include situations where certain characteristics of a polyp make complete endoscopic removal unlikely, or increase the likelihood of serious complications, or where there is a high risk of cancer within the lesion. These factors include the size, location in the colon and access to a lesion to allow a stable position for its removal (6), or where endoscopic features may suggest a lesion to be cancerous and have deeper invasion into the bowel wall with possible nearby malignant spread (14-16). In these cases endoscopic removal with EMR may be insufficient and likely delay definitive treatment, with surgical removal of the affected bowel required as first line

management. Conversely, certain large polyps with no features suggestive of cancer may unnecessarily be managed surgically, which increases costs and exposes a patient to unnecessary hospital stay and potential increased morbidity and mortality (11).

These factors highlight the great importance of the decision making process when considering how to manage large colorectal polyps. Key decisions include when endoscopic treatment (endotherapy) or surgical management should be used in the first instance, and in the case of the former, who should be undertaking the procedure if high complexity is identified (6).

There is a limited evidence base for the management of large colonic polyps and it could be argued that this results in management being subjective and less than optimal in many cases. No prior structured guidelines or consensus framework exist for the endoscopic management of large non-pedunculated colorectal polyps (LNPCPs) including EMR, or the decision making process when deciding on an optimal management strategy, and the possibility exists for wide variation in practice, including decision making and the deployment of available equipment. Recent figures from the BCSP demonstrated considerable variation in the management of LNCPs, even by experienced endoscopists (17). In addition, recent surveys not only suggest a wide variety in polypectomy practice, but also a wide range of experience of those tackling complex lesions endoscopically. In addition, over 50% of responders to these surveys who practice EMR stated that they were self-taught (18, 19). Incomplete excision rates vary between individual endoscopists, with variation wider as polyp size increases (20). In addition, the surgical and endoscopic services available for the management of LNCPs appear to differ between centres and this may also influence management.

Reported complication rates and negative outcomes vary significantly, even between different study groups at high volume centres. Varying endoscopist skills and a lack of standardised evidence-based practice may account for this (17, 21).

Trials asserting good EMR outcomes have stressed the importance of using standardised polyp assessment and management at all stages of the endoscopy process (5, 22). It has also been speculated that additional modalities, such as the use of multidisciplinary meetings (MDMs) may better coordinate and improve outcomes as is considered to be the case in

other specific conditions (23, 24). Whilst variation in certain aspects of management such as endoscopic technique may not be problematic if comparable outcomes are achieved, it may be of benefit to teach standardised practice where possible for those seeking to develop EMR skills. This is already felt to be the case in conventional polypectomy where a standardised training and accreditation framework is now used. In addition, in the USA, whilst there is no detailed programme for training in LNPCP endoscopic management, various principles relating to lesion assessment and equipment use have been advocated in a 'core curriculum' (25). There appears to be strong opinion within the endoscopic community that a more coordinated, evidence based approach is required for large colonic polyps and that it may improve the decision making processes and ultimately the outcomes achieved. This is likely to involve ensuring that individual endoscopists are able to ensure minimum acceptable standards through the identification of key performance indicators (KPIs) and guidelines for best practice which as yet do not exist. It does not seem likely that improving outcomes will involve centralising advanced endoscopic polyp removal to tertiary centres. Although the bulk of EMR cases take place in high volume tertiary centres, there have been reports of favourable outcomes in the district hospital setting (8, 26).

Programmes such as the BCSP have sought to unify and standardise endoscopic practice and associated outcomes. A sizeable proportion of LNPCPs are managed within the BCSP, by highly experienced endoscopists. This is perhaps due to the nature of patients involved who have provided abnormal stool samples containing occult blood (positive faecal occult blood test (FOBT)). In addition, detailed and accurate data for both units and individual endoscopists is recorded and scrutinised both locally and nationally within a BCSP database for all therapeutic procedures performed with close regional alignment and data-sharing. These factors suggest that the BCSP provides a suitable population for work seeking to improve LNPCP management and to test new measures. Improvement in the management of LNPCPs is proposed via the following.

- Appraising and collating the evidence currently available
- Identifying areas where further evidence is required
- Building on the evidence base for the evaluation of LNPCPs by the development and validation of a lesion assessment tool to improve the decision making process

- Using national expert consensus to develop a standardised management algorithm and to identify key performance indicators that allow measurement and evaluation of polypectomy performance
- Providing a model for apprenticeship and training in LNPCP management
- Assessing the efficacy of these measures through an endoscopic multidisciplinary network to improve the decision making process and optimise management.

Chapter 1: A Review of the Literature

1.1) Colorectal Polyps: An Overview

Colorectal polyps exist in several different forms and can be subdivided as hyperplastic, adenomatous, metaplastic, inflammatory and serrated (27).

Adenomas can undergo malignant transformation to become an adenocarcinoma via the adenoma to carcinoma pathway. Adenomas contain abnormal glands with a varying amount of villous tissue and so can be subdivided as being tubular, tubulovillous and villous (27, 28).

The 'adenoma-carcinoma sequence' is the most important described pathway for the development of colorectal cancer and is thought to account for up to 90% of CRC cases (29, 30). The removal of adenomatous polyps using colonoscopy and endoscopic resection (polypectomy) has been shown to be the most effective method of reducing CRC incidence. The US National Polyp Study (1993) conducted a prospective cohort study (n=1418) of patients who underwent a colonoscopy with ≥ 1 adenoma removed with a mean follow-up of 5.9 years. In comparison with three reference groups used to calculate expected incidences of CRC of 48.3%, 43.4% and 20.7%, reductions in CRC of 90% , 88% and 76% ($p < 0.001$) respectively were reported (4). These findings confirm the importance of polypectomy as an essential skill for endoscopists.

Various genetic alterations have been implicated in the adenoma-carcinoma sequence. These include mutations of the adenomatous polyposis coli gene, mutation or over-expression of the p53 gene with allele loss at chromosome 17p, and allele loss at the chromosome 18q region (encompassing the tumour suppressor genes SMAD 2 and SMAD 4) (31).

Other evidence to support the adenoma to carcinoma sequence includes:

- The presence of adenomatous tissue in CRC resection specimens (32)
- Increased incidence of malignant cells in larger adenomas (33)
- The similar distribution of adenomas and carcinomas seen in the colon (34)

1.1.1) Polyp Morphology

Structural features are commonly used to classify polyps with non-stalked polyps characterised as sessile (raised), flat and depressed lesions whereas stalked polyps are known as pedunculated lesions. Polyps also exhibit surface pits and vasculature which can be used to further characterise a lesion. The use of classification systems, although still not universal, appears important in characterising lesions. Classification systems such as Paris Classification, NICE NBI and Kudo Pit pattern have been shown to be useful in the identification of possible malignant features in lesion assessment and assessing suitability of endoscopic resection and will be covered in greater detail later in this chapter.

1.1.2) Polyps and Risk of Malignancy

Polyp size, evidence of dysplasia and villous histology appear to be risk factors for subsequent malignant transformation. A 1987 study documenting the natural history of unmanaged colorectal polyps >1cm found the risk of diagnosis of cancer at the polyp site at 5, 10, and 20 years was 2.5%, 8%, and 24% respectively. Polyps under 1cm appear to have a vastly lower risk of malignant transformation (3). A retrospective analysis of 751 patients with polyps < 1cm found only 18 cases of CRC in over 10,000 person-years of follow-up, whereas 15.27 cases were expected (relative risk, 1.2) (35). These findings were supported in a 1992 study (n=1618) where patients with adenomas >1cm were associated with a significantly higher risk of colorectal cancer on multivariate analysis (OR: 2.4, p<0.001). The risk of colorectal malignancy also appeared to increase further with increased size (Rectal cancer standardised incidence ratio (SIR): **0.6** (95% CI: 0.2-1.5) vs. **2.1** (95% CI: 0.8-4.3) vs **2.6** (95% CI: 0.5-7.6), p=0.02), (Colonic Cancer SIR: **1.5** (95% CI: 0.8-2.4) vs **2.2** (95% CI: 1.1-4.6) vs **5.9** (95% CI: 2.8-10.6), p=0.002)(36). The study also identified the degree of villous histology as a significant risk factor for malignancy on multivariate analysis (OR: 4.1, p<0.0001) (36). The amount of dysplasia (high grade/low grade) was also identified as a significant risk factor for malignancy on univariate but not multivariate analysis (**Rectal cancer SIR: mild dysplasia (0.6 (0.2-1.5)) vs moderate dysplasia (1.5 (0.5-3.4)) vs severe dysplasia (5.1 (1.6-11.9), p=0.003 (Colonic cancer SIR: mild dysplasia (1.4 (0.7-2.3)) vs moderate dysplasia (3.4 (2.0-5.4)) vs severe dysplasia (3.3 (1.1-8.0)), p=0.01. Muto et al (1975) reported similar findings in an analysis of 2552 polyps felt to be benign. With regards to the degree of atypia, malignancy was found in 5.7%, 18% and 34.5% in lesions with mild, moderate and severe dysplasia respectively. Malignancy was found in 4.8 % of tubular**

adenomas, 22.3% of tubulovillous lesions and 40.7% of lesions with villous histology. Lesion size over 2cm appeared to be a strong predictor of malignancy. Malignancy was found in only 1.3% of lesions under 1cm, rising to 9.5% with lesions 1-2cm in size with almost half of lesions >2cm (46%) malignant (32). Recent estimates suggest that 10-15% of non-pedunculated lesions > 2cm may harbour malignancy and the increased risk of malignancy along with the more complicated nature of their removal (see later) suggests that these lesions are deserving of separate consideration (37).

1.1.3) Malignant Polyps

A malignant polyp may refer to a macroscopically benign appearing lesion in which adenocarcinoma is found in the resection specimen on histological examination. The degree of dysplasia has been found to have a clear association with risk of the polyp harbouring malignancy (38). Management of malignant lesions generally requires oncological surgical resection including associated lymph nodes as endoscopic removal does not remove or sample the lymph node drainage basin and so may be insufficient. Endoscopic attempts at removal of lesions subsequently found to be malignant have increased, in part due to increased recognition of adenomas during the bowel cancer screening programme. Whilst in many cases this may be due to incorrect assessment of a lesion, in certain cases, 'en-bloc' removal either endoscopically or surgically (removal of lesion in one whole piece) may be sufficient management in the case of superficial submucosal invasion (37, 38). The depth of invasion of a lesion is an essential criterion in determining whether endoscopic resection is appropriate, as deeper invasion is associated with an increased risk of lymph node metastasis (16). The risk of residual or recurrent tissue is another important consideration when considering the possibility of en-bloc removal of a lesion containing adenocarcinoma (39).

Stalked (pedunculated) lesions, although easier to remove endoscopically, may also carry a risk of malignant submucosal invasion (40). Haggitt introduced a classification system for pedunculated tumours (see figure 2) which classified lesions based on the depth of invasion of adenocarcinoma (40). Lesions with Haggitt levels 1-2 are felt to be appropriate to remove endoscopically with malignancy confined to the polyp head and incidence of lymph node metastases thought to be less than 0.3%. Whilst there is some debate about the suitability of level 3 lesions for endoscopic resection, level 4 lesions are associated with submucosal involvement, a markedly higher risk of lymph node spread and often require surgical

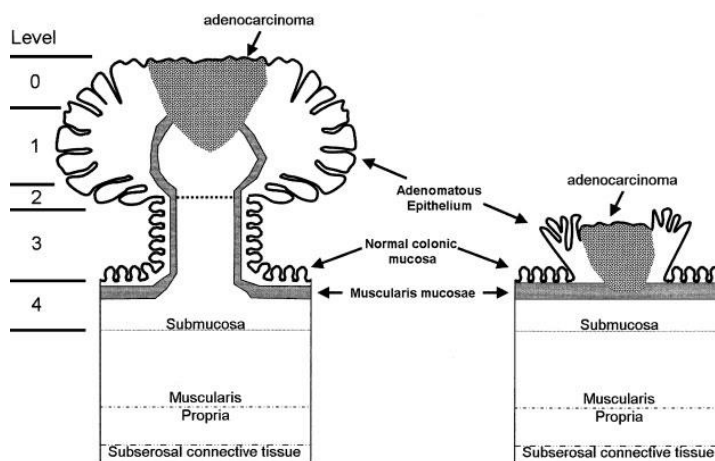
resection (40). As with benign lesions, the removal of malignant pedunculated lesions is more straightforward than with non-pedunculated lesions and can be achieved in an en-bloc fashion routinely. A 2005 series (n=453) reported successful endoscopic resection in 85.4% of cases of malignant pedunculated lesions compared with 46.3% of non-pedunculated polyps ($p<0.0001$) (41). A model describing levels of submucosal invasion in malignant lesions in 3 levels after dividing the depth of the submucosa into thirds (sm1, sm2, sm3) is also established, known as Kikuchi levels (16, 42). The depth of invasion was found to correlate with the risk of lymph node metastases with moderate (sm2) and deep (sm3) submucosal invasion strongly associated with a higher risk of lymph node metastases than superficial (sm1) invasion (n=182, $p<0.01$) (16). Deep submucosal invasion (sm3) has been reported to have an incidence of lymph node metastases of up to 25% compared with 3% and 8% for sm1 and sm2 lesions respectively ($p=0.001$) (37, 39). In addition, the requirement of surgical resection as definitive management for sm3 lesions has been reported uniformly in multiple case series (39, 43). Whilst it may be possible to achieve adequate endoscopic removal of lesions with superficial invasion ($<1000\mu\text{m}$), where the risk of lymph node metastases (LNM) involvement is less likely, recording an accurate description of submucosal invasion may prove difficult and render successful endotherapy less feasible. A 2002 retrospective series (n=353) also identified lymphovascular invasion ($p=0.005$) and location in the lower third of the rectum ($p=0.007$) as consistent with a significantly increased risk of LNM (39).

Where a concern about malignancy exists, adequate specimen retrieval is of paramount importance to allow optimal histological analysis staging and management. An important oncological principle underpinning this is en-bloc lesion resection where possible, which allows the identification of resection margins and completeness of resection, the depth of lesion invasion and other prognostic features. Piecemeal resection provides suboptimal histological specimens meaning that these features cannot be identified. In the discovery of malignancy in this scenario, formal resectional surgery is often required to ensure definitive assessment and treatment. A 2005 meta-analysis (n=1900) identified positive resection margins (OR: 22, $p<0.0001$), poorly differentiated carcinoma (OR: 9.2, $p<0.05$) and vascular invasion (OR: 7, $p<0.05$) as major risk factors for LNM whilst a 2012 series found indeterminate resection margin status, a frequent issue with piecemeal removal, to be strongly associated with residual/recurrent disease (n=143, resection margins $<1\text{mm}$: 16%, indeterminate margins: 21%, negative resection margins ($\geq 1\text{mm}$): 0%, $p=0.009$) (41, 44).

Further details regarding assessment and management in the context of suspected malignancy are described later in this chapter. A summary of the histological features conferring poor prognostic features in malignant polyps and necessitating formal oncological resection is described below:

- Poor differentiation
- Lesions with submucosal invasion >1000µm
- Resection margins < 1mm
- Evidence of lymphovascular invasion
- Incomplete resection or inability to detect resection margins (associated with piecemeal removal)
- Location in lower third of rectum

Figure 1. Poor prognostic histological features. (37, 38, 41, 44)



Haggitt Level	Description
0	Malignancy confined to mucosa
1	Invasion of submucosa but limited to the head of a polyp
2	Invasion of malignancy extending to neck of a polyp
3	Invasion of malignancy extending to polyp stalk
4	Invasion of malignancy beyond stalk into submucosa but above muscularis propria

Figure 2. Anatomic landmarks of pedunculated and sessile malignant polyps with respect to Haggitt level. (37, 40)

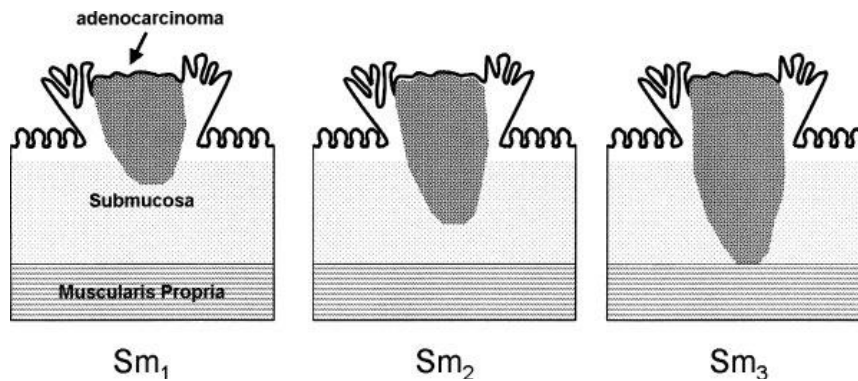


Figure 3. Depth of submucosal invasion in sessile malignant polyps; Sm1: Invasion into upper third, Sm2: Invasion into middle third, Sm3: Invasion into lower third. (37)

1.2) The NHS Bowel Cancer Screening Programme

A large proportion of large colonic polyps are now identified by the NHS Bowel Cancer Screening Programme which has been in operation in England since 2006. The early identification of malignant colonic tumours may be associated with improved patient prognosis, less complicated surgery and reduced treatment costs. This factor combined with the ability to identify and remove adenomas before malignant development suggests that colorectal cancer is amenable to screening and numerous studies have examined various approaches to colorectal cancer screening.

Whilst colonoscopy is the 'gold-standard' test for the identification of adenomas and colorectal cancer, it is not considered economically nor logistically viable to use mass population screening with colonoscopy in the UK as healthcare resources do not permit this. The potential harms and risks of colonoscopy also need to be taken into account (17).

Faecal occult blood testing (FOBT), first described in 1967, allows mass population screening, is economically viable and is both safe and acceptable for patients. Identified high risk asymptomatic individuals undergo subsequent colonoscopy. Larger adenomas and colorectal cancers tend to bleed intermittently, meaning that the detection of blood in the faeces by FOBT may allow their detection (45).

1.2.1) Predicted outcomes of Bowel Cancer Screening

Based on data from the pilot studies around 98 in 100 people will receive a normal FOBT result and will be returned to routine screening. They will be invited for bowel cancer screening every two years if still within the eligible age range.

Around 2 in 100 people receive an abnormal result and will be offered a colonoscopy. 40-50% of patients who go onto to have colonoscopy will be found to have one or more adenomas. Around 10% will be found to have bowel cancer (46).

1.2.2) Colonoscopy and Polypectomy in the Bowel Cancer Screening Programme

Adenomatous colonic polyps are a precursor to colorectal cancer and have malignant potential if left untreated over time with change to adenocarcinoma (3).

Patients with abnormal FOBt (those with 5-6 abnormal windows) are referred for colonoscopy at an accredited national bowel cancer screening centre. Given the established relationship between adenomatous and serrated colonic polyps with malignant transformation, and up to a 90% reduction in CRC due to polyp removal, polypectomy is considered an essential skill for BCSP colonoscopists. In the context of an abnormal FOB result, a large number of polyps including large polyps are anticipated to be diagnosed within the BCSP(47). As approximately 10% of adenomas discovered at colonoscopy are over 1cm in size and have greater malignant potential than smaller lesions, the importance of BCSP endoscopists being competent to successfully remove these larger lesions is apparent (3, 47).

In the BCSP, all colonoscopies are performed at an accredited centre with strict protocols and auditing of individual performance data. Screening colonoscopists are experienced individuals who have performed over 1000 colonoscopies, have extensive experience of performing polypectomy and have been through a comprehensive certification process involving both a written and practical assessment. Polyp identification and assessment form vital components of BCSP colonoscopy. Adenomatous polyps identified during colonoscopy are removed with snare polypectomy or advanced resection techniques such as endoscopic mucosal resection (EMR) where possible. Subsequent follow-up is based on the endoscopic findings (see figure 3) with low risk patients not requiring surveillance in the BCSP.

SURVEILLANCE FOLLOWING ADENOMA REMOVAL

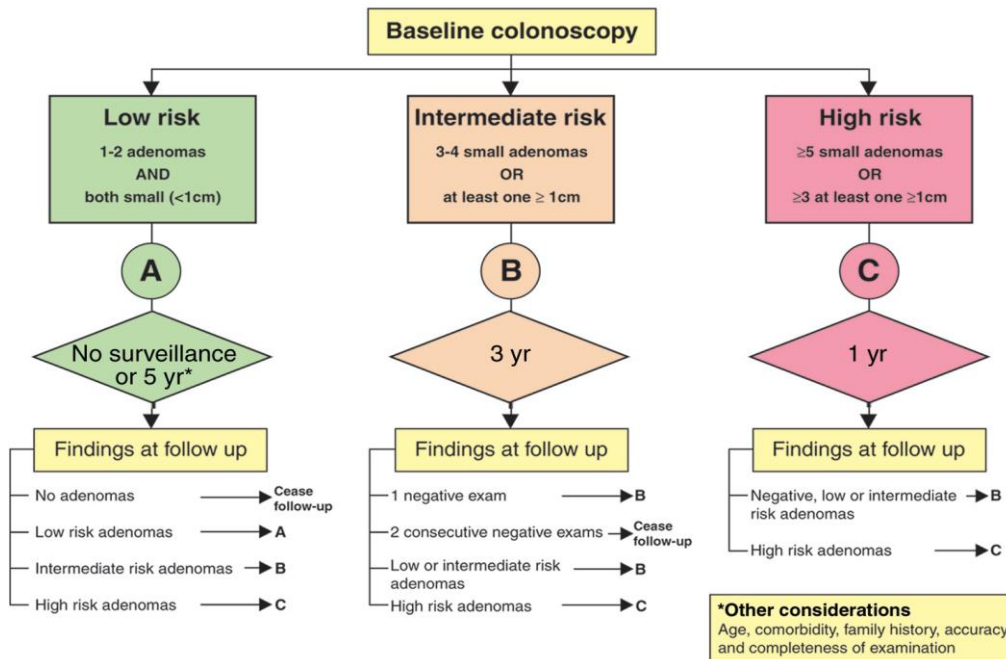


Figure 4- BSG Adenoma surveillance guidelines (48).

1.2.3) The Management of Large Colorectal Polyps in the Bowel Cancer Screening Programme

The BCSP manages a large proportion of large colorectal polyps within the UK. A 2013 BCSP case series (n=557) LNPCPs asserted the safety and effectiveness of the management of large colonic polyps in the BCSP (17). 78.3% were managed endoscopically in the first instance with 16.1% of these lesions subsequently requiring surgery meaning that of the endoscopically managed cases, 366 (83.9%) were managed successfully and required no further management. The increased complexity associated with the endoscopic removal of larger LNPCPs was reflected by an increase in both endoscopic procedures and surgical therapy as lesion size increased, however, low rates of complications were reported (perforation and post polypectomy bleeding 0.5% and 3% respectively) (17). The outcomes of this case series appear comparable to various international series, suggesting that LNPCP management within the BCSP is effective.

1.2.4) New developments in the Bowel Cancer Screening Programme

As larger adenomas and colorectal cancers bleed only intermittently, FOBt may miss up to 50% of these lesions and improvements to the BCSP have been investigated. Population

screening with flexible sigmoidoscopy was shown to be more sensitive and specific for distal cancers and polyps than FOBt) (49). 30-40% of cancers arise proximal to the reach of the sigmoidoscope and thus would be missed. However, distal adenomas may serve as a marker for more proximal lesions and would prompt colonoscopy in such patients(49).

A randomised controlled trial of one-off sigmoidoscopy between the ages of 55 and 60 demonstrated a 23% reduction in colorectal cancer incidence and a 31% reduction in colorectal cancer mortality (49). In view of these findings one off flexible sigmoidoscopy screening for patients aged 55 or over has been piloted from March 2013 to complement FOBt with national rollout anticipated in 2017 (46).

1.3) The Removal of Colonic Polyps

Diminutive (<5mm) and small lesions (5-9mm) can be removed in a number of ways. In addition to conventional snare polypectomy, removal by cold biopsy forceps and cold cutting with a snare (cold snare polypectomy) is possible. Forceps removal with the addition of diathermy known as 'hot biopsy' removal can be used to remove diminutive lesions, especially where the position of a lesion makes entrapment with a snare difficult. However, this technique is associated with greater thermal tissue injury than snare polypectomy and its use is now often avoided, especially in the thinner right colon (50).

Pedunculated polyps are considered easier to remove endoscopically than sessile and flat lesions, although large lesions with broad stalks in a less spacious part of the colon such as the sigmoid colon may be more complex (51). Although there is a reduced risk of perforation when compared to sessile polyps, pedunculated polyps with broader stalks (over 1cm) are associated with increased post-polypectomy bleeding due to the presence of large blood vessels in the stalk and often require the use of interventions such as intra-stalk adrenaline injection, clip placement and endoloop either pre or post polypectomy (46).

The removal of LNPCPs appears more complex than with smaller non-pedunculated colorectal polyps (NPCPs) under 2cm in size. Key LNPCP assessment and management principles are described below:

Endoscopic resection is recommended as first line therapy for the removal of large non-pedunculated colorectal polyps (LNPCPs)

Surgical intervention has historically been used to manage LNPCPs. However, modern advanced endoscopic methods such as endoscopic mucosal resection (EMR) and more recently, endoscopic submucosal dissection (ESD) have been developed, allowing endoscopic removal of even very large lesions, thus reducing the need for surgery (Moss et al, 2010). EMR is an endoscopic technique where a mucosal lesion is lifted away from the underlying submucosa by injecting fluid around and underneath it to create a 'submucosal cushion'. The polyp is then removed using an electrocautery snare in either an en bloc (one piece) or piecemeal fashion (where multiple smaller pieces of a lesion are sequentially removed to achieve complete resection) (52).

Endoscopic submucosal dissection (ESD) is a more advanced and technically challenging technique that allows en-bloc retrieval of larger lesions. Its availability is still very limited in the Western World as opposed to EMR which is widely available, whilst technical considerations such as procedure time and a higher level of perforation (up to 10%) have also limited the feasibility of its uptake in a non-Japanese setting(53). These factors ensure that EMR currently appears the most viable option for LNPCPs that are presumed benign until proven otherwise. Therefore, whilst ESD is discussed in more detail later in this chapter, endoscopic removal via EMR is covered in greater detail in this thesis. (54, 55).

In the appropriate setting, endoscopic resection provides highly effective management of LNPCPs with success in approximately 90% of cases. The ACE study demonstrated treatment success in 91% of treatment naive lesions and 74.5% of previously attempted lesions, with 89.2% of LNPCPS successfully removed in a single session (5). In addition, a 2012 US study of 315 'defiant' polyps referred to an expert centre reported successful endoscopic single session removal in 91% of cases whilst a 2013 UK study (n=220) demonstrated successful endoscopic treatment in 96% of cases with 87.5% of LNPCPs felt to be the most complex (SMSA level 4) successfully removed (9, 56). The economic argument for endoscopic management as first line treatment is strong. In addition to a cost saving of £3301.31 (\$5108.45) per patient compared to surgery demonstrated by Longcroft-Wheaton et al, an Australian study of 186 LNPCPs with a mean size of 30mm demonstrated similar findings. Cost savings of \$6990 USD per patient were estimated, with an average reduction of hospital stay of 6.7 days as advanced polypectomy can commonly be performed as a day-stay procedure (10, 56). Endoscopic removal appears safer than surgical resection which has reported rates of morbidity and mortality of 20% and 1% respectively (11). Whilst there is a

concern about a high level of early lesions recurrence with piecemeal endoscopic resection (pEMR), repeated endotherapy is often successful in achieving complete resection with comparable efficacy to en-bloc techniques in the longer term. Reported recurrence figures after 12 months vary between 2-6.9% (5, 9, 57)

	Moss et al (2011)	BCSP (Lee et al, 2013)	Buchner et al (2012)	Longcroft-Wheaton et al (2013)
Number of NPCCs	479	436	308	187
Mean size (mm)	35.6	29.5	23	41.5
Cases with complete resection considered achieved after single session (%)	89.2	NA	91	90%
Malignancy in resection specimen (%)	6.9	6	4.4	5.9
Need for surgery (%)	16.3	16.1	10	9
3 month recurrence (%)	20.4	16.5	27	14.5
12 month recurrence (%)	2	6	16.3	3.9
Delayed Bleeding	2.9	3	7.2	2.7
Perforation	1.3	0.5	0.4	0.45

Table 1. A comparison of outcomes from trials of endoscopic management of NPCCs

1.3.1) Optimising service delivery for large colorectal polyps

- **A structured LNCP referral pathway may allow patients access to a full range of therapeutic services, including laparoscopic surgery and endoscopists capable of performing endotherapy on complex NPCCs**

A structured referral pathway may allow better inter-specialty communication with more timely and efficient management of LNCPs (58). A pathway enables the creation of an audit trail and subsequent monitoring of performance. It is desirable that patients, irrespective of their location, should have access to a full range of management options that minimises the risk of morbidity and mortality. This includes access to endoscopists capable of performing advanced therapy on LNCPs. In expert hands, over 90% of lesions may be

successfully removed, and surgery avoided, including lesions previously felt to be endoscopically unresectable (5, 9, 59).

The management of rectal lesions also requires special consideration given the availability of specific therapies, the complexity and morbidity associated with resectional surgery in this area and the possible need for a permanent stoma (60). In this context it is important to differentiate between complex benign polyps (the main subject of this thesis) and early rectal cancer (stage I rectal cancer), where the indications for specific interventions, type of interventional procedures used and outcomes are often different. The management of rectal LNPCPs is discussed in greater detail later in the chapter.

The provision of advanced endoscopy services is also likely to be more cost effective for hospital trusts given the reduced costs associated with endotherapy and so a regional referral network may be appropriate if the necessary expertise is not available locally (56). In the case of lesions where surgery is required, laparoscopic surgery appears preferable as a minimally invasive option with an equivalent lesion resection rate and accelerated post-operative recovery (61)

Improved endoscopist experience results in improved outcomes

Whilst advanced polypectomy is an effective modality in most circumstances, the increased technical demands mean that the potential for serious complications such as haemorrhage and perforation is higher than for standard snare polypectomy. Patient safety is paramount and the ability to accurately identify underperformance allows prompt remedial action (2, 62). In addition, failure to achieve complete resection complicates further management and means the risk of subsequent malignancy is sub-optimally managed (63). Increased endoscopist experience is associated with superior outcomes. A 2002 study comparing endotherapy outcomes between an expert and non-expert group reported significantly increased successful LNPCP clearance by the expert group (76% vs 40%, $p=0.01$) (12). As previously discussed, endoscopist inexperience conclusively appears to impact directly on patient safety with an increased rate of adverse events. An almost 3 fold increase in the risk of heavy bleeding and perforation with the least experienced endoscopists and significantly increased adverse events for therapeutic colonoscopy with less experienced endoscopists in large volume trials strongly highlights the importance of endoscopists managing LNPCPs

independently gaining sufficient experience beforehand (64-66). Technical endotherapy skill appears to vary widely even amongst experienced endoscopists. The CARE Study (n=418) found outcomes of incomplete resection varied widely between endoscopists of similar experience. The incomplete resection rate for polyps thought to have been completely resected was higher than expected (IRR): 10.1% (95% CI: 6.9%–13.3%), and increased significantly with larger polyp size (IRR 10-20mm vs <10mm: 17.3% vs 6.8%, p=0.003) (20).

These findings suggest that advanced endoscopic polypectomy is not a universal skill as quality between endoscopists appears to vary markedly. The auditing of outcomes using identified key performance indicators (KPIs) may ensure that endoscopists managing LNPCPs independently are able to demonstrate competency with consistent high quality outcomes and result in improved outcomes and safety (59, 67).

A multidisciplinary network may provide more robust LNPCP assessment and management to limit unnecessary surgery and ensure that all therapeutic options have been explored

There is increasing support for multidisciplinary management of large complex polyps. Key stakeholders include those who may remove these lesions and those that can help to differentiate between benign and malignant LNPCPs and/or are able to establish whether successful management has occurred. Relevant specialists would likely include a LNPCP endoscopist, a laparoscopic colorectal surgeon and a gastrointestinal histopathologist. Positive reports of the use of a specialised multidisciplinary team meeting (MDM) within the fields of gastroenterology and endoscopy have commented on increased, more rounded, clinician input contributing to a more robust decision-making process and closer analysis of the range of management options (8, 23). A 2011 analysis compared the effect of management of a benign hepatopancreatobiliary MDM prior to ERCP compared to control cases in a prospective study of 1909 patients. The use of an MDM was associated with improved safety, with a decreased overall complication rate of (6.9% vs. 12.0%, p<0.001) and severe complication rate (0.4% vs. 2.5%, p=0.035))(24). Increased interaction between endoscopists and colorectal surgeons may allow all possible management options to be evaluated. The capabilities and quality of endoscopists is not uniform and growing evidence suggesting that many LNPCPs initially felt to be endoscopically unresectable and therefore initially referred for surgery can be removed in an expert setting (20). Friedland et al (2013)

reported that 71% of lesions initially referred for surgery without biopsy proven cancer were managed successfully endoscopically including 26% of lesions that had previous unsuccessful endotherapy whilst Moss et al (2011) and Longcroft Wheaton et al (2013) were able to achieve complete endoscopic resection in 74.5% of previously attempted lesions and 87.5% of the most complex NPCPS respectively (5, 56, 67). It can be argued that the availability of a multidisciplinary network with access to an expert centre may result in increased endoscopic options and surgery being avoided in many cases (5, 56, 59). This appears preferable given the increased cost, mortality and morbidity associated with surgery (10, 11). The discussion of benign lesions in a complex polyp MDT setting prior to surgical resection may allow more robust assessment of a lesion. As well as an interaction with colorectal surgeons, the additional involvement of endoscopists, including those with established competency in the removal of complex LNPCPs, may make endotherapy more feasible and avoid the use of surgical resection in some cases (59). Close interaction with a histopathologist may also be facilitated to obtain and establish comprehensive information about the adequacy of histopathology specimens, the possibility of malignant features, and establishing whether complete resection post endotherapy can be determined.

Timely management of LNPCPs is desirable due to the associated risk of malignancy

It appears logical to ensure that patients diagnosed with LNPCPs do not wait for inappropriately long periods of time for therapy in view of the risk of malignancy in this patient group with up to 15% of NPCPs thought to already harbour malignancy (68). However, this is balanced with ensuring that patients are managed by endoscopists with the appropriate expertise rather than being purely target driven where a patient may be managed by an inappropriate endoscopist to ensure a timeframe target is met. A timeframe in line with Department of Health policy that all diagnostic procedures should take place within six weeks may not be feasible from a service provision point of view in ensuring that therapy is undertaken by an endoscopist with the requisite expertise. There is also a need to ensure that a lesion has been adequately assessed either at the referring or receiving centre prior to therapy, which may necessitate additional diagnostic endoscopy and assessment time to ensure optimal management. A target more aligned with the NHS 62 day treatment target pathway may prove more feasible (69). Whilst the exact time sequence for adenoma to carcinoma transformation with NPCPs is unclear, growth model studies have sought to estimate progression times. A 2001 polyp growth model study reported a transformation

rate of 3% per year for lesions \geq 1cm and 20% per year for lesions with carcinoma in situ (70). A barium enema pre-colonoscopy study of polyps \geq 1cm left untreated between 12 and 229 months estimated a cumulative risk of cancer at the polyp site at 5, 10 and 20 years as 2.5%, 8% and 24% respectively (3). Whilst this data is not specific for LNPCPs it appears unlikely that a projected time frame of several weeks will compromise patient safety as there is no evidence that patients will come to harm in this time period, including with lesions that may harbour malignancy, whilst more time is available to ensure that an appropriate endoscopist is available.

Piecemeal endoscopic therapy appears inadequate if malignancy is suspected

An important oncological principle is that malignancy is removed in an en-bloc fashion. Rationale for this includes strong evidence that en-bloc lesion removal is associated with a lower level of lesion recurrence and a higher early cure rate than piecemeal resection (71). In addition, en-bloc resection allows precise histological analysis such as definitive evaluation of lateral and vertical resection margins and depth of invasion and as such is essential to ascertain the presence of favourable or unfavourable histological criteria (72, 73). En-bloc resection is difficult to achieve with lesions $>$ 2cm with EMR, however the likelihood of achieving this with LNPCPs is higher with endoscopic submucosal dissection (ESD), with various studies demonstrating en-bloc resection with this technique at a rate of approximately 90% (21). A Japanese retrospective analysis comparing lesions managed by ESD (n=145, 66% containing malignancy) with EMR (n=228, 69% containing malignancy) demonstrated only 2% recurrence with ESD compared with 14% recurrence with EMR ($p < 0.0001$), reporting a markedly higher cure rate with no significant difference in complications between the two groups (74). Another comparison study between en-bloc endoscopic removal (ESD/EMR) and piecemeal resection (pEMR) of benign lesions reported a similar trend for recurrence (n=269, ESD: 0%, EMR: 1.4%, pEMR 12.1%, $p < 0.001$) with similar complication rates (73). Where there is a suspicion of malignancy on lesion assessment, whilst piecemeal therapy is suboptimal, there is evidence that en-bloc resection may be effective as both a diagnostic and therapeutic tool. A 2012 Japanese retrospective series (n= 589) compared ESD outcomes for lesions with suspected but not proven malignancy at endoscopic assessment with those of laparoscopic surgery for early malignancy. En-bloc and curative resection was achieved in 87% and 80% of cases respectively with ESD, with lower complication rates than with laparoscopic surgery(75). A

2013 multicentre Japanese study reported outcomes from a series of lesions removed by ESD that were retrospectively found to contain submucosal malignancy. Lesions were described as 'low risk' if they displayed negative vertical margins, were reported as well or moderately differentiated adenocarcinoma, displayed no lymphovascular invasion, and had an invasion depth < 1000 µm. Lesions were defined as 'high risk' if any of these features were present. In the low risk group 5 year recurrence free survival was reported in 98% managed with ESD, whilst figures of 87% and 97% were reported in the high risk group for lesions managed with ESD and ESD + surgery respectively (76). However, whilst the potential efficacy of ESD is clear, as previously discussed, there are significant challenges with appropriate training, access and standardisation in a non-Japanese setting. The use of multidisciplinary networks appears important in ensuring increased access to ESD for UK patients.

Aside from surgical resectional therapy, the use of minimally invasive surgical therapy such as transanal endoscopic microsurgery (TEMs) resection in the management of rectal polyps can be used to achieve en-bloc resection of rectal lesions where malignancy requires exclusion. TEMs for the management of rectal LNCPs has been associated with lower rates of early recurrence with TEMs when compared with pEMR, in addition to allowing more robust histological examination. It should be noted however that late recurrence rates appear equivalent when allowing for repeat EMR and that TEMs has been associated with longer hospitalisation (77). TEMs is discussed in greater detail later in the chapter.

Whilst piecemeal endoscopic resection (pEMR) is already established as resulting in a higher level of recurrence, the risk appears larger with malignant colorectal lesions. One study examining the management of malignant LNCPs with pEMR found recurrence to be 10 times higher when compared with benign lesions (n=50, 33.3% vs 3.1%, p<0.05) whilst a 2009 Japanese study (n=572) also reported significantly higher recurrence with piecemeal resection of malignant polyps compared with benign lesions (17.1% vs 25%, p<0.01) (78, 79). Whilst piecemeal endoscopic resection (pEMR) is already established as resulting in a higher level of recurrence, the risk appears even larger with malignant colorectal lesions. One study examining the management of large malignant polyps with pEMR found recurrence to be 10 times higher when compared with benign lesions (n=50, 33.3% vs 3.1%, p<0.05) whilst a 2009 Japanese study (n=572) also reported significantly higher recurrence with piecemeal resection of malignant polyps compared with benign lesions (17.1% vs 25%, p<0.01)(78, 79). Piecemeal EMR removal of malignant colorectal polyps has also been identified as an

independent risk factor for incomplete resection by a 2011 Korean study (n=236, OR: 3.365, 95% CI: 1.295-8.744, p=0.013) (80). In addition, unlike en-bloc retrieval, it results in the retrieval of poorer quality histological samples and it is often not possible to evaluate the completeness of resection, depth of invasion, lateral resection margins and other prognostic features. Surgery is often required in this scenario due to inadequate staging (56).

The ability to evaluate resection margins is vital as it helps to ascertain completeness of resection and can predict the likelihood of residual disease. A meta-analysis of 31 studies (n=1900) identified positive resection margins (< 1mm) as a strong risk factor for residual disease (OR: 22, p<0.0001) (41). A finding of indeterminate resection margin status, a frequent issue with piecemeal removal, may also predict an increased risk of residual/recurrent disease as demonstrated by Butte et al (n=143, resection margins <1mm: 16%, indeterminate margins: 21%, negative resection margins (\geq 1mm): 0%, p=0.009) (44). Evaluation of the depth of submucosal invasion is also important as the depth of submucosal invasion has been shown to correspond to the risk of lymph node metastases. A large analysis of T1 colorectal carcinomas in 2002 (n=7543) found that lesions with deep submucosal invasion (sm3) were associated with a highly significant risk of lymph node metastases (p<0.001)(39). This supported the findings of a 1995 study that demonstrated that moderate (sm2) and deep (sm3) submucosal invasion was associated with a higher risk of lymph node metastases than superficial (sm1) invasion (n=182, p<0.01) (16). This histological information is therefore vital in establishing whether a patient has been cured, their risk of recurrence and planning of relevant subsequent therapy.

Whilst piecemeal endotherapy is effective in the management of benign lesions, in the context of malignancy, it seems less desirable to undertake an invasive treatment that is associated with a higher level of recurrence and incomplete resection, and often provides less useful information about definitive cure. Also, in the context of endoscopic features suggestive of malignancy and possible lymph node metastases (e.g. non-lifting sign in treatment naïve lesions, Pit Pattern V, Paris 0-IIc, LST-NG, NICE Type III, Sano capillary pattern type 3), endoscopic therapy may be inadequate as it cannot sample or remove the lymph node basin whilst piecemeal therapy is likely to result in the retrieval of suboptimal histological specimens (37).

Whilst endoscopic therapy has been used with success in lesions found to have early malignancy, it should be specified that this only applies to lesions identified as having low

risk of lymph node metastases. These are early invasive adenocarcinomas with negative resection margins (>1mm), minimal submucosal invasion, well or moderate differentiation and no lymphovascular invasion (81, 82). Deep submucosal invasion (>1000µm), positive/unidentified resection margin status, poorly differentiation (OR: 9.2, p< 0.05) and lymphovascular invasion (OR: 7, p< 0.05) are identified as high risk features indicating significant risk of lymph node metastases and histological exclusion of these features is therefore vital before deciding on en bloc endoscopic removal as primary therapy (41). Special consideration should also be given in the context of rectal location which is also identified as an additional risk factor for lymph node involvement (39).

In addition, concerns have been expressed about the potential for tumour seeding from the submucosa into deeper layers as a result of endotherapy in the context of malignancy, whilst malignant tumours may also be more vascular than non-malignant lesions and therefore more likely to be subject to a large volume bleed during endotherapy (83). Another note of caution is that several reports indicate high level of residual malignancy on surgical resection specimens where complete polypectomy had been considered to have taken place. A study of 143 malignant lesions managed endoscopically reported residual malignancy in 19% of cases whilst another analysis of 63 lesions resected endoscopically with a retrospective finding of early malignancy found residual malignancy in the colon wall and/or lymph nodes in almost 50% of cases managed surgically (44, 84).

Conservative management may be appropriate on an individualised patient basis

Whilst LNCPs are associated with a risk of malignant transformation and may sometimes already harbour malignancy, the risk of symptomatic malignancy and cancer-related mortality from these lesions may be outweighed by patient factors that may more imminently reduce life expectancy. In this context, subjecting a patient to the additional immediate risks of endoscopic or surgical resection may not be in their best interests and the risks and benefits of undertaking therapy require consideration. As previously discussed, adenoma to carcinoma transformation to a point where a lesion becomes symptomatic may take several years (70). Patient factors requiring consideration include advanced age, frailty, comorbidities such as chronic cardiorespiratory conditions and other established malignancy. The use of mortality index models may help to stratify individual patient risk prior to attempting invasive therapy. One such example is a validated model proposed by

Schonberg et al using a scoring system predicting 5 year mortality risk based on performance status and comorbidities (see tables 2 & 3) (85)

Demographic	Score
Patient Age (Years)	
65-69	0
70-74	1
75-79	3
80-84	5
85+	7
Male Sex	3
Smoking Status	
Never	0
Former	1
Current	3
Body mass index <25 kg/m²	2
Comorbid conditions	
COPD [†]	2
Diabetes mellitus	2
Cancer	2
Overnight hospitalizations in past year	
None	0
One	1
Two or more	3
Perceived health	
Excellent/very good	0
Good	1
Fair/poor	2
Functional measures	
Dependent in at least one IADL [†]	2
Difficulty walking several blocks	3

Table 2. Schonberg Scoring System (85)

Point Score	Estimated 5 year mortality risk (%) (5% Confidence Interval)
0-1	3 (1-6)
2-3	5 (3-8)
4-5	8 (6-10)
6-7	12 (10-15)
8-9	19 (16-23)
10-11	29 (25-33)
12-13	37 (32-42)
14-15	49 (43-55)
16-17	55 (48-62)
18+	62 (54-70)

Table 3. Schonberg Score with corresponding estimated 5 year mortality risk (85)

Procedural issues may also pose a concern about reduced life expectancy. For patients with increased age or severe comorbidity, both endoscopic and surgical therapy may prove hazardous, with the use of sedation and general anaesthetic posing a significant cardiopulmonary safety concern. An Australian study reported increased risk in 30 day mortality in non-cardiac surgery in patients over 70 (OR: 1.09 per year over 70 years, 95% CI: 1.04-1.13, $p < 0.001$) (86). Increased surgical mortality and morbidity risk is an important factor as is consideration about whether a patient might survive a serious endoscopic complication and subsequent therapy. Conservative management may therefore prove an appropriate strategy where life expectancy is already greatly reduced.

1.3.2) Pre-Removal Assessment

- **Adequate planning (including length of time booked for procedure, endoscopist and nursing staff skills and endoscopic equipment) may improve endoscopist confidence regarding achieving single session complete resection**

Given the potential complexity of advanced polypectomy, adequate planning is required for the procedure. In addition to the exclusion of features suggesting malignancy and potential complications related to endotherapy, an important aim, where possible, is to attempt complete endoscopic resection in a single session (87). The significance of single session completion is reflected by its regular reporting as an important outcome in large volume trials with approximately 90% success reported whilst the ACE study demonstrated an increased risk of resection failure in previously attempted lesions (OR 3.75; 95% CI: 1.77–7.94; $p = 0.01$) (5, 9). Key to achieving this aim is ensuring adequate time is allocated for the procedure and that all relevant professionals and equipment are readily available (62).

Another important consideration is that the complete removal of a lesion after one session also reduces the risk of malignant transformation at the earliest opportunity (88).

1.3.3) Lesion Assessment and Identification

- Features in non-pedunculated colorectal polyps (NPCPs) associated with increased malignancy risk, increased complexity in relation to achieving successful endoscopic removal and avoiding adverse events have been identified
- The identification of large non-pedunculated colorectal polyps (NPCPs) associated with increased malignancy risk and increased complexity may lead to improved therapeutic outcomes and the avoidance of adverse events
 - Lesions with Increased risk of malignancy – Lesions exhibiting; pit pattern type V, Paris 0-IIc or 0-IIa+IIc morphology, non-granular LST (laterally spreading type polyp, LST-NG), granular LSTs (LST-G) with a dominant nodule, distorted surface pattern, colour and vessels (NICE NBI type III), thick and irregular microvessels (Sano capillary pattern type III)
 - Lesions with an increased risk of incomplete excision/recurrence – Size ≥ 40 mm, location involving ileocaecal valve, appendix, diverticulum or dentate line; within an inflamed segment of colitis; prior failed attempt at resection or recurrence at site of previous resection (excluding unifocal, diminutive and easily resected/ablated residual adenoma on first site check); non-lifting sign after submucosal injection; endoscopist concern about difficult location (e.g. behind flexure or fold, in stenotic diverticular disease);
 - Advanced polypectomy is associated with a vastly higher risk of serious complications compared to conventional snare polypectomy. Factors associated with a further increased risk of adverse events include caecal location, size ≥ 40 mm and endoscopist inexperience
 - Complex NPCP- A term to describe NPCPs with any of the following features: (a) increased risk of malignancy; (b) increased risk of incomplete resection/recurrence; (c) increased risk of adverse event; (d) SMSA level 4

Lesions with Increased risk of malignancy – Lesions exhibiting; pit pattern type V, Paris 0-IIc or 0-IIa+IIc morphology, non-granular LST (laterally spreading type polyp, LST-NG), granular LSTs (LST-G) with a dominant nodule, distorted surface pattern, colour and vessels (NICE NBI type III), thick and irregular microvessels (Sano capillary pattern type III)

NPCPs with morphological features of depression (Paris 0-IIc/IIa+c) appear to strongly correlate with malignancy. A 2002 Paris workshop quoted an unpublished study of 3680 lesions where 61% of 0-IIc lesions displayed submucosal invasion. This was markedly higher than the morphological group with the next highest incidence of submucosal invasion (Paris Is: 34%)(15). Lesions displaying surface characteristics of pit pattern Type V have also been shown to be strongly associated with deep submucosal malignant invasion. Specific analysis of lesions with type V pit pattern found a vastly higher incidence of malignancy compared with other pit pattern types (56% vs 4.4% (pit pattern III) vs 5% (pit pattern IV) vs 0% (pit patterns I + II), n=479, p<0.001) (5, 89). Other lesion surface characteristics also associated with an increased risk of malignancy include a non-granular surface or a dominant nodule (>10mm) on laterally spreading type lesions and irregular microvascular network patterns (Sano Capillary Pattern type III) (90, 91).

LSTs may be divided into granular (LST-G) and non-granular (LST-NG) types (54). In a study of 511 LSTs, the frequency of submucosal invasion with LST-NG type lesions was twice that of LST-G type lesions (14% vs 7%, p<0.01) (90). Closer scrutiny of LST-NG type lesions suggests that pseudo-depressed LST-NG lesions are associated with a substantially higher risk of submucosal invasion than flat elevated LST-NG lesions. A Japanese study of 1363 LSTs of at least 10mm in size demonstrated submucosal invasion in 42.1% of pseudo depressed LST-NG lesions compared with 6.1% flat elevated LST-NGs (p<0.01) (92). LST-G lesions with a nodule>10mm were also demonstrated to be strongly associated with submucosal invasion (>10mm nodule: (29.8%) vs<10mm nodule: (2%), OR: 71.01, p<0.001) (90). In view of these results it has been suggested that both LST-G type lesions with a large dominant nodule and LST-NGs are better suited to en-bloc removal whilst other LSTs may be suitable for piecemeal endoscopic therapy (92).

The identification of irregular and thickened microvessels using narrow-band imaging (NBI) (Sano capillary pattern (CP) classification) has also been identified as an accurate method of determining depth of submucosal invasion of NPCPs (91). A study of 130 lesions reported that the Sano CP type III pattern was associated with a 84.8% sensitivity, 88.7% specificity

and 87.7% diagnostic accuracy for differentiating deep submucosal invasion (sm2/3) from more superficial involvement (mucosal/sm1), indicating the value of this classification system (93).

Another method of identifying deep submucosal invasion has recently been validated. The NICE NBI classification allows examination of the surface characteristic of a polyp based on its surface appearance, colour and vessel pattern without the aid of magnifying colonoscopy (94). NICE Type 3 lesions are differentiated from type 2 (adenoma) and type 1 (hyperplastic) lesions by virtue of a dark brown surface, disrupted or missing vessels and an amorphous or absent surface pattern (95). A 2013 Japanese study demonstrated an overall sensitivity and negative predictive value for high confidence prediction of deep malignant submucosal invasion of 92% in a tertiary centre setting (94).

Lesions with an increased risk of incomplete excision/recurrence – Size \geq 40mm, location involving ileocaecal valve, appendix, diverticulum or dentate line; within an inflamed segment of colitis; prior failed attempt at resection or recurrence at site of previous resection (excluding unifocal, diminutive and easily resected/ablated residual adenoma on first site check); non-lifting sign after submucosal injection; endoscopist concern about difficult location (e.g. behind flexure or fold, in stenotic diverticular disease);

Various features have been identified that may predict the difficulty of achieving complete endoscopic resection of LNPCPs (6, 37). Very large lesions are more technically challenging and time-consuming to remove as they are associated with a higher likelihood of needing eventual surgical management (17, 54, 96). A US study demonstrated that very large lesions (occupying over 75% of colonic wall circumference) were associated with an increased endotherapy failure rate on univariate analysis (n=315 OR: 1.11; 95% CI: 1.06-1.17; p<0.001) (9). A study of LNPCPs managed within the UK Bowel Cancer Screening Programme identified lesions \geq 40mm as more likely to require surgery (20mm-29mm (7.8%) vs 30mm-39mm (23.9%) vs \geq 40mm (27.5%), p<0.001) and requiring an increased number of endoscopic procedures to achieve clearance (20mm-29mm (1.84%) vs 30mm-39mm (2.31) vs \geq 40mm (2.33), p<0.001) (17).

Polyps that cross over 2 haustral folds are felt to pose difficulty as the space between the folds can be difficult to access whilst there is a concern about ensnaring the full thickness of the colonic wall, thereby increasing the risk of perforation. Polyps behind a fold or that have

a 'clamshell' distribution around a fold can also pose an issue with obtaining adequate endoscopic access for visualisation and removal (96).

Polyps that fail to lift in response to an accurately placed submucosal fluid injection (non-lifting sign) without prior intervention have an increased risk of deep submucosal invasion, indicating a reduced likelihood of successful removal with snare polypectomy (see later)(5, 97). NPCPs subject to a previously failed endoscopic attempt, that have occurred in the context of IBD or are located in a site of previous endoscopic resection are likely to be subject to scarring and submucosal fibrosis and may not lift adequately after submucosal fluid injection. An analysis of cases of failed endotherapy highlighted non-lifting lesions as a major risk factor (RR 4.96, 95% CI: 3.51–7.01, $p < 0.001$) (5). These lesions may require consideration for en-bloc removal with ESD or surgery (see later) (96).

Peri-diverticular polyps may also pose an issue with endoscopic access as this portion of the colon may be narrower and less amenable to a stable endoscopic position. Moreover, polyp tissue may encroach into a diverticulum. Lesions involving the ileocaecal valve have also been associated with a higher failure rate (RR 2.61, 95% CI: 1.28–5.32, $p = 0.020$)(5). These lesions may be difficult to access and visualise (especially in distinguishing ileal mucosa from adenomatous tissue) whilst ileal involvement adds further complexity (54, 96). Rectal polyps involving the dentate line can be complicated due to their location in a position of high vascular supply and sensory nervous innervation. The endoscopic removal of these lesions is thus associated with a higher risk of peri-procedural pain and delayed post polypectomy bleeding. In addition, their location means that they often need resection in a retroflexed position (54).

A summary of features statistically identified as independent risk factors for failed endotherapy include:

- Previous intervention (n=479; OR: 3.75; 95% CI: 1.77–7.94; $p = 0.001$)
- Ileocaecal valve involvement (OR: 3.38; 95% CI: 1.20–9.52; $p = 0.021$)
- Difficult position (OR: 2.17; 95% CI: 1.14-4.12; $p = 0.019$)
- Lesion size >40mm (OR: 4.37; 95% CI: 2.43-7.88; $p < 0.001$)
- Previous APC use (OR: 3.51; 95% CI: 1.69-7.27; $p = 0.001$) (5)

Advanced polypectomy is associated with a vastly higher risk of serious complications compared to conventional snare polypectomy. Factors associated with a further increased risk of adverse events include caecal location, lesion size >40mm and endoscopist inexperience

The most serious complications related to advanced polypectomy procedure such as EMR and ESD are bleeding, perforation and incomplete resection. Reported figures for EMR are far higher than with standard polypectomy where rates of up to 1 in 100 and 1 in 500 have been reported for delayed bleeding and perforation respectively (2). The incidence of perforation with EMR appears to range between 0.5-1.3% whilst severe post procedure bleeding has been reported in approximately 3-10% of cases in large volume studies (5, 9, 17, 57).

LNPCPs located in the right colon, especially in the caecal pole, and lesions ≥ 40 mm have been associated with an increased risk of adverse events following advanced polypectomy. Right sided lesions are associated with an increased risk of perforation due to thermal tissue injury with polypectomy in the thinner right sided colon (98). Lesions involving the caecal pole, including those that involve the appendiceal orifice are considered to be associated with an increased risk of perforation as this is where the colonic wall is at its thinnest and it has also been suggested that the front-on angle at which polyps are accessed increases the potential for the entire colonic wall to be ensnared during polypectomy (54). An Australian study analysing risk factors for post procedure haemorrhage identified right sided location as an important risk factor (Adjusted OR: 4.4, 95% CI: 1.3-14.1, $p=0.014$) with the highest incidence found in the caecum (98). These findings were similar to that of a retrospective analysis of 146 lesions where multivariate analysis demonstrated an almost five fold increased risk of delayed haemorrhage with right sided polyps (OR: 4.67, 95% CI: 1.88 – 11.61, $p=0.001$) whilst univariate analysis suggested that caecal polyps conferred the highest risk (OR 13.82, 95% CI: 2.66–71.73). Multivariate analysis also reported an increase in bleeding risk by 13% for every 1mm increase in polyp diameter (OR: 1.13, 95% CI: 1.05 – 1.20, $p < 0.001$) (99).

A polyp size of ≥ 40 mm was identified as a risk factor for increased post polypectomy bleeding (PPB) in a study of 493 LNPCPs where PPB increased markedly post resection of lesions ≥ 40 mm compared with resection of lesions < 40 mm (OR=43.043, 95% CI: 4.306–430.314, $p=0.001$) (100).

Further evidence of caecal location and lesion size ≥ 40 mm as risk factors for adverse events were reported in a study of adverse events from 167208 polypectomies (130831 colonoscopies) performed within the English Bowel Cancer Screening Programme. Caecal location (OR: 2.13, 95% CI: 1.36-3.34, $p < 0.01$) and polyp size of ≥ 40 mm (OR: 3.90, 95% CI: 3.35-4.94, $p < 0.001$) were both identified as strong risk factors for adverse events in endoscopic polypectomy. The risk of adverse events increased further with combination of both these factors with a predicted risk of bleeding of 1 in 8 (101).

Endoscopist inexperience also appears to be a clear risk factor for adverse outcomes. A 2008 study comparing adverse outcomes between endoscopists of varying experience demonstrated an almost 3 fold increase in the risk of heavy bleeding and perforation with inexperienced endoscopists (OR: 2.96, 95% CI: 1.57–5.61, $p = 0.0008$) (66). A trend of increased adverse events post therapeutic colonoscopy by less experienced endoscopists has also been demonstrated in large volume studies by Singh et al ($n = 24509$, RR: 5.4, 95% CI: 3.0-9.0, $p = 0.02$) and Chukmaitov et al ($n = 2315126$, OR: 1.18, 95% CI: 1.07-1.30) (64, 65).

The potential complexity of achieving successful endoscopic resection can be estimated

Complex NPCPs may be described as lesions with a greater than average risk of malignancy, incomplete resection/recurrence or complications that may be best suited to management by clinicians with the relevant skills and experience within a multidisciplinary environment. An additional method of stratifying lesion complexity has also been devised. The SMSA scoring system predicts the difficulty of achieving successful endoscopic polypectomy based on the size, morphology, site and access of a polyp (see tables 4 and 5 below). A study stratifying lesions ($n = 220$) using the SMSA scoring system reported that it was both accurate and simple to use and provided valuable information on the lesion complexity and success and complication rates of endoscopic resection. A lower level of endoscopic clearance was achieved with lesions felt to be the most complex (SMSA level 4) than with less complex lesions (SMSA level 2 and 3) (87.5% vs 97.5%, $p = 0.009$). This system may aid in service planning and stratifying lesions that require referral to an expert centre (6, 56).

Parameter	Range	Score
Size	<1cm	1
	1-1.9cm	3
	2-2.9cm	5
	3-3.9cm	7
	>4cm	9
	Morphology	Pedunculated
Sessile		2
Flat		3
Site		Left
	Right	2
Access	Easy	1
	Difficult	3

Table 4. SMSA Scoring system to assess polyp difficulty (6)

Polyp Level	Range of Scores
I	4-5
II	6-8
III	9-12
IV	>12

Table 5. SMSA scores with corresponding difficulty levels (6)

1.3.4) Considerations with anti-thrombotic medication

British Society of Gastroenterology Anticoagulation Guidelines advocate the cessation of warfarin at least 5 days prior to endoscopic resection of NPCPs with an INR confirmed as below 1.5. General recommendations regarding the management of newer anticoagulants which have differing properties, such as rivaroxaban and dabigatran, are not currently in place due to a lack of evidence.

Cessation of warfarin prior to endotherapy is advocated by both the BSG and ASGE (102, 103). A study of 1657 patients undergoing colonoscopic polypectomy demonstrated that warfarin was strongly associated with post procedure bleeding (OR: 13.37, 95% CI: 4.10-43.65, $p < 0.001$) (104). The findings of a further retrospective analysis ($n=1225$) concurred with this (interrupted warfarin use vs uninterrupted warfarin use: 0.2% vs 2.6%, adjusted OR 11.6, 95% CI: 2.3-57.3, $p < 0.005$) (105). A single dose of warfarin can be detectable up to 120 hours after ingestion and therefore cessation 5 days prior to endoscopy has been recommended with an INR established as near normal (< 1.5) (103)

Newer anticoagulants such as dabigatran, rivaroxaban and apixaban are being used increasingly instead of warfarin as they do not require regular monitoring. In addition they have a much shorter half-life (dabigatran: 14-17 hours, rivaroxaban: 4-9 hours) meaning that they may be stopped closer to the time of endoscopy than warfarin. As they are renally excreted, caution is required with their use in the context of renal impairment especially prior to endoscopic polypectomy with earlier cessation likely to be needed to achieve normal patient clotting function (106). In the current absence of evidence based recommendations, obtaining specialist input regarding the management of these medications pre and post endoscopy appears appropriate.

British Society of Gastroenterology Antiplatelet Guidelines advocate the cessation of medications such as clopidogrel and prasugrel, and newer antiplatelet agents such as ticagrelor at least 7 days prior to advanced polypectomy

Clopidogrel and prasugrel are classified as thienopyridines and have a different antiplatelet mechanism to aspirin. The BSG, ESGE and ASGE advise their cessation based on an increased haemorrhage risk (102, 103, 107). A meta-analysis of 5 observational studies concerning

clopidogrel use with polypectomy compared 574 patients who continued clopidogrel therapy prior to polypectomy with 6169 control patients. A significantly increased risk of delayed post- polypectomy bleeding RR of 4.66 (95% CI: 2.37-9.17, $p < 0.00001$) was demonstrated, concurring with another study where the incidence of delayed bleeding post polypectomy was over 3 times higher in the clopidogrel group ($n=375$, 3.5% vs 1%, $p=0.02$) but immediate bleeding incidence was similar in both groups (108, 109). Prasugrel and newer antiplatelet agents such as ticagrelor appear to be more potent than clopidogrel and also require cessation. An RCT comparing prasugrel with clopidogrel ($n=13608$) found prasugrel to be associated with a significantly higher rate of major bleeding (2.4% vs 1.8%, Hazard Ratio: 1.32, 95% CI: 1.03 to 1.68; $p=0.03$) (110). Pharmacological studies have demonstrated that clopidogrel, prasugrel and newer, theoretically shorter acting agents such as ticagrelor may affect platelet aggregation for up to 7 days and so cessation at around 7 days prior to LNPCP endotherapy appears appropriate (103, 107).

The continuation of low dose aspirin prior to endotherapy appears safe but may require individualised patient assessment

There are conflicting reports about the safety of continuing aspirin prior to advanced polypectomy. Whilst it appears that many endoscopists do stop aspirin, UK and US guidelines advise that it can be continued (102, 103). Multiple case-control studies have suggested that it does not increase haemorrhage risk in colonoscopy and polypectomy (107). An example includes a case-control study of 20636 patients undergoing colonoscopy with polypectomy which showed no significant difference with aspirin use in bleeding (40%) and non-bleeding groups (33%) ($n=20636$, OR: 1.41, 95% CI: 0.68 to 3.04, $p=0.32$) (111). Another example is a 2008 study demonstrating a similar frequency of PPB in aspirin and control groups (41% vs 39%; $n=4592$; $p=0.80$) (112). Whilst specific LNPCP data is limited, a Japanese study examining the risk of bleeding with aspirin with ESD ($n=582$) demonstrated similar levels of PPB with both aspirin interruption (15.4%) and cessation groups (16.1%), suggesting aspirin continuation appears safe (113). Given conflicting data and opinion, it does appear appropriate to manage aspirin use according to individualised patient risk, such as a scenario that an LNPCP presents a high risk of PPB.

1.3.5) Peri-procedural management

Carbon dioxide improves patient comfort and safety compared to air insufflation during colonoscopy

There is evidence that CO₂ insufflation improves patient comfort during colonoscopy when compared with air insufflation, especially with longer procedures such as advanced polypectomy. A trial of 219 patients found that CO₂ was associated with significantly reduced pain ($p=0.014$) and bloating ($p<0.001$) than air insufflation as well as increased patient satisfaction ($p=0.04$) (114). Another study demonstrated that CO₂ use was associated with significantly reduced post procedure admission following endoscopic polypectomy (OR: 0.39, 95% CI: 0.16-0.95, $p=0.04$) (115). CO₂ insufflation has also been associated with increased patient safety. As CO₂ is non-inflammable, the risk of combustibility with the use of diathermy and argon plasma coagulation (APC) (both of which are important components of advanced polypectomy) is eliminated as oxygen is required for an explosion (116). The use of CO₂ insufflation appears to improve patient experience and may allow for longer procedure times and enable the completion of endoscopic resection which has previously been limited by patient discomfort.

1.3.6) Polyp Assessment









Size estimation of LNCPs, ideally by measuring against an open snare, is considered to improve lesion assessment

Whilst pathological estimation appears to be the most accurate method of assessing lesion size, a size estimate of a polyp during endoscopy is important, not only for deciding upon surveillance intervals, but also when considering the malignant potential of a NPCP and technical considerations such as deciding on en-bloc or piecemeal resection or the resection plane (117). There is extensive evidence that visual size estimation during endoscopy by clinicians continues to be inaccurate. A 1997 study using pathological size estimation as a reference, examined size estimation of lesions up to 36mm in size ($n=61$), finding that 20% of lesions were inaccurately estimated (118). A 2013 study ($n=230$) found that 62.6% of lesions were mis-sized by $>33\%$, with 47.8% of lesions undergoing inappropriate surveillance because of this (119). Specific underestimation of lesion size has been demonstrated in numerous cases. A 2009 study found that endoscopist size estimates made during endoscopy, irrespective of experience, appeared to be inaccurate, with lesions over 2cm significantly underestimated in size (polyp mean deviation -5.80mm , 95% CI: 0.44-0.62) (32,

117, 120). This finding was replicated in a 2014 study with lesion size underestimation in 20% of estimates (n=2812, range: 4-46%) (121). The use of measurement tools has been shown to improve the accuracy of endoscopic size estimates. The use of a linear probe was supported by a 1997 study, reporting that its use appeared to correlate closely with pathological measurement (0.88:Pearson correlation,95% CI: -0.16 to 0.64) (122). A readily available modality is the use of an open snare and its use as a size reference may improve accuracy.

The use of Paris Classification to describe polyp morphology has high accuracy in predicting malignancy risk

Participants in a Paris workshop proposed a classification model for the description of polyps based on morphology in view of a previous Japanese classification model in 2002 (15). This was further revised in 2003 to enable the evaluation of superficial lesions with respect to the depth of submucosal invasion. Lesions were classified as protruding (0 – I; incorporating pedunculated and sessile polyps), non-protruding and non-excavated (0 – II; flat - further divided as elevated (IIa), flat (IIb) and depressed (IIc)), and excavated (0 - III) (123). Lesion morphology appears to accurately predict the risk of malignancy. Non protruding depressed lesions were highlighted as having an increased risk of malignant submucosal invasion and more likely to require surgical intervention (15). The initial finding of a markedly increased risk of submucosal invasion with Paris 0-IIc lesions compared with sessile lesions (n=3680, 61% vs 3%) has been repeated in a more recent study of LNPCPs (n=479) (IIc or IIa+c: 31.8% vs IIb: 11.1% vs Is: 7.5% (p=0.001)) (5, 15). Furthermore, these lesions also correlate with Kudo Pit Pattern type V, a robust and more established indicator of likely malignancy(14). This demonstrates the reliability of the Paris Classification in predicting malignancy and its use in guiding optimal management (15, 123)

Endoscopic appearance	Paris classification	Description	Visual description
Protruded lesions	Ip	Pedunculated polyp	
	Ips	Subpedunculated polyp	
	Is	Sessile polyp	
Flat elevated lesions	0-IIa	Flat elevation of mucosa	
	0-IIa/c	Flat elevation with central depression	
Flat lesions	0-IIb	Flat mucosal change	
	0-IIc	Mucosal depression	
	0-IIc/IIa	Mucosal depression with raised edge	

Adapted from Participants in the Paris Workshop (2003)

Figure 5. Illustration showing subtype of polyps using Paris classification method (46)

The use of classification systems that describe the surface characteristics of a polyp such as the NICE NBI classification and the Kudo Pit Pattern allow accurate lesion assessment whilst the use of image enhancement techniques (either digital or chromoendoscopic) can improve diagnostic accuracy further

The characterisation of polyps by pits and vessels was first described by Kudo et al in 1994(14). The use of pit pattern classification is well described and is not only a robust method of delineating between hyperplastic and adenomatous polyps, but is also accurate in predicting deep malignant submucosal invasion based on polyp surface characteristics (14, 124, 125). As previously discussed, a finding of ‘type V’ pit pattern is strongly associated with a risk of deep submucosal malignancy compared with other pit pattern types (5, 89). Further scrutiny with sub-classification of type V pit pattern to V_I (irregular arrangement) and V_N (amorphous structure) can further stratify malignancy risk. A study of 272 lesions found deep submucosal invasion in 95.7% of lesions with type V_N pattern compared with 30.7% of lesions with type V_I pattern (126). The increased association of type V_N pattern with malignancy was confirmed by a finding of malignancy in 100% of these lesions in data from a 2008 Japanese analysis (127). Further sub-classification of the type V_I pattern to mildly irregular and severely irregular has been proposed due to a marked difference in malignancy incidence between the two groups (7-17% and 56-85% respectively)(126, 127). A potential limitation of pit pattern use is the learning curve required to interpret pit pattern and the potential for interobserver variation. However, the use of training modules suggests

that successful pit-pattern recognition can be achieved even by inexperienced endoscopists (128). The diagnostic accuracy of Kudo Pit Pattern indicates that it may be used to predict submucosal invasion, recognise malignancy and determine the suitability of a polyp for endoscopic resection (14, 89, 129, 130).

Enhanced imaging techniques may help improve diagnostic accuracy when assessing NPCPs. Narrow band imaging (NBI) is a form of digital image enhancement that uses narrow-band filters and high intensity blue light to enhance surface mucosal and vascular pattern visualisation (131). A multicentre prospective RCT (n=667) found that NBI had greater accuracy than both standard and high definition white light endoscopy at correctly predicting polyp histology with a sensitivity of 90% (95% CI: 85.3-93.4, p<0.001) and accuracy of 82% (95% CI: 77.4-85.4%, p<0.001) (132). The importance of NBI is also reflected in its role in the examination of polyp surface characteristics using the NICE classification system which has demonstrated accuracy in identifying deep submucosal malignant invasion. In addition, it has high availability due to the lack of requirement for magnification endoscopy whilst it appears that it can be used by inexperienced endoscopists with appropriate training. A Japanese study demonstrated 90% accuracy (95% CI: 85.1-93.3) by a student group using the system (54, 94).

Both NBI and magnifying chromoendoscopy appear to be accurate in delineating between neoplastic and non-neoplastic polyps. A study comparing NBI and magnifying chromoendoscopy with white light endoscopy reported that both techniques were associated with a diagnostic accuracy of over 90% compared with white light endoscopy which was found to have only 59% diagnostic accuracy (133). The usefulness of magnifying chromoendoscopy has also been confirmed by a large prospective study (n=4215) which demonstrated the accuracy of magnifying chromoendoscopy at estimating the depth of invasion of early colorectal neoplasms using combined mucosal and morphological patterns. The sensitivity, specificity and diagnostic accuracy to differentiate mucosal cancer or superficial invasion (sm1) (<1000 μ m) from deeper invasion (sm2-3) (\geq 1000 μ m) was reported as 85.6%, 99.4%, and 98.8%, respectively (134).

The use of virtual chromoendoscopy techniques such as flexible spectral imaging colour enhancement (FICE) and I-Scan may have a role in lesion assessment. A Japanese 2010 study (n=235) reported comparable diagnostic accuracy between FICE and NBI magnification in correctly predicting histopathological diagnosis in lesions up to 130mm (FICE: sensitivity

(77.7%) and specificity (100%) vs NBI magnification: sensitivity (63.6) and specificity (99.0%)) whilst FICE diagnosis of benign and malignant lesions was strongly associated with the correct histopathological diagnosis ($p < 0.01$) (135). A study of 110 lesions examining the accuracy of I-Scan in determining polyp histology when used by endoscopists reported a diagnostic accuracy between 74-94% which was independent of lesion size. However, the use of a training module prior to commencement of the study reflects the learning curve required for its use (136).

Further endoscopic tools such as confocal electromicroscopy appears to demonstrate diagnostic accuracy in distinguishing neoplastic and non-neoplastic polyps but their availability is limited (137).

ESGE guidelines (2014) support the use of enhanced imaging by recommending the use of conventional or virtual (NBI) magnified chromoendoscopy to predict the risk of invasive cancer and deep submucosal invasion (138).







Pit pattern	Description	Image	Expected histology
I	Round pits		Normal histology
II	Asteroid pits		Hyperplastic or serrated adenoma
III _S	Tubular or round pits smaller than normal pits		Adenoma
III _L	Tubular or round pits larger than normal pits		Adenoma
IV	Gyrus, branched, dendritic-like pits		Tubulovillous adenoma
V	Irregular, non-structural pits		Malignancy (adenocarcinoma)

Figure 6. Kudo Pit Pattern Subtypes (46)

1.4) To Resect or Refer?

- Major considerations include whether a lesion is endoscopically resectable and if so whether the detecting endoscopist has the technical ability to achieve this.

- **Resection of LNPCPs may not be appropriate at the time of discovery**

Given the potential complexity of advanced polypectomy, adequate prior planning is required. This includes ensuring that the correct management strategy has been selected, that the patient has given informed consent, that an endoscopist and assistants with the requisite experience are available, and that adequate time has been allocated for the procedure and having relevant equipment available (62). Important management aims include the exclusion of features suggesting malignancy and potential complications related to endotherapy and, where possible, achieving complete resection in a single session. In the case of many complex lesions, additional multidisciplinary support is often required to achieve these aims (87). Previous incomplete endotherapy as a result of inadequate planning has been shown to reduce the likelihood of successful endoscopic removal compared with treatment naïve lesions, primarily due to submucosal fibrosis. The ACE study demonstrated significantly lower treatment success with a previously attempted lesions (75.4%) than with treatment naïve lesions (91%) (OR 3.75, 95% CI: 1.77–7.94, p=0.01) (5). Outside the expert setting, successful removal rates are likely to be lower still and this suggests that injudicious attempts at therapy in suboptimal circumstances can complicate further management (9, 59, 139).

As previously discussed, it is considered imperative that patients understand the specific risks of advanced polypectomy, in addition to all available management options (140). Management of an LNPCP at the time of discovery may not allow this, especially if a patient has been given sedation.

Retrieval of lesion biopsies may complicate subsequent endoscopic resection attempts

Taking biopsies of the colonic mucosa can result in fibrosis and a subsequent non-lifting sign, also associated with malignancy and previous endoscopic resection attempts. This makes successful endoscopic removal more difficult to achieve (5). Multiple studies have reported that taking biopsies can complicate the removal of colorectal lesions by compromising the submucosal lift from a fluid injection due to submucosal fibrosis from a post-biopsy scar. A 2008 Korean study demonstrated a significantly reduced rate of submucosal elevation in a biopsy group compared to a non-biopsy group (n=42, 77% vs 45%, p=0.03) (141). Another study assessing the effect of biopsies taken before an attempt at ESD reported that biopsies

prior to endotherapy did not provide useful information and interfered with endoscopic removal, finding a significant association between the use of biopsy and subsequent fibrosis (n=89; OR: 3.45; p=0.014) (142). A delay between taking biopsies and subsequent endotherapy may also increase the difficulty in achieving successful resection. A 2008 study reported that a history of previous biopsy significantly increased the incidence of the non-lifting sign, especially if lifting was attempted over 21 days post biopsy (n=76, OR: 16.208, 95% CI: 1.024-256.442, p=0.048) (139). All lesions assessed under 21 days post biopsy did lift however and a conclusion was drawn that biopsies should be minimised with an advanced endoscopy attempt made as soon as possible after biopsy. These factors suggest that caution is required with biopsy use, especially when malignancy is not suspected and prompt repeat endoscopy cannot be guaranteed (139).

Obtaining biopsies of a polyp may not be helpful in contributing towards an accurate diagnosis. A 2005 study of 532 polyps asserted that colorectal biopsies were inadequate for grading of colorectal neoplasia with findings that the histopathological diagnosis was underestimated in up to 10% of cases whilst advanced neoplasia was underestimated in up to 60% of cases (143). A 2011 Taiwanese study of 1027 polyps demonstrated a false negative rate of 86% for early colorectal cancer and high grade dysplasia with a randomised biopsy practice of adenomatous polyps whilst an earlier UK study of 433 colorectal polyps reported that the biopsy of malignant polyps gave a false negative rate of 18.5%(144, 145). Whilst biopsies are appropriate if malignancy is a concern, careful targeting should be used to improve diagnostic accuracy and minimise submucosal fibrosis in the event of subsequent endotherapy (142).

1.5) Endoscopic Resection Principles

- **Large colonic polyps can be removed either 'en-bloc' or 'piecemeal' with multiple pieces of a lesion taken to achieve complete resection.**
- **En-bloc endoscopic snare resection of NPCPs is recommended where feasible to reduce the risk of recurrence and to enable more accurate histopathological interpretation.**

- **Caution has been advised regarding attempts at en-bloc snare resection with NPCPs \geq 20mm (LNPCPs) due to an increased risk of diathermy associated thermal injury and perforation**

En-bloc snare resection where possible is desirable due to reduced recurrence and the ability to obtain more accurate histological analysis. In addition, a Korean study suggests the risk of incomplete resection in piecemeal resection is significantly higher with lesions \geq 30mm (n= 497, OR: 2.688, 95% CI: 1.036–6.993, p= 0.042) (100).

A 2014 meta-analysis of 33 studies examining snare removal of non-pedunculated lesions unequivocally demonstrated lower recurrence with en-bloc resection compared to piecemeal removal (3% (95% CI: 2-5%) vs 20% (95% CI: 16-25%), p<0.0001) (146).

Whilst it is possible to remove lesions over of 2cm en-bloc with snare resection due to the availability of snares up to 45mm in size, it may be technically difficult to achieve due to reduced snare stiffness whilst uncertainty about the resection plane may lead to concerns about perforation due lack of control of tissue volume and from thermal injury due to an inability to control the cutting plane (120, 147). A 2012 Korean study also demonstrated that where EMR was carried out for NPCPs > 30 mm, the chance of using piecemeal resection increased significantly due to technical reasons (OR: 7.246, 95% CI: 4.672– 11.235, p < 0.001) (100). Where en-bloc specimen retrieval is required, such as suspected malignancy, techniques such as ESD and surgery may be required. However, in the case of benign lesions, piecemeal EMR has been shown to have comparable efficacy, especially when allowing for repeat treatment of recurrence with less morbidity. The high complete eradication rates reported by various studies such as 90% by Buchner et al and 96% quoted by Longcroft-Wheaton et al including 87.5% of SMSA level 4 lesions support this (9, 56). In addition whilst a 2009 study reported lower rates of early recurrence with en-bloc TEMS for rectal lesions when compared with pEMR, it should be noted that late recurrence was similar in both groups when allowing for repeat endoscopic therapy (TEMS: 9.6% vs EMR: 13.8%, p = 0.386) whilst TEMS was associated with greater morbidity and longer hospitalisation (3 days vs 0 days, p<0.001) (77)

The creation of submucosal cushion with a fluid injection is widely recommended to facilitate successful endoscopic resection

A submucosal injection is commonly made around a lesion to create a 'submucosal cushion' prior to diathermy assisted snare polyp removal with the benefits relating to both increased efficacy and safety. A 1994 Japanese study comparing efficacy of submucosal assisted polypectomy with non-submucosal assisted polypectomy (n=1075, 788 sessile lesions) reported that submucosal injection facilitated the endoscopic removal of lesions initially felt to be unresectable such as flat polyps with improved resection rates in the submucosal injection group (75.7% vs 70%, p<0.05) and a reduced rate of complications (148). The creation of a submucosal cushion lifts a mucosal lesion away from submucosa and deeper muscular layers and reduces the risk of perforation due to diathermy induced thermal tissue injury whilst also reducing the risk of perforation due to capturing excess tissue within a snare resulting in deep resection lesions (149).

Lesions which do not lift after adequate submucosal injection are unlikely to be amenable to removal with conventional snare polypectomy technique.

The use of a submucosal injection, although not intended as a diagnostic tool, may also be informative about lesion characteristics as an inability to lift a treatment naïve lesion, known as the 'non-lifting sign', is strongly associated with malignant submucosal invasion(97).

Uno et al first described an association between non-lifting lesions in response to a submucosal injection and malignancy in 1994 (150). All cases defined as non-lifting were found to contain malignancy. A 1999 Japanese study supported this finding by also demonstrating an association between the non-lifting sign and deep submucosal invasion (n=60). All lesions with deep submucosal invasion (sm3), lesions associated with a higher rate of lymph node metastases and so requiring surgery, displayed the non-lifting sign whereas most lesions with more superficial submucosal invasion were able to achieve lifting (93.5% of sm1 lesions) (97). A later study repeated these findings with only 20% of sm3 lesions lifting as opposed to 82.4% of sm1 lesions (p<0.05)(139) whilst a 2007 study reported that the non-lifting sign displayed an accuracy rate of 94.8% (n=271, p< 0.05) (151). Previous interventions such as biopsy may cause potentially endoscopically removable lesions to also display the non-lifting sign but in lesions with no prior intervention, correlation between the non-lifting sign and deep submucosa invasion with lymph node involvement appears strong (67, 139). In view of this, whilst en-bloc removal may be possible, the mucosectomy action of snare polypectomy is less likely to be effective in treatment naïve non-lifting lesions due to irregularity of the submucosal plane (37).

Colloidal type submucosal injection solutions are recommended in preference to normal saline lifting solution for 20mm and larger lesions.

Whilst normal saline (0.9%) is commonly used in polypectomy and is effective in creating a submucosal cushion, a review of available evidence suggests that colloidal type solutions appear to be superior for submucosal injection in view of technical and safety factors. The use of colloidal type solutions in submucosal injection solutions has been recommended as it is felt to produce a longer lasting lifting effect and facilitate easier resection than normal saline(59, 152). Animal models demonstrated that colloidal type solutions such as hydroxypropyl methycellulose and succinated gelatin (gelofusin) enabled a longer lasting lift (mean of 36 minutes) and increased en-bloc resection (153, 154).

Sodium hyaluronate (SH) commonly used for ESD, has also demonstrated superiority over normal saline in porcine models (155). A 2004 Japanese study found that SH produced a longer lasting lift than both normal saline and hypertonic solutions and later reported that it is also associated with reduced tissue injury (149, 156).

These findings appear to have been replicated in human studies. A 2005 study compared 113 NPCPs removed with EMR with glycerol with 110 lesions removed by EMR with normal saline. The glycerol group demonstrated a higher en-bloc resection rate (63.6% vs 48.9%, $p<0.05$) and complete resection rate (45.5% vs 24.6%, $p<0.01$) (157). A double blind RCT found that the use of succinated gelatin, an inexpensive solution, significantly reduced procedure time (GS: 12.0 min (interquartile range:8.0-28.0) vs. NS: 24.5 min (15.0-36.0), $p=0.006$) and reduced the number of piecemeal resections made when compared with normal saline solution (GS; resections=3.0 (1.0-6.0) vs. NS; resections 5.5 (3.0-10.0), $P=0.028$) (154, 158)

There is evidence to suggest that the use of hypertonic solutions may have a role in the removal of LNPCPs. A prospective double blind RCT ($n=1370$) reported that 50% dextrose was associated with a reduced injection volume ($p=0.033$) and number of injections ($p=0.028$) to maintain a mucosal lift compared to normal saline. It was also associated with a longer lasting submucosal lift, an effect that became more pronounced as lesion size increased ($>20\text{mm}$; $p=0.039$, $>40\text{mm}$; $p=0.025$). However, the use of 50% dextrose was

associated with a higher incidence of post polypectomy syndrome, a finding also confirmed by Fujishiro et al with dextrose solutions >20% concentration, and the risk of tissue injury is a limiting factor in the use of hypertonic solutions (156, 159).

The addition of low concentration adrenaline to the submucosal injection solution is considered helpful to keep the resection field clear during endoscopic resection

The addition of adrenaline to submucosal injection solutions at a dilution of 1/10000 has been advocated to reduce the risk of immediate post-polypectomy bleeding (PPB). A 2001 study demonstrated reduced immediate PPB with a 1:10000 adrenaline containing solution compared with a saline only solution (1/75 vs. 7/76, $p = 0.03$) whilst a 2004 study also reported this result (1/50 vs 8/50; $p < 0.05$). No improvement has been demonstrated with delayed PPB (160, 161). A 2007 Korean study, despite reporting that adrenaline use did not confer an additional advantage over a saline only submucosal solution, did demonstrate significantly reduced immediate PPB with NPCPs. (1/75 vs 7/76; $p = 0.03$) (107, 162).

The use of contrast agents such as indigo carmine or methylene blue in the submucosal injection solution may enable lesion demarcation, its resection margins, and outline a clear submucosal plane

There appears to be uniform acceptance of the importance of the use of contrast agents, which allow the demarcation of lesion extent and submucosal cushion as well as enabling complete resection through identification of the correct plane of resection as well as lateral margins in order to achieve visual complete resection (51, 55, 62, 68, 115, 163, 164). A study of 445 patients described how the use of indigocarmine facilitated the recognition of deeper planes of resection and identification of tissue deep to submucosa. This enabled the identification of all cases of post resection perforation which were subsequently managed at the earliest opportunity (164).

It should be noted that an association between methylene blue and potential DNA damage to colonocytes has been reported in laboratory based work, a finding not associated with indigocarmine (165). However, no clinical evidence has been reported that precludes its use.

1.6) Equipment

1.6.1) Snares

A number of different snare conformations and sizes exist. However there is no evidence to support the use of a specific type

Snare polypectomy is the method of choice for polyps larger than 1cm, however, there appears to be a paucity of evidence suggesting an optimal snare for use in advanced polypectomy. There are various sizes, shapes and textures available. Larger snares (> 2 cm) are preferred by some operators with the intention of en bloc resection or wide field resection of larger polyps though this is thought to carry a potentially increased risk of perforation if a large volume and depth of tissue is within the snare (166). Smaller, thinner (monofilament) snares are often preferred where increased precision is required and spiral or stiffer snares are often used by some operators where gripping of a flat elevated lesion is thought to be optimised (167). A combined injection needle and stiff large snare device ('I-Snare') was recently reported to be superior to another large snare (braided 'Snare Master' snare) very commonly advocated for advanced polypectomy. The device was reported to both reduce polypectomy procedure time and allow piecemeal polyp retrieval in fewer, larger pieces using the Sydney resection quotient (SRQ), the size of the polyp divided by the number of pieces resected and the amount of tissue per snare attempt (n=140, 13.8mm vs 7.1mm, p=0.019) (168). However, reports favouring the use of a particular snare such as spiral or crescentic snares appear subjective and variations in operator experience and expertise in these studies make a particular choice difficult to recommend (68, 169).

1.6.2) Diathermy and coagulation

Pure cutting current is associated with an increased risk of immediate post polypectomy bleeding whilst prolonged pure coagulation current forms are associated with increased risk of delayed post polypectomy bleeding and thermal tissue injury respectively

International surveys of endoscopic practice have indicated variation in the choice of diathermy settings used for polypectomy. A US survey of endoscopic practice in 2004 (n=198) found blended current (46%) and coagulation current (46%) to be in more common use with lower reported use of varied (4%) and pure cutting current (3%) (170). A 2013 survey of Israeli endoscopists (n=100) found that 42% used pure coagulation current with

38% using blended current and 20% using pure cutting current (171). Pure cutting current is likely to relate to higher rates of immediate post polypectomy bleeding (PPB) due to poor haemostasis properties, and the avoidance of its use in endoscopic polypectomy has been advocated by some groups including the ESGE (107, 172). Cutting current does have good incision properties, however, enabling high quality resection specimens and inducing less thermal tissue injury (50, 173). A 1992 study comparing the use of coagulation current with 'blended current' (which appeared to be predominantly cutting current) in snare polypectomy (n=1485) demonstrated a significant difference in the timing of haemorrhage between the two groups with the former more associated with delayed haemorrhage and the latter associated with immediate haemorrhage (p=0.03). The incidence of major haemorrhage was low in both groups however (6/727 and 8/758 respectively) (174). A subsequent multicentre study (n=5152) identified pure cutting current as one of the greatest risk factors for immediate post-polypectomy bleeding (OR: 6.95, 95% CI: 4.42–10.04) (107, 175).

Pure coagulation current appears to be commonly used and has good haemostasis properties. However, higher settings and prolonged use induce higher levels of thermal tissue injury. Porcine models have demonstrated a greater depth of tissue injury with coagulation current than both blended (p=0.0157) and pure cut current, (p=0.0461)(50). The increased risk of tissue injury is of particular concern in the thinner right colon which is more susceptible to diathermy induced perforation (62, 173, 176, 177). The use of blended current or automated current that regulates coagulation and cutting current (such as Endocut) have been advocated as safer diathermy options with the rationale that they provide adequate incision properties combined with effective haemostasis. A trial comparing blended and microprocessor controlled automated current (n=148) found that automated current produced less tissue damage than blended current with a conventional electrosurgical generator (p<0.02) whilst also producing higher quality resection specimens (p=0.024) allowing for more accurate histological evaluation (p=0.046) (178). These findings suggest that the rationale for use of automated current appears sound. (50, 107)

Thermal coagulation techniques such as argon plasma coagulation (APC) and soft coagulation are available management options when snare resection of small residual fragments of polyp is not possible.

APC has been advocated as a safe non-contact method of thermal coagulation for use in therapeutic endoscopy due to its provision of a 'limited and predictable depth of tissue injury' (179). The use of APC as an adjunct to endoscopic snare resection has been supported by various studies. Zlatanovic et al reported that the use of APC in lesions where residual adenoma had been left after initial therapy resulted in a reduction of 50% of residual adenoma on follow up endoscopy compared with no APC use (n=77, 100% reduced to 50%) (180). A 2003 Czech study also demonstrated successful endoscopic clearance with the additional use of APC in 90% of lesions with incomplete endoscopic snare resection (n=77) (181). A larger study in 2011 commented that the use of APC on visible residual adenoma following piecemeal polypectomy did not reduce lesion recurrence (n=105; OR: 0.46, p = 0.29). This finding may be due to the application of APC to larger areas of tissue but also highlights that APC should not be relied upon as a sole treatment of residual adenoma (182, 183).

A 2002 study where the use of APC on post resection margins was examined found that the use of APC as an adjunctive therapy reduced the rate of adenoma recurrence following piecemeal EMR in lesions where complete resection was thought to have been achieved (1/10 APC, 7/11 no APC; p = 0.02). This effect may be due to the treatment of microscopic residual foci at the resection margins not visible to the endoscopist (184). In addition, whilst not a primary outcome, multiple large volume trials demonstrating successful clearance of the majority of cases of residual and recurrent tissue describe routine use of APC as an adjunctive therapy (5, 9). The use of hot biopsy avulsion has also been advocated as an ablative technique for flat polyp tissue considered unsnarable, with a small 2014 study (n=20) reporting no residual tissue on surveillance in 85% of cases (185).

Thermal coagulation may also be provided by the use of soft coagulation from diathermy applied to tissue via the snare tip, however no data to definitively support its use has as yet been demonstrated. A prospective RCT known as the SCAR trial examining the use of soft coagulation in the prevention of adenoma recurrence is currently recruiting patients in Australia.

1.7) Post Resection

Careful post-procedure inspection of the resection site may allow accurate assessment of completeness of resection

Imaging of a resection site is important not only to document and confirm whether complete resection has taken place, but also to confirm inspection and exclusion of a perforation. Taking steps to assess for complete resection appears important as it appears incomplete resection appears to be far more prevalent than first thought, even amongst experienced endoscopists. The CARE study demonstrated increasing rates of incomplete resection with larger lesions. 23.3% of lesions between 10 and 20mm felt to be completely resected at endoscopy were found to be incompletely resected, despite the endoscopist considering complete resection to have taken place significantly higher than with smaller lesions (17.3% vs 6.8%; $p=0.003$) whilst almost half of serrated lesions were incompletely resected (20). A 2014 study demonstrated histological evidence of recurrence in 7% of NPCPs where complete resection was felt to have occurred both on initial resection and follow-up ($n=252$).

The use of a pigmented contrast agent in the submucosal injection fluid, allowing close inspection of the resection site and also of the underside of the resected specimen (looking for a 'target sign'), may help to identify a perforation almost immediately. This would allow management of the defect at the earliest opportunity (164).

The ASGE also recommend photo documentation in relation to the area of a tattoo post endoscopic resection as it may enable identification of a scar site where no residual tissue is present (186, 187).

Tattoo application is recommended to aid endoscopic follow up or subsequent surgical resection.

The use of tattoo application with an indelible marker such as India Ink has been highlighted as an important practice post endoscopic removal to enable identification of the resection site on follow up and enabling lesion identification in cases requiring surgical resection. Tattooing is often not required in the caecum or rectum as lesions are more easily identified in these areas (188).

Caution has been advised with regards to tattoo practice with regards to avoiding complicating endoscopic resection (188, 189). Various case series have reported sub-lesional submucosal fibrosis resulting from tattoo application compromising subsequent endoscopic resection by both EMR and ESD (190, 191). A distance of at least 3cm from a lesion has been recommended in one Australian case series (190).

Retrieval of specimen

Retrieval of the resected polyp allows histopathological analysis. Devices such as nets and graspers may be used to trap and retrieve resected tissue whilst smaller fragments from piecemeal resection may be retrieved via aspiration through the endoscope.



Figure 7. Large sessile polyp identified

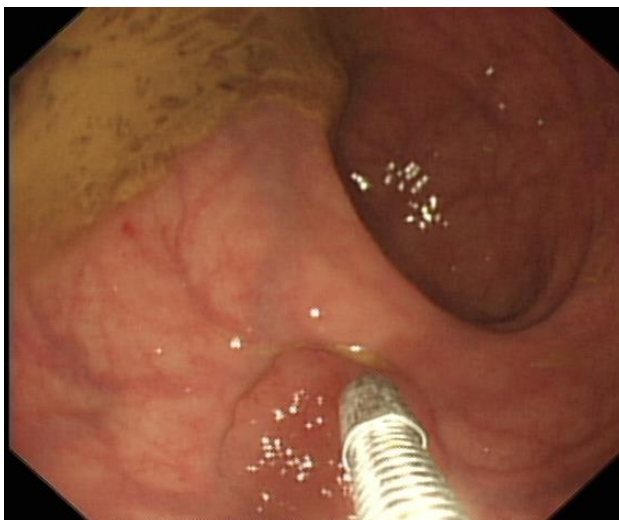


Figure 8. Submucosal injections made to lift lesion

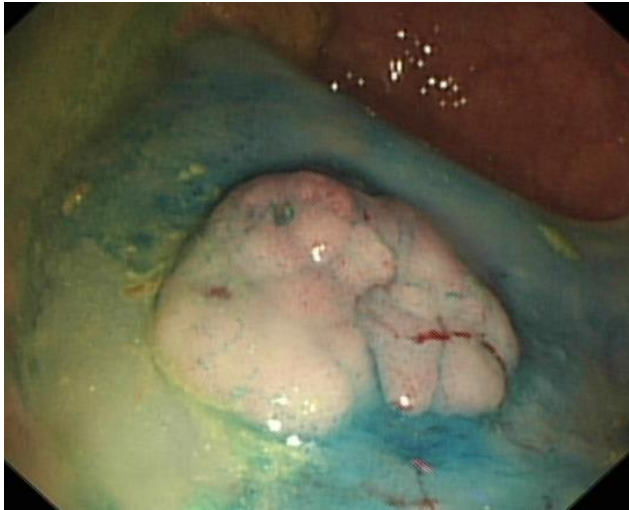


Figure 9. Sessile adenoma with submucosal lift



Figure 10. Snare passed around adenoma

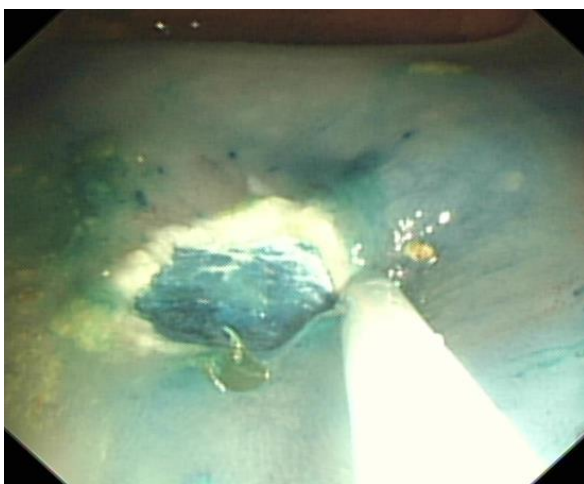


Figure 11. Post polypectomy site with clear base

1.7.1) Complications

Post-procedure bleeding (both immediate and delayed), perforation and persistent recurrence are recognised complications

The most serious complications related to advanced polypectomy procedure such as EMR and ESD are bleeding, perforation and incomplete resection. Figures of up to 1 in 100 and 1 in 500 have been reported for delayed bleeding and perforation respectively related to standard colonoscopy and polypectomy (2). However, reported delayed bleeding and perforation figures for large polyps requiring EMR are markedly higher. Reported rates of perforation in studies using EMR appear to be between 0.5 and 1.4% whilst severe post procedure bleeding has been reported in approximately 3-10% of cases in large volume studies (5, 9, 17, 57). Information pertaining to the risk of serious complications and alternative treatment may be given in a written form and this practice appears to be in place across various centres (140). Larger lesions carry a higher risk. Perforation may be due to a full thickness bowel wall tear causing peritonitis or localised perforation with a serosal burn causing localised tenderness (postpolypectomy syndrome). Peritonitis is usually an indication for surgical intervention whereas localised perforation will usually resolve with conservative management (51). Perforation seen at the time of endoscopy can sometimes be managed with endoclip and loop placement (9).

Significant bleeding is reported if a patient requires hospital admission, requires a transfusion or repeat endoscopy for haemostasis management. It can be classified as immediate (occurring within 24 hours) and delayed (up to 14 days post procedure). The incidence is unclear with various studies reporting rates between 0.7 and 10% (104). Bleeding can often be managed with adrenaline injection, clip placement and APC. In more severe cases, radiological embolisation and even surgery may be required. Increased bleeding is noted with anticoagulant use, piecemeal resection, larger polyps, pedunculated polyps with a broad stalk (over 1cm) and patients with clotting abnormalities (51). Serositis is post procedural pain resembling localised peritonism with no evidence of perforation. Conservative management with antibiotics is usually required (51).

Incomplete resection (failure of EMR) occurs in up to 10% of cases in expert centres, and is far more likely to occur in non-expert centres or if a previous unsuccessful attempt has been made resulting in submucosal fibrosis (5).

Early recurrence with the need for additional therapy is also a prominent issue with the use of piecemeal endotherapy. A US study of 308 NPCPs quoted an initial recurrence rate on follow-up of 27% (rising to 38% for piecemeal resection) with a mean size of 23mm (OR 11.68 (1.47-92.76), p=0.02) (9). The ACE study reported recurrence in 20.4% of cases in a study of 479 LSTs with a mean size of 35.6mm (piecemeal resection ≥ 6 pieces=34.2%, <6 pieces =18.2% (OR: 2.25; 95% CI: 1.45–3.50; p=0.002) (5). A 2014 meta-analysis examining piecemeal endoscopic resection suggests that early recurrence occurs in up to 20% of cases (146). It would be appropriate to advise patients that early recurrence does not represent treatment failure as lesion clearance was achieved in the vast majority of cases with follow up endotherapy in almost all studies (5, 9, 146). The potential for late recurrence after 12 months, which may suggest treatment failure, should also be mentioned. Recent estimates from studies with large follow-up numbers after 12 months suggest a figure of approximately 4-7% (56, 57). Data from the English Bowel Cancer Screening Programme (BCSP) of 436 NPCPs with a mean size of 29.5mm reported a recurrence rate at 12 months of 6% whilst Longcroft-Wheaton et al's 2013 data reported late recurrence in 3.9% of cases(17, 56). A 2010 Italian study reported 6.9% recurrence with 182 LSTs on 19 month follow up (mean size 24.7mm) (57)

Complications may occur weeks after endoscopic resection

There is evidence that patients with serious complications related to polypectomy, such as haemorrhage and perforation, may not present with symptoms until several days post-procedure. An analysis of post polypectomy bleeding (PPB) cases from 14,575 colonoscopies with polypectomy reported a mean presentation time of 5 days post procedure with a cases occurring up to 17 days after polypectomy, whilst there have been reports of PPB occurring up to 30 days post procedure (192, 193). An analysis of post colonoscopy perforations found that 24% of cases presented over 48 hours post colonoscopy with 9% presenting over 15 days after (194). In view of this, the provision of a clear post procedure plan is important and may expedite appropriate management and improve patient safety.

A copy of the endoscopy report with clear written instructions may be given to a patient post procedure with instructions about the course of action to take should they experience pain or significant bleeding following EMR. It should be explained that severe bleeding can occur up to 14 days post resection and they should return to hospital for emergency assessment with a view to blood transfusion and endoscopic haemostasis.

1.7.2) Follow-Up Arrangements

In the case of piecemeal EMR, initial follow-up is recommended within 2-6 months, with 12 month follow-up for en-bloc resection

Early follow-up endoscopy after piecemeal resection is advocated due to potentially high rates of incomplete resection and early lesion recurrence after primary endoscopy. With piecemeal resection, histological evaluation is often unable to assess for completeness of resection. In the case of successful en-bloc removal, follow-up is required due to a risk of new adenomas with 12 month follow-up considered sufficient in view of low recurrence rates and the important ability to establish complete resection on histological analysis after initial resection (195). There is evidence to suggest that recurrence levels increase the longer the period of time left to follow up on initial treatment, and early intervention of recurrent/residual tissue allows prompt treatment in an attempt to fully clear a lesion and prevent adenoma to carcinoma transformation (196). A Japanese study reported recurrence rates of 18.4%, 23.1%, and 30.7% for follow up at 6, 12 and 24 months respectively whilst a US study reported a similar trend with recurrence almost 3 times higher after 24 months than at 12 months (79, 197). Initial follow up at a later point such as 6 months also appears safe with similar levels of recurrence between 3 and 6 months and reports of recurrence identified at 6 months not seen at 3 months. However, follow-up may also be appropriate sooner such as in the context of finding malignancy or high grade dysplasia on histology (21, 79). Follow-up within 6 months for piecemeal resection and at 12 month with en-bloc resection is in line with the position of the US Multisociety Task Force for Colorectal Cancer and the American Cancer Society who also recommend that lesions removed piecemeal should be considered for follow-up endoscopy between 2-6 month intervals until complete excision is completed (198).

1.7.3) Residual and Recurrent Tissue

- **Residual neoplasia occurs at a level higher than previously understood**
- **Image enhancement with techniques such as dye spray and digital enhancement may aid detection of residual neoplasia on a polypectomy scar.**
- **Areas of possible residual polyp require tissue diagnosis and definitive treatment**

There is evidence to suggest that incomplete resection occurs at a higher rate in cases of apparent complete resection than previously considered. The CARE study found a high incidence of incomplete resection (10.1%) in cases where complete resection was considered to have been achieved, including incomplete resection in almost half (47.6%) of sessile serrated adenomas, with a wide variety in rates of incomplete polyp resection between different endoscopists. The results of this study appear highly noteworthy as the endoscopists involved were all highly experienced and were aware of their involvement in a clinical trial and as such heightened scrutiny is likely to have been taken to ensure complete resection was considered achieved (20). Further justification for careful analysis of the scar site on follow-up endoscopy is provided by reports of 'late-recurrence' in an area where complete resection was believed to have occurred. This phenomenon was first described by Walsh et al in 1992 where almost half of cases of recurrence occurred in cases where no recurrence had been identified on earlier examination (88). A 2009 study reported late recurrence of residual adenoma in 4.4% of cases at 12 month follow-up (n=138). In eight (7.2%) cases, evidence of residual adenoma was present in biopsy from scar sites where no visible adenoma was seen. Negative biopsy results at early follow up appeared to be predictive of continued eradication on late follow up in 97.9% of cases when compared with the remaining lesions (RR; 0.15, 95% CI, 0.035-0.618, p=0.005)(199). The practice of biopsy retrieval as part of follow-up resection site examination was supported by Knabe et al's analysis of 252 NPCPs in which biopsy evidence of residual/recurrent adenoma in 7% of cases where no visible adenoma was present whilst late recurrence was seen in 10.47% of cases where no adenoma was identified at initial follow-up (200). Taking biopsies from the polypectomy scar site when complete resection is considered to have taken place can be justified as it appears in some cases to have identified residual tissue for eradication treatment that would otherwise have been undetected.

High rates of unknown incomplete resection and the finding of late occurrence of residual tissue after no reported macroscopic recurrence may be due to the presence of recurrent tissue too small to visualise using standard endoscopy. This suggests that image enhancement may improve diagnostic accuracy (201). Magnification endoscopy appears accurate in identifying residual tissue. A study of 77 NPCPs compared prediction of completeness of excision with magnifying endoscopy with histological evaluation. The sensitivity of magnification endoscopy for predicting residual tissue at resection margins was 98% (95% CI: 90–100). Specificity was 90% (95% CI: 79–100), with an overall accuracy of

94.5% (95% CI: 87.2–98.6) (202). The use of chromoendoscopy was found to be accurate in predicting completeness of endoscopic resection in a 2004 study of 684 lesions (sensitivity 80%; specificity 97%; accuracy 94% (203). A 2011 study comparing the accuracy of NBI with WLE (white light examination) in the detection of residual neoplasia found that NBI increased detection of residual neoplasia at the resection site with 63% of identified lesions found to be more extensive with NBI than initially thought with WLE (204).

The use of confocal endomicroscopy (CEM) was been reported to have high diagnostic accuracy in predicting completeness of resection in vivo post EMR by a 2011 Chinese study of 24 lesions (diagnostic accuracy: 91.7%; sensitivity: 100%; specificity: 89.5%). Similar findings were reported by a 2012 US study also reporting increased sensitivity in detecting residual neoplasia using CEM (n=129; sensitivity: 97%(p=0,045); specificity:77% positive predictive value (PPV): 55%; negative predictive value (NPV): 99% diagnostic accuracy: 81%) (137, 201). However the small sample sizes of these studies and the fact that CEM is not widely available indicate that these findings are not likely to be currently relevant in everyday wider practice.

The management of residual/recurrent polyp tissue appears challenging with only limited data supporting endoscopic methods

Whilst a proportion of recurrent/residual polyp tissue can be successfully treated with repeat snare resection, complete eradication with repeat therapy may be much more difficult to achieve such as with larger areas of recurrence. Repeat therapy with EMR may not be achievable due to submucosal fibrosis (59).

The use of ESD appears to be a less invasive management option in a scenario of complex recurrence. There have been various reports of its efficacy in scar embedded polyps and subsequent avoidance of surgical resection. A 2009 study reported successful clearance of lesion recurrence with ESD in 15 cases where EMR had failed to clear the original polyp (205, 206). A Japanese study also reported the successful use of ESD in large areas of recurrence (>2cm) where EMR was not possible with no subsequent recurrence (207). However it should be noted that these studies are small and ESD availability in the West is still limited. Surgical resection remains an effective management option in this scenario whilst conservative management appears appropriate if patient comorbidity suggests that no management will not significantly affect life expectancy. Various factors such as patient

wishes and comorbidity and availability of treatment modalities may affect management and access to a multidisciplinary network may optimise management. (8, 51, 208)

Secondary surgical management is commonly required in cases of unsuccessful endoscopic resection, a finding of malignancy after an initial attempt at endoscopic resection and in the management of complications.

Failed endoscopic attempts at removal can complicate subsequent management. Incomplete or inadequate attempts at EMR can result in more complicated management, secondary surgical management and development of colorectal cancer and so the decision making process in the assessment and subsequent management of large colonic polyps is of great importance (12).

There is broad variation in large polypectomy practice:

A large 2004 survey of polypectomy practice demonstrated broad variation between endoscopists(170). This included advanced polypectomy, where the threshold for the use of submucosal injection appeared to vary widely. For large pedunculated lesions with a broad stalk, there was no uniform technique used for bleeding prophylaxis. A possible reason given for variation in practice was the probability that many practitioners performed polypectomy as they were taught and the lack of available evidence from clinical trials for several aspects of advanced polypectomy meant that a change in practice that they were comfortable with was unlikely (170). For example, many trials conducted, such as trials for diathermy and submucosal injection solutions, involved the use of animal models. Variation in practice appears to have continued. A more recent survey reported similar findings, with variation not only in the use of submucosal injection for polypectomy and bleeding prophylaxis for stalked polyps, but also in the choice of snares used, the constituents used in the submucosal injecting solution, diathermy settings used and use of imaging enhancement techniques such as NBI (171). Further variation was demonstrated in a 2013 UK survey captured variation between UK endoscopists with aspects such as the use of biopsies and video recording whilst a training survey found that over 50% of respondents to a national survey who regularly practiced advanced polypectomy were self-taught (19). It appears plausible to suggest that variation in technique may affect outcomes (209).

Based on subjective opinion, survey results, lack of evidence in certain areas and conflicting trial reports, reasons for variation in practice may include:

- Cessation of antiplatelet agents such as aspirin
- Use of carbon dioxide or air insufflation,
- Routine use of classification systems
- Use of chromoendoscopy, high definition imaging or NBI to inspect a lesion
- Endoscopic position used to resect lesion
- Type and constituents of lifting solution used
- Snare sizes and type used
- Upper limit threshold for attempting en-bloc resection
- Threshold for attempting non-lifting lesions, whether previously attempted or not
- The amount and type of electrocautery used
- The use of argon plasma coagulation (APC) used at excision margins in piecemeal EMR
- The use of snare tip coagulation or APC for residual tissue
- Post polypectomy bleeding prophylaxis management such as clip application to the resection site and management of bleeding
- The management of visible perforation
- Documentation of procedure (photos, classification systems used to describe systems on report).
- Aftercare instructions given to patient
- Timing and frequency of follow up endoscopy
- Technical ability of the endoscopist and individual complication rates (18)

1.8) Other therapeutic modalities

1.8.1) Endoscopic Submucosal Dissection

Endoscopic submucosal dissection (ESD) is a more invasive, time-consuming technique that allows en-bloc retrieval of larger specimens than possible with EMR, with a single ESD procedure potentially taking up to several hours (71, 73). As with EMR, a submucosal cushion is made to lift the lesion away from the submucosa with a lifting solution. Given the comparatively longer procedure time, the use of colloidal type solutions that provide a longer lasting cushions such as hyaluronic acid and glycerol (in combination with 1:10000 adrenaline and a pigment dye) has been advocated (210). Resection is performed with the use of an electrosurgical knife, of which various types exist much like endoscopic snares.

The knife is used to make an initial circumferential mucosal incision and then submucosal dissection is performed parallel to the muscle layer under endoscopic visualisation. The knife has coagulation properties but the use of diathermy and clips may also be required to prevent and control bleeding, with the latter used to treat small visible perforations (211). The largest reported study of the use of colorectal ESD was a multicentre Japanese study of 1111 NPCPs in 2010 with NPCPs up to 140mm in size, which reported en-bloc resection and curative resection rates of 88 and 89% respectively. Procedure times varied between 1-4 hours with a perforation rate of 4.9% and a post-procedure bleeding in 1.5% of cases (212). A review of studies examining the use of colorectal ESD suggests that it is highly effective with reported en-bloc resection rates of around 90%. Reported rates of perforation, the most recognised complication with ESD, in larger studies (n>200) vary between 4.9-8.2% which is markedly higher than reported with piecemeal EMR (0.5-1.5%)(212, 213).

ESD has only limited availability in both the UK and the western world and there is a relative paucity of data with only low volume studies when compared with Asia (71). A 2007 UK study of 42 NPCPs managed with ESD reported en-bloc resection in 78.6% of cases with a curative resection rate of 74% and perforation and post procedure bleeding at 2.6% and 11.9% respectively (214). A 2013 Italian study featuring lesions up to 80mm in size (n=40) reported figures comparable to many reported Japanese series with en-bloc resection and curative resection rates of 90% and 80% respectively and comparatively low rates of perforation (2.5%) and post procedure bleeding (5%)(215). However, it should be noted that in addition to a small sample size, this series consisted entirely of rectal lesions which are felt to be easier to remove safely due to good accessibility and thicker mucosa.

One explanation for the low availability of ESD in the West includes the steep learning curve associated with a highly advanced technique. Data from Saito et al's 2010 study demonstrated significantly reduced perforation rates with an increased number of ESDs performed (< 50 ESDs: 17.6% vs 50-99: 8.2% vs \geq 100: 5.1%, $p < 0.0001$)(74, 212). In addition, there are high complication rates compared to piecemeal EMR and potential lengthy procedure times of several hours which may reduce the feasibility and cost effectiveness of providing such a service (216). There is also evidence that the use of piecemeal EMR, which is widely available and less time consuming, has comparable efficacy with en-bloc resection techniques with benign NPCPs when allowing for repeat endotherapy (77, 217). A hybrid EMR/ESD procedure where circumferential incision around a lesion is followed by en-bloc snare resection has been increasingly described. The use of this technique appears to allow

en-bloc snare resection of larger lesions due to reduced issues with judging the submucosal plane prior to snare resection, with snare resection having been demonstrated to reduce procedure times compared with ESD (Saito et al, 2010: n= 373, ESD procedure time: 108 ± 71 min (15–360 min) vs EMR procedure time: 29 ± 25 min (3–120 min), p<0.0001) (73, 218). A porcine model reported in 2010 demonstrated that a hybrid technique using circumferential incision allowed en-bloc resection in 70% of lesions over 4cm in size with procedure times substantially shorter than for ESD as dissection beneath the lesion, the most time consuming part of the ESD procedure is not required (219). A 2012 Japanese study (n=269) compared ESD with hybrid ESD/EMR and EMR/pEMR. Hybrid ESD/EMR was undertaken in 27 cases with a perforation rate of 7.1% (as a result of submucosal dissection rather than snare use), a delayed bleeding rate of 0% and a recurrence rate of 0% reported. Whilst treatment efficacy was comparable, the median procedure time was 85 min (30–360) for ESD versus 57.5 min (9–150) for hybrid ESD/EMR (73). A similar technique called ‘Insulated-Tip Knife Endoscopic Mucosal Resection’ has previously been described in Italy. In a study of 29 patients where 55% of lesions over 3cm were removed en-bloc with a median procedure time of 59 min (41–130 min) (220). In view of the ability to achieve reasonable en-bloc resection rates with comparable efficacy to conventional ESD and shorter procedural times, in addition to the suggestion of a reduced learning curve, it has been suggested that the hybrid technique may be a preferable modality in the West, where reduced cost effectiveness due to long procedure times has limited uptake of ESD (209, 216).

1.8.2) Cap assisted EMR

Cap assisted EMR (EMR-C) is commonly used to remove areas of high grade dysplasia in Barrett’s Oesophagus as well as in upper gastrointestinal EMR. Its use has also been described with large colonic lesions using a principle known as the ‘suck and cut’ method (221). A single use plastic cap is attached to the tip of the endoscope with most systems using a band ligation device similar to that used to band oesophageal varices. As with conventional colonic EMR, a submucosal injection is made below a lesion to create a submucosal cushion. The raised lesion is then aspirated using suction into the affixed cap device with the subsequent deployment of a rubber band to trap the lesion. A snare is then used to resect the lesion below the band (222, 223). A 2010 Italian study examining the use of piecemeal EMR-C on NPCPs (n=255) reported 96% clearance after a median follow-up of approximately 12 months with no cases of perforation, intra-procedural bleeding in 7% of cases and no reports of post-procedural bleeding. EMR-C was suggested as an effective

technique at removing large colonic polyps in a piecemeal technique (224). A potential advantage over conventional snare polypectomy is that it is felt to improve accessibility for lesions that are entirely or partially in a difficult position (e.g. behind a mucosal fold) whilst flat lesions felt difficult to grasp with a snare can be trapped with aspiration (222). There are concerns about perforation associated with EMR-C due to the possibility of aspirating the muscularis propria into the suction cap, and use with rectal lesions where the mucosal tissue is thicker has been suggested for main application (224).

1.8.3) Underwater EMR

Whilst the use of a submucosal injection is widely described to reduce the risk of perforation, there have been reported concerns that creating a submucosal cushion may alter the resection plane and complicate endoscopic resection whilst there is also a theoretical risk of needle tracking neoplastic cells to deeper tissue layers. A novel 'underwater EMR' (UEMR) technique without the use of a submucosal injection has been described (225). The procedure commences with the evacuation of air and total immersion of the lumen with water during colonoscopy. Underwater immersion is intended to 'float' the mucosa and submucosa' away from the muscularis layer to reduce perforation risk. The lesion margins are marked using APC and snare polypectomy is then used (225-227).

In a 2012 study using UEMR with 62 LNCPs, residual tissue was found in only one case on follow-up after 4 months with no reports of perforation. Delayed bleeding incidence was comparable in series describing conventional pEMR with a rate of 4.8%. It should be noted however that this was a small single centre study and larger studies are likely to be required before uptake of this technique increases (225). It has also been suggested that that this technique may provide an important modality for the management of LNCP recurrence. A 2014 retrospective analysis (n=80) compared the outcomes of UEMR vs conventional EMR for the management of recurrent tissue following attempted EMR resection of LNCPs. En bloc resection (47.2% vs 15.9%, p=0.002) and complete resection (88.9% vs 31.8%, p<0.001) rates were higher in the UEMR group. In addition, APC ablation of visible residual tissue during salvage procedures was lower with UEMR (11.1% vs 65.9%, p<0.001), whilst further recurrence was also significantly lower (10% vs 39.4%, p=0.02) (226).

1.8.4) Surgical Therapy

Surgical therapy provides effective management where malignancy is suspected or concerns about the likelihood of incomplete endoscopic resection arise

Whilst expert endoscopic management is considered preferred first line management in benign lesions due to superior patient safety, surgical resection can be used to provide an effective therapy in certain circumstances with approximately 10% of large colonic adenomas managed surgically (10, 11). Surgery may be preferred therapy where:

- a lesion is felt to have features suggesting possible submucosal malignant invasion such as Kudo Pit Pattern type 5, depressive features or a failure to lift with submucosal injection in the absence of prior intervention
- there are technical issues regarding endoscopic access or achieving a stable endoscope position for removal
- the lack of availability of an endoscopist with expertise to safely remove a lesion endoscopically
- other features raise a concern about potential iatrogenic perforation or bleeding such as lesion size or right sided location

Although morbidity and mortality are likely to be higher for surgical resection than with endotherapy, the chances of complete resection are better and there is a markedly reduced need for endoscopic follow up (61). Morbidity and mortality rates for both open and laparoscopy surgery has been reported at approximately 20% and 1% respectively (11). Complications associated with surgical management include infection, an anastomotic leak, wound dehiscence, ileus, electrolyte imbalance and pain (228).

Surgical resection is also a secondary effective management option where recurrence cannot be managed endoscopically (5, 17, 21, 57). Even with the most advanced polypectomy techniques such as ESD, deeper submucosal invasion cannot be managed, with surgery often required when it is encountered at endoscopy. Surgery offers the highest chance of oncologically complete resection for these malignant lesions. A study of 1111 colorectal ESD procedures featuring both benign and malignant lesions reported an en-bloc resection rate of 88% with a curative rate of 89% (212, 215). Surgical resection is currently the only therapy where deep submucosal infiltration and lymph node infiltration may be

managed effectively. Reported curative rates for surgical resection are 100% for stage 1 disease with a rate above 91% for stage IIIa disease which indicates its efficacy (229). There is a considerable rate of malignancy found post-surgically in lesions previously thought to be benign though this varies considerably depending on patient selection and operator expertise. A study analysing histopathology post-surgical resection for 750 polyps felt to be benign found invasive malignancy in 17.7% of lesions (11). This supported the findings of an earlier smaller study (n=63) where evidence of invasive malignancy was found in 22% of polyps that were considered to be both endoscopically unresectable and benign (230). In view of this, where expert endoscopic resection is considered difficult or where there is diagnostic uncertainty, surgical resection appears to be an appropriate management option due to the ability to fully resect a lesion en-bloc in addition to sampling or removing adjacent lymph nodes providing an oncological resection (37, 38, 230).

In addition, in cases where endoscopic access is considered difficult with a concern about causing complications or achieving a successful resection, surgical therapy may provide a safer more effective option as a primary therapy rather than as an additional invasive procedure to provide secondary treatment (231). This may be instead of or combined with endotherapy with increasing reports of the use of laparoscopically assisted endoscopic polypectomy (LAEP) following complex polyp MDT discussion (232).

Laparoscopic therapy is preferred to open surgery in the surgical management of colorectal NPCPs

Laparoscopic surgery has largely replaced open surgical resection for the removal of NPCPs where endoscopic resection is deemed unsuitable (233). Initial concerns about laparoscopic surgery included the possibility of longer and more complex procedures than with open surgery and the retrieval of a shorter resection specimen, with suggestions that this may result in reduced oncological efficacy (234). A meta-analysis demonstrated comparable therapeutic efficacy to open surgery (OS), describing laparoscopic surgery (LS) with similar 3 year recurrence rates, including in the management of colorectal cancer whilst also being minimally invasive. (Tumour recurrence at 3 years for LS: 16% vs OS: 18%; 95% CI: 0.63 to 1.17; p=0.32). Laparoscopic surgery for malignancy is therefore considered oncologically safe (13, 235, 236). A retrospective UK analysis of surgical outcomes over 10 years (n=192,620, 3709 laparoscopic procedures) reported that laparoscopic surgery was associated with a

reduced 30 day (OR: 0.57; 95% CI: 0.44-0.74; $p < 0.001$) and 365 day mortality (OR: 0.53; 95% CI: 0.42-0.67; $p < 0.001$) after correction for age, gender, diagnosis, operation type, comorbidity, and social deprivation (237). Other studies have commented that the rate of mortality and post-operative complications appears similar between open and laparoscopic groups but have clearly demonstrated that laparoscopic surgery is associated with accelerated post-operative recovery with reduced pain, the earlier return of bowel function. This may also be important from a financial consideration with a shorter associated hospital stay. (Salimath et al, n=261; OS: 4.4 days (95% CI: 4.2–4.6) vs LS: 3.7 days (95% CI: 3.9–3.5); $p < 0.001$) and reduced hospital stay (Vlug et al, n=427; $p < 0.001$), (Salimath et al; OS: 8.01 days (95% CI: 7.1 to 8.9) vs 4.38 days (95% CI: 4.0 to 4.8); $p < 0.001$) (238, 239). It is also still associated with higher a level of co-morbidity than EMR (13, 61).

Patient factors may ensure that laparoscopic surgery is not always possible, necessitating open resection. Cited indications for open surgery include patient factors such as obesity and previous abdominal surgery with subsequent adhesions which may reduce laparoscopic efficacy due to reduced accessibility and manoeuvrability. In addition, complications during laparoscopic surgery may necessitate conversion to open surgery to allow for more rapid resolution (61, 237).

Laparoscopic surgery may be combined with endoscopic polypectomy to avoid bowel resection

Laparoscopic surgery may also be used in combination with endoscopic polypectomy. The use of laparoscopic assisted endoscopic polypectomy (LAEP) has been described for polyps where endoscopic removal was previously considered too difficult. Reported benefits include the potential to manipulate polyps into a more favourable position for resection whilst a visible perforation may be sutured immediately. In addition, the discovery of malignancy allows for laparoscopic surgical resection during the same procedure, reducing the need for a subsequent procedure (232, 240). The largest reported series currently comes from a 2009 US study (n=209) which reported that in all cases where LAEP was possible, complete eradication was found in all cases in all follow-up up to 5 years post procedure (240). Whilst there is a view that LAEP may reduce surgical bowel resection, its use internationally has only been described in small numbers (232).

Minimally invasive surgical techniques may be considered as a suitable primary therapy for rectal LNPCPs where en-bloc resection is desired due to a concern of malignancy

The surgical management of rectal lesions requires special consideration due to the complexity and morbidity associated with both open and laparoscopic resectional surgery in this area and the availability of endotherapy and minimally invasive local resectional surgery such as TEMS. A 1998 study reported (n=591) 3.2% mortality at 30 days with 30% post-operative morbidity with open proctectomy (241) whilst a 1999 study (n=681) cited a 0.6% peri-operative mortality and 22% post-operative morbidity (242). A 2010 laparoscopic low anterior resection series (n=132) reported similar morbidity (20.5%) (243). In addition, with low rectal lesions where non-sphincter saving surgery such as an abdominoperineal resection (APR) is often used, a permanent stoma will be required (244).

Transanal surgical techniques, have been developed for the management of anorectal lesions and It is associated with significantly lower morbidity and cost than major resectional rectal surgery and avoids the need for a permanent stoma (77).

TEMS (Trans-anal Endoscopic Micro-Surgery) is a surgical technique developed in the 1980s performed under general anaesthetic that allows removal of rectal lesions using submucosal dissection via a transanal approach (245). TEMS allows en-bloc removal of large lesions by either submucosal dissection or full thickness rectal wall excision and is performed with the patient in the lithotomy position. The procedure can last for up to three hours and can be performed as a day-stay procedure (246).

TEMS and variants of this technique can be used treat large rectal adenomas where en-bloc resection is preferred and ESD is not available, for example if there is a concern about malignancy. Where suspicion about malignancy exists and en-bloc resection is considered desirable to ensure adequate histological analysis, the use of either ESD or minimally invasive local resectional surgery such as TEMS is preferable to conventional resectional surgery, however ESD availability, as previously discussed, is still limited. A 2014 meta-analysis of 111 ESD and 10 TEMS series (n=2077) comparing LNPCP management outcomes found en bloc resection to be higher with TEMS (TEMS: 98.7 % (95 %CI: 97.4–99.3 %) vs ESD: 87.8 % (95 % CI: 84.3–90.6), (p<0.001) whilst the curative resection rate was also superior (TEMS: 88.5 % (95 % CI: 85.9–90.6 %) vs ESD: 74.6 % (95 %CI: 70.4–78.4 %), p<0.001). (247). A 2010 meta-analysis of TEMS also demonstrated a significantly reduced post-operative complication rate compared with resectional surgery (n=629, OR: 0.16 (95% CI: 0.06-0.38), p<0.003), whilst a 2012 study also demonstrated significantly reduced morbidity (n=78, 14.6 % (TEMS) vs. 37.1 % (resectional surgery), p=0.046) (60, 248).

The available evidence suggests that pEMR is preferable to TEMS for the management of rectal NPCPs where malignancy is not suspected and en-bloc resection is therefore not considered essential. A retrospective comparison between TEMS and piecemeal EMR for the management of large rectal NPCPs (n=292) found that whilst early recurrence rates were lower in TEMS (10.2% vs 31.0%, $p < 0.001$) when allowing for repeat endoscopic therapy on follow-up, late recurrence after 12 months was similar (9.6% vs 13.8%, $p = 0.386$). TEMS was also associated with greater morbidity (postoperative complications: 24% (TEMS) vs 13% (EMR), $p = 0.038$) and a longer hospital stay (median hospitalization post procedure: 3 days (TEMS) vs 0 days (EMR), $p < 0.001$) (77). Another consideration is evidence that pEMR appears more cost effective. International cost analysis suggests the cost of EMR is around \$2000, with subsequent follow-up roughly half this figure. In comparison, the cost of TEMS is estimated to be around \$7800 (10, 56, 249). However, TEMS may be indicated as first line treatment for selected benign rectal NPCPs such as mid or low rectal large flat 'carpet-like' lesions (usually villous adenomas) that occupy significant rectal circumference and are technically difficult to remove with snare retrieval due to its soft texture and the risk of significant bleeding (245, 246).

Further developments have continued to be made with regards to transanal surgery. A hybrid procedure called TAMIS (Trans-Anal Minimally Invasive Surgery) combining transanal surgery with single port laparoscopic access under GA was first described in 2010 (250). A single-incision laparoscopic surgery port is introduced into the anal canal with manual pressure with a patient in either a prone or lithotomy position. Air insufflation is then undertaken until pneumorectum is achieved. At this point, laparoscopic instruments such as graspers, thermal energy devices, and needle drives, are used to perform transanal excisions. 6 patients with rectal lesions (including 2 with malignancy) with a mean lesion size of 2.93cm underwent TAMIS with a mean procedure time of 86 minutes, shorter than with TEMS (average procedure time of 120-140 minutes (251)). An 100% cure rate was achieved with all patients discharged within 24 hours. Overall costs were reported as being substantially lower than with TEMS due to shorter procedure times and lower equipment costs. In addition, there were no cases of anal dysfunction, a feature that has been reported post TEMS (250, 251). A subsequent case series of 50 patients (25 benign neoplasms, 23 malignant lesions, and 2 neuroendocrine tumours) was described in 2013. Almost all cases were undertaken as a day-stay procedure. A mean procedure time of 74.9 minutes was achieved with no cases of anorectal dysfunction and no long term complications noted at 20

months. Positive resection margins were seen in 3% of cases necessitating AP resection. Recurrence at between 6-18 months was 4% (251). The reported benefits of TAMIS compared to TEMS in addition to shorter procedure times include increased rectal visibility, quicker equipment setup and the ability to use existing laparoscopic equipment. In view of established efficacy, reduced costs, shorter procedure times, and improved visibility, TAMIS has been proposed as a safe and effective advanced transanal option for the removal of both benign large rectal adenomas and selected early stage rectal cancers (251, 252).

1.9) Histological and Radiological Considerations

1.9.1) Histopathology

Whilst important, histopathological assessment appears to have a less significant role in the management of benign polyps than with malignancy, in which the pathological assessment, including depth of invasion (by Haggitt level, Kikuchi level, and quantitative measures), differentiation, lymphovascular invasion, tumour budding etc. are all important in consideration of subsequent management. The major histopathological considerations regarding LNPCPs as described below:

- Judicious use of targeted biopsies: Recommended only when there is suspicion of malignancy in a LNPCP, to help ensure endotherapy is not compromised.
- Awareness of significant potential for under calling of malignancy in the endoscopic biopsy setting.
- In polypectomy evaluation, confirmation of the adenomatous nature of the polyp and confirmation of benignity i.e. exclusion of adenocarcinoma arising within the adenoma
- Emphasising the distinction between invasive neoplasia and so-called 'epithelial misplacement'.
- Assessment of adenoma subtype according to WHO 2010 classification as tubular, tubulovillous, villous or traditional serrated.
- Assessment of grade of dysplasia/neoplasia using a two tier system.
- Assessment of margin involvement by dysplasia, where possible, in accordance with the nature of the specimen received (en-bloc or piecemeal) and endoscopic correlation regarding completeness of excision

Figure 12. Major Histopathological Considerations in the Management of LNPCPs (253).

1.9.2) Radiological Investigations

Radiological input may be warranted in certain cases, such as where there is difficulty in determining whether a lesion is benign or malignant. Whilst CT and MRI imaging may provide information regarding local lesion invasion for colonic and rectal lesions respectively where malignancy is suspected, there is an absence of evidence to suggest that radiological investigation commonly affects LNPCP management. It appears that radiological input may therefore not be uniformly essential in LNPCP assessment but considered on a case by case basis.

Chapter 2: Consensus Methodology

2.1) Consensus Methodology: An Introduction and Background

Consensus methodology is a process where a group of individuals with relevant expertise are asked to record the extent to which they agree with a statement and secondly the extent to which participants agree with each other (254). The use of consensus methodology in providing healthcare frameworks and solutions is now commonplace, with the field of gastroenterology an important example. It is seen as a more robust than the previous approach of guidelines formulation involving by one or a few individuals as it allows for the learned opinion from a variety of experts involved in the management of a specific condition (254, 255). A review of various consensus based approach exercises in healthcare suggests inter-participant agreement of at least 80% is considered to be of sufficient robustness. Areas considered ideal for consensus methodology use have been described as those where there is a lack of a structured framework, a limited evidence base and conflicting evidence about best practice (254). The three main consensus approaches are described below.

2.1.1) Delphi technique

Delphi Technique is a group communication exercise designed in the USA in the 1950s by the RAND Corporation as a tool in program planning, needs assessment, policy determination, and resource utilization. It uses participants to achieve a consensus opinion on a topic using a multi-stage process with a convergence of opinions (256). Subjects used are commonly considered experts in relevant fields to provide learned, holistic and robust opinion. The process usually begins with a comprehensive literature review by a steering group with the results commonly used to define statements or questions used in a first voting round. Prior to beginning the process, a minimum figure should be set that signifies an acceptable consensus level for each statement used (e.g. 80%). The voting process may have been undertaken using mail and email contact as well as the use of voting keypads and a summary of the process is shown below (256).

Development of statements

Relevant statements may be formulated via a literature review, via a questionnaire of a participant group or input from a steering committee, some of whom maybe part of the subsequent consensus process.

Round 1:

This round can be used to revise and streamline the statements delivered for consideration by the Delphi group prior to further iterations.

Round 2:

The statements collated from the first round are evaluated by participants who are asked to grade their level of agreement with each statement. Participants are often asked to provide supporting statements for their answers

Round 3:

Prior to the next round the answers are collated with variation in responses recorded. Participants who give answers that vary widely from the bulk of the responses may be asked for justification for their decisions. The process continues with the results of the previous round available to the participants who are able to reconsider their initial responses. The results are collated with the intention of achieving a convergence of opinion. Further rounds may be added where required to achieve consensus as appropriate. Following the completion of the process, the strength of evidence and strength of recommendation for a particular statement may be reported (257).

Strengths and weaknesses of process

A strength of the Delphi consensus process is the format of anonymised voting which allows group members to vote without a fear of being influenced by more domineering members of the group, whilst they are also able to change their vote without fear of judgement (256, 258). In addition, it is considered to be a robust consensus technique with regards to the utilisation of evidence based medicine. The dissemination of a comprehensive literature review and relevant references, in addition to a substantial time allowance for a participant

to review and potentially add to the evidence base, increases the likelihood of informed, evidence based decisions. The reliability of decisions made appears to increase with a larger group size and participants with outlying views have less of an influence on final results (255). An advantage of non face-to-face discussion between experts is that it is less costly and easier to organise than a group meeting. However, this aspect of the process has been criticised, as this interaction can enhance complex decision-making processes by allowing the clarification of terminology and points made. In view of this, a modified Delphi technique is often used that combines the standard voting process with face-to-face interactions.

2.1.2) Nominal Group Technique

This is a structured meeting process using a panel of experts to obtain relevant information. Each member of the panel is asked to develop ideas and solutions for a specific problem prior to meeting. At the group meeting, each member presents their ideas in turn with statements (such as recommendations) recorded for evaluation. Participants are then asked to anonymously rate, evaluate and re-evaluate the recorded statements until consensus is reached. An advantage of this process is that it allows both anonymised voting and group interaction. However it may be both difficult and costly to arrange a group meeting, especially with a national or international process. Another criticism of the nominal group technique is that it does not allow for the integration of evidence based medicine into the decision making process, making it a less robust process. As previously highlighted, a modified Delphi process (a modified Delphi technique), combining the face to face interaction of this technique with rigorous evidence supported voting rounds is often preferred (254, 259).

2.1.3) National Institutes of Health (NIH) Conference Approach

This approach has been compared to the deliberation of a jury in a courtroom style process. A selected group of expert individuals present evidence and data to a separate panel with general methodological expertise but not considered experts in the field being discussed. The decisions making panel evaluate the evidence presented and may ask questions when appropriate. They then deliberate over the evidence in a private setting with the leadership of a chairperson to reach a decision. Unlike a jury, the views presented by a minority are also captured and reported. This approach has been long established and the lack of experts in

the decision making panel is advantageous in potentially reducing bias and conflict of interest. A disadvantage with an approach of having no experts within the decision making panel is that there is the possibility for misinterpretation of data and the significance of evidence presented may be inappropriately estimated. An additional criticism of this methodology is that the lack of anonymised decision making may result in some group members being overpowered by more dominant members of the group whilst it has also been felt to allow insufficient time to both deliver and deliberate over information (259).

2.2) The use of consensus methodology in endoscopic research

The Delphi process has recently been utilised in endoscopic research with success. This process was by the Canadian Association of Gastroenterology in 2012 to achieve consensus guidelines for quality and safety indicators in endoscopy (257). More recently, Delphi methodology was used to formulate a system of assessing the difficulty of colonic polyps based on specific features. The site, morphology, size and endoscopic access (SMSA) of a colonic polyp were used as parameters with 4 levels of difficulty to achieve complete successful removal (see tables 4 & 5) (6). The SMSA system has subsequently been demonstrated as accurate in predicting the likelihood of complete lesion removal in a 2013 study (56). This is an example of qualitative research in an area with conflicting option and low evidence base allowing a framework to create accurate quantitative data.

2.2.1) The Use of Consensus Methodology for the Management of Large Colorectal Polyps

The use of consensus methodology seems to be appropriate in work aimed at improving the management of large colonic polyps. This topic appears to fulfil criteria described by Jones (1995) by being a subject where there is a lack of a structured framework, a limited evidence base and conflicting evidence about best practice (see table 6)(254). It can be argued that the benefit of using an expert panel to achieve consensus in the management of large colonic polyps includes the involvement of specialists with high volume practice that are abreast of the evidence available and have already contributed significantly to the available evidence base.

Area with conflicting evidence	Evidence for	Evidence against
Adrenaline should be added to injection solution to reduce risk of bleeding	Hsieh et al (2001) Dobrowski et al (2004) Shirai et al (1994)	Lee et al (2007)
Clipping for prophylaxis of bleeding following polypectomy	Liaquat et al (2013)	Shijoi et al (2003)
Use of APC on resection margins	Brooker et al (2002)	Moss et al (2011) Mannath et al (2011)

Table 6. Areas of LNPCP management with conflicting evidence base

Practices in advanced endoscopic lesion removal commonly cited and recommended as good practice but for which a paucity of evidence exists include:

- Gelofusin/Hyaluronic Acid should be used for lesions over 3cm
- The snare should be marked prior to use
- Blended current should be used for diathermy
- Pigmented solution such as methylene blue or indigocarmine should be used in lifting solutions to help to demarcate lesions and its resection margins
- The continuation of aspirin prior to advanced polypectomy

2.3) Aims and Methods

The purpose of developing guidelines and key performance indicators was to provide an evidence based resource and expert opinion on the optimal assessment and management of large non-pedunculated colorectal polyps (LNPCPs) for clinicians involved in their care. These include gastroenterologists, nurse practitioners, physicians, colorectal surgeons, radiologists and pathologists. These lesions are important as they carry an increased risk of colorectal cancer, yet are the most challenging lesions to resect endoscopically and carry an increased risk of incomplete excision and complications. In the absence of an existing

framework and an unknown UK incidence of LNPCPs, key questions we sought to cover included:

1. What are key definitions and terms associated with LNPCPs?
2. What are key principles for optimal management, including both assessment and therapy?
3. What are the available management options?
4. What information should patients be given about their management?
5. When is surgical or conservative management more appropriate than endoscopic therapy?
6. Which are the most complex lesions and how should they be managed?
7. What histopathological considerations are important in the management of LNPCPs?
8. Can multidisciplinary input into assessment and therapy optimise management and what information is required to achieve this?
9. How should anticoagulant and antiplatelet medications be managed pre and post procedure?
10. How should patients be followed up following endoscopic removal of LNPCPs?
11. What are the most appropriate key performance indicators for monitoring the quality of management of LNPCPs?
12. What can be done to improve formal training in the management of LNPCPs?
13. What aspects of LNPCP management have the weakest evidence base and what are the key research questions which will help address these?

The British Society of Gastroenterology (BSG) Endoscopy committee was approached for permission to lead a BSG sanctioned process towards developing an evidence based framework for the management of LNPCPs with the use of a working group. The use of a BSG sanctioned process was felt to be the most appropriate as the lead clinician for this project (Professor Rutter) had previously been approached to chair a BSG working party for large polyp management. The proposal was subsequently approved by the BSG along with logistical support for the process. This included use of the BSG offices and the covering of travel expenses for members of a BSG working group for any face to face meetings.

BSG guidance on guideline development was used. This included details about the use of a 'guideline development group' (GDG) with multidisciplinary key stakeholders involved in

LNPCP management including a patient representative. A 'writing committee' subgroup was also recommended. A guideline development group (GDG) including gastroenterologists, endoscopists, colorectal surgeons, gastrointestinal pathologists and a patient representative was selected in accordance with BSG/NICE criteria to ensure wide ranging expertise across all relevant disciplines. In addition to a patient representative, other members proposed included both 'expert' endoscopists and endoscopists who undertake advanced polypectomy but may refer on lesions to expert centres (referring endoscopist), colorectal surgeons who undertake both endoscopic and surgical polyp removal and a histopathology representative. This composition was approved by the BSG endoscopy committee who proposed several endoscopic representatives who had both national and international recognition in this field. Professor Rutter was appointed GDG chairperson whilst I served as the GDG coordinator and lead author for document creation in a non-voting capacity. The chairs of the ACPBI and the Royal College of Pathologists were then approached to nominate at least 2 surgical and histopathological representatives whilst the BSG research committee nominated a patient representative. Nominated persons were subsequently contacted via email to ascertain availability and interest to participate as a GDG member and a writing committee subgroup member. Acceptance was indicated by email with their consent to participate confirmed with the return of a signed conflict of interest form. A GDG of 14 people including Professor Rutter and myself was finalised.

The GDG consisted of:

- 8 Expert endoscopists,
- 1 Non-expert endoscopist,
- 2 Colorectal surgeons,
- 1 Gastrointestinal Histopathologist,
- 1 Patient representative
- 1 Coordinator (myself, non-voting)

2.3.1) Consensus Methodology Use

A modified Delphi process combining elements of both the Delphi technique and the nominal group technique was agreed upon as the most robust way of undertaking consensus methodology, combining the strengths of allowing participants the opportunity to vote anonymously without the potential of being intimidated by another group member

whilst also allowing for focussed group discussion where appropriate such as with training models and potential research questions, and to allow face to face clarification of points made where appropriate to allow for participants to be better informed prior to voting. A four stage process was undertaken.

1: Literature review and writing of draft document with recommendation statements and reference database:

2: Preliminary voting round where participants were asked to vote for level of agreement and make comments on the appropriateness of statements, in addition to proposing additional or modified statements along with additional references. This round was conducted to ensure as robust a voting document as possible.

3: Voting Round 1: A finalised list of recommendation statements/parameters to vote on following feedback from GDG. The GDG were also able to review their own position on retained statements with voting scores and comments from other members whilst they were also allowed to comment on deletions/modifications made to statements from the pilot round

4: Voting Round 2: Undertaken at round table meeting using electronic keypad voting for parameters where consensus had not been reached. Voting also for proposed amendments to statement and the creation of quantitative targets and minimum standards. The meeting was also used to allow focus group discussions to create recommendation documents for training programmes and research questions.

A writing sub-committee, led by myself as lead author, was formed to identify key search terms for a comprehensive literature review about the management of NPCPs from which several recommendation statements relating to multidisciplinary management were made. Studies were classified based on their methodology including systematic reviews, meta-analyses, randomised controlled trials (RCTs), cohort studies, diagnostic studies and observational studies.

The 'Scottish Intercollegiate Guidelines Network (SIGN) Methodology Checklist System', a BSG approved critical appraisal tool for the assessment of research articles, was used to evaluate the rigidity and quality of studies reviewed with studies considered to be of suboptimal quality excluded unless they were appropriate to a specific issue (260).

A literature search for English language articles published up to the present was performed using PubMed. The term 'colonic polypectomy' was entered into the PubMed MeSH database. 5989 articles were returned. The terms 'therapy' and 'surgery' were used to filter the results based on relevance following which, 2230 articles were returned and scrutinised for relevant articles. Additional PubMed searches were performed using additional search terms agreed by the writing sub-committee. The search terms used were:

'colorectal laterally spreading type polyps', 'endoscopic mucosal resection', 'complex colonic polyps', 'difficult colonic polyps', 'surgical management of colorectal laterally spreading type polyps', 'endoscopic polypectomy', 'anticoagulation in endoscopic polypectomy', 'obtaining informed consent for endoscopic procedures', 'diathermy in polypectomy', 'argon plasma coagulation for polypectomy', 'submucosal injection for endoscopic mucosal resection', 'malignant colonic polyps', 'piecemeal endoscopic mucosal resection', 'colorectal endoscopic submucosal dissection', 'surgical management of colonic polyps', 'laparoscopic surgery of colonic polyps', 'training in endoscopic polypectomy', 'transanal endoscopic microsurgery', 'key performance indicators in healthcare' and 'healthcare improvement measures'

Returned abstracts and articles were reviewed for relevance with additional references obtained from cross-referencing of references and recommendations from the GDG. Relevant published guidelines from groups such as the British Society of Gastroenterology (BSG), the American Society of Gastrointestinal Endoscopy (ASGE), The NHS Bowel Cancer Screening Programme (NHS BCSP) and the European Society of Gastrointestinal Endoscopy (ESGE) were also scrutinised.

Following a comprehensive review of relevant literature, recommendation statements and parameters were formed by the writing subcommittee in relation to three sections as below:

1. Guideline development
2. Key Performance Indicators
3. A minimum datasheet to guide complex polyp discussion and management with the intention of use in a complex polyp multidisciplinary meeting.

Further information for each of the three sections is described in more detail in the relevant chapters. A preliminary round including formulated recommendation statements was undertaken by the GDG to assess the suitability of the statements, to allow for modification in subsequent voting rounds and increase the evidence base used with recommendation of additional references for guideline and KPI development. The writing subcommittee considered the creation of a complex polyp minimum dataset to be a less complex process than for the other two sections with no preliminary voting round required prior to formal voting. For each section each statement/parameter was scored by each member of the GDG using a five point scale in a primary voting round. Following the preliminary round, modifications, additional statements and deletion of statements were made to the additional list of statements/parameters based on GDG comments and suggestions.

The modified document was then sent to the GDG and a first formal voting round was then undertaken. All modifications and deletions made from the preliminary document with supporting comments were included for GDG review to provide a further opportunity for members to record comments about modifications such as if they disagreed with a modification or deletion.

In voting on statements and parameters, at least 80% participant agreement was required to consider consensus reached. Further discussions and a final round of voting for statements where consensus had not been reached took place at a round table meeting at the BSG offices on 26th March 2014. Voting was anonymous throughout with the final round of voting made using an electronic keypad system. Feedback from the GDG members was disseminated after each round to allow members to reconsider their original position. Proposed modifications to statements were evaluated with anonymous voting with $\geq 80\%$ agreement required for modifications to be made. A secondary voting process was also in place for voting for parameters with ongoing conflict of opinion (under 80% agreement) where reaching consensus, either positive or negative, was considered essential by the GDG. For consensus to be considered reached in this scenario, over 50% agreement with less than 20% disagreement was required. The GRADE tool was used to evaluate the strength of evidence and the strength of recommendations made (see table 7).

GRADE – Strength of evidence	GRADE- Strength of recommendation
<p>High quality: Further research is very unlikely to change our confidence in the estimate of effect</p>	<p>The trade-offs: Taking into account the estimated size of the effect for main outcomes, the confidence limits around those estimates, and the relative value placed on each outcome</p>
<p>Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate</p>	<p>The quality of the evidence</p>
<p>Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate</p>	<p>Translation of the evidence into practice in a particular setting: Taking into consideration important factors that could be expected to modify the size of expected effects</p>
<p>Very low quality: Any estimate of effect is very uncertain</p>	<p>Uncertainty about the baseline risk for the population of interest</p>

Table 7. An overview of the GRADE system (261)

The GRADE system allows evaluation of evidence to make recommendations in two forms, based on the **strength of evidence** and the **strength of a recommendation** following consensus by an expert panel. Whilst the strength of recommendation may often reflect the evidence base, the GRADE system allows for occasions where this is not the case, for example where there appears good sense to make a recommendation in spite of an absence of high quality scientific evidence such as a large randomised controlled trial.

Following Voting Round 2, the results were collated and sent to the GDG to ensure accuracy and a draft document featuring guidelines, KPIs, a training template and research questions was then created and sent to the GDG for evaluation and further input. Following suggested amendments the GDG re-reviewed the document and when all members were satisfied, it was sent to the BSG Endoscopy Committee and the ACPBI committee for further feedback. Once this feedback was received, the document was modified accordingly in conjunction with the GDG, and formally submitted to the BSG for international review and ratification.

Chapter 3: British Society of Gastroenterology/Association of Coloproctology of Great Britain and Ireland Large Non- Pedunculated Colorectal Polyps Guideline Development

3.1) Introduction

The use of consensus methodology both nationally and internationally in the formation of several gastroenterological guidelines is a reflection of its strength for this purpose. A recent UK example of where consensus methodology has been used in guideline development is the 2013 BSG Guidelines for the management of Barrett's Oesophagus whilst an international example is the 2013 Canadian Association of Gastroenterology guidelines for endoscopic practice (257, 262). Both guidelines were formulated using a 'modified Delphi technique' with methodology similar to that proposed for the creation of these guidelines. As previously discussed, the development of a framework for the management of LNPCPs appears suitable for the consensus as it appeared to fulfil criteria as a field where there is a lack of agreed current practice, in part due to a lack of objective scientific evidence in some areas and conflicting opinion about best practice in others (see table in consensus chapter) (254).

3.2) Methodology

A guideline development group with a writing subcommittee was created as described in chapter 2. As detailed in chapter 2, the writing subcommittee suggested various search terms for a comprehensive literature review as below. The term 'colonic polypectomy' was entered into the PubMed MeSH database. 5989 articles were returned. The terms 'therapy' and surgery' were used to filter the results based on relevance following which, 2230 articles were returned and scrutinised for relevant articles. Additional PubMed searches were performed using additional search terms agreed by the writing sub-committee. The search terms used were:

'colorectal laterally spreading type polyps', 'endoscopic mucosal resection', 'complex colonic polyps', 'difficult colonic polyps', 'surgical management of colorectal laterally spreading type polyps', 'endoscopic polypectomy', 'anticoagulation in endoscopic polypectomy', 'obtaining informed consent for endoscopic procedures', 'diathermy in

polypectomy’, ‘argon plasma coagulation for polypectomy’, ‘submucosal injection for endoscopic mucosal resection’, ‘malignant colonic polyps’, ‘piecemeal endoscopic mucosal resection’, ‘colorectal endoscopic submucosal dissection’, ‘surgical management of colonic polyps’, ‘laparoscopic surgery of colonic polyps’, ‘training in endoscopic polypectomy’, ‘transanal endoscopic microsurgery’

Returned abstracts and articles were reviewed for relevance with additional references obtained from cross-referencing of references and recommendations from the GDG. Relevant published guidelines from groups such as the British Society of Gastroenterology (BSG), the American Society of Gastrointestinal Endoscopy (ASGE), The NHS Bowel Cancer Screening Programme (NHS BCSP) and the European Society of Gastrointestinal Endoscopy (ESGE) were also scrutinised.

The ‘SIGN Methodology Checklist System’ was used to evaluate the rigidity and quality of studies reviewed with studies considered to be of suboptimal quality excluded unless they were appropriate to a specific issue(260).

The Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument provided a methodological framework for the development of the guidelines and was used to assess their quality.

Following a literature review, the writing committee selected various domains, subdomains and subsequent areas within these domains from which statements may be formulated. Domains included: governance issues, endoscopic considerations (pre, peri and post-procedure), anticoagulation management, surgical management and histological and radiological considerations.

Following the identification of potential domains and subdivisions, numerous statements with supporting evidence were created and subsequently discussed and finalised by the writing subcommittee via audioteleconference for review by the GDG (see results section). In the absence of evidence to support a specified training regimen for complex polyp management, members of the GDG were to be asked for their ideas and views on developing a training plan prior to a discussion forum at a later date.

As discussed in detail in chapter 3, the statements created by the writing subcommittee were sent in an emailed document to the GDG who were asked to vote to record their level of agreement with the proposed statements, in addition to recording comments, proposed

amendments or additional statements and additional evidence that could be used. All voting throughout the process was conducted anonymously.

The GDG responses were then reviewed by the writing subcommittee with modifications proposed by the GDG incorporated where relevant to create a finalised document for voting. This document also contained anonymised GDG comments for consideration by members prior to voting. Modifications included the removal of statements felt to be duplicated elsewhere or not suitable for inclusion, in addition to additional wording to statements. The changes made were highlighted to allow for GDG member comments about changes made.

A first round of anonymous voting using a scale of 1-5 as previously described was conducted with $\geq 80\%$ agreement required for consensus to be considered achieved for each statement. On receipt of all GDG responses, a full summary of results including anonymised member comments was sent to the group.

Statements where consensus had not yet been reached were put forward for a second round of voting with GDG comments from the previous round intended to allow GDG members to reconsider their initial responses based on the comments from other members.

A second round of voting took place using electronic keypad voting at a round table meeting held at the BSG headquarters. Once this process had been completed, the GDG used electronic keypads to vote on any proposed modifications to the wording of the statements whilst research questions, primarily concerning areas in which evidence regarding best practice was felt to be absent or limited, were also formulated.

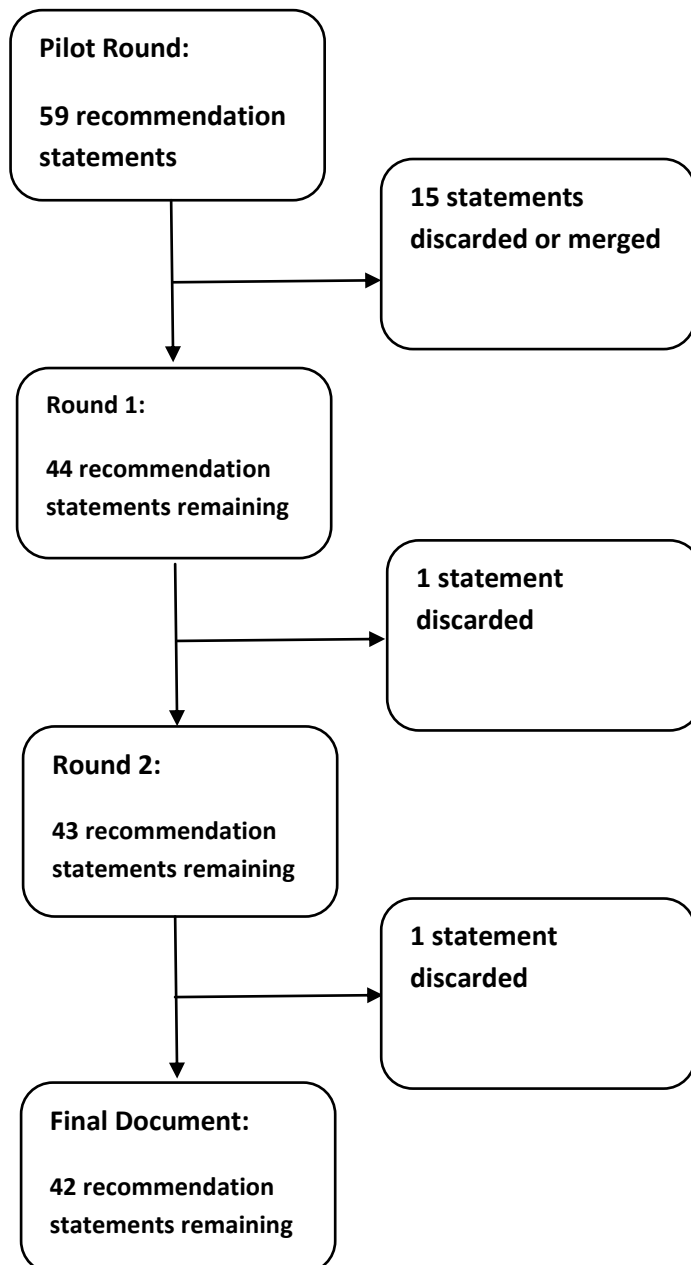
A structured group discussion also took place during the round table meeting to discuss a format for the development of a training programme for the endoscopic management of large colorectal polyps. The framework for the discussion was based on GDG comments from the preliminary voting round with the discussion recorded to be transcribed into a summary document.

Following the conclusion of the voting process, a draft guidelines document including recommendation statements pertaining to best practice, a framework for training and research questions was created and sent to the GDG for comments. The responses were reviewed by the writing subcommittee and modifications were made where appropriate. The amended document was sent back to the GDG for final comments and was then sent to the BSG endoscopy committee and the ACPBI for consultation. Alterations proposed by

these groups were made and the document was then sent back to the BSG and ACPGI for final approval. Subsequent to this the document was submitted to 'Gut' journal.

3.3) Results

A Summary of statements used/discarded at each round (Figure 13)



3.3.1 Summary of Key Recommendations

- **Definitions**

- We suggest that the term 'Non-pedunculated colorectal polyp' (NPCP) is the most appropriate term to define sessile and flat colonic lesions whilst Paris classification and the term 'laterally spreading type polyp' (LST) may be used to sub-classify lesions further.
- We suggest that the term 'Large NPCP' (LNPCP) may be used to describe NPCPs ≥ 2 cm in size
- We recommend that lesions displaying the following characteristics are identified as those with an increased risk of malignancy: Lesions exhibiting; pit pattern type V, Paris 0-IIc or 0-IIa+IIc morphology, non-granular LST (laterally spreading type polyp, LST-NG), granular LSTs (LST-G) with a dominant nodule, distorted surface pattern, colour and vessels (NICE NBI type III), thick and irregular microvessels (Sano capillary pattern type III) (GRADE of evidence: Moderate; Strength of recommendation: Strong)
- We recommend that the following lesions with the following characteristics are identified as having with an increased risk of incomplete excision/recurrence: Size ≥ 40 mm, location involving ileocaecal valve, appendix, diverticulum or dentate line; within an inflamed segment of colitis; prior failed attempt at resection or recurrence at site of previous resection (excluding unifocal, diminutive and easily resected/ablated residual adenoma on first site check); non-lifting sign after submucosal injection; endoscopist concern about difficult location (e.g. behind flexure or fold, in stenotic diverticular disease); (GRADE of evidence: Low; Strength of recommendation: Strong)
- We recommend that endoscopic factors associated with an increased risk of adverse events include: Caecal location, size ≥ 40 mm and endoscopist inexperience (GRADE of evidence: Low; Strength of recommendation: Strong)
- Complex NPCP- We suggest this term to describe NPCPs with any of the following features: (a) increased risk of malignancy; (b) increased risk of incomplete resection/recurrence; (c) increased risk of adverse event; (d) SMSA level 4 (GRADE of evidence: Low; Strength of recommendation: Weak)

- **Service provision and management principles**

- We recommend that hospitals that detect or manage LNPCPs should develop a referral pathway to facilitate their management and processes to monitor the quality of the service. The pathway should ensure that patients have access to and information about a full range of therapeutic options, including laparoscopic surgery, a provision for the management of complex rectal lesions and endoscopists capable of performing endotherapy on complex NPCPs (GRADE of evidence: Very low; Strength of recommendation: Strong)
- We suggest that clinicians involved in the management of LNPCPs should have access to a multidisciplinary network such as a multidisciplinary meeting (MDM) to discuss complex cases (complex as defined in these guidelines). Membership should include at

least one complex NPCP endoscopist, at least one colorectal laparoscopic surgeon and a gastrointestinal histopathologist. (GRADE of evidence: Very low; Strength of recommendation: Weak)

- We recommend that all endoscopists performing endotherapy on LNPCPs should be highly experienced in standard polypectomy, should have endoscopy service approval for this work, and should be subject to regular audit to ensure their key performance indicators are above minimum quality standards (GRADE of evidence: Low; Strength of recommendation: Strong)
- We suggest that patients with benign NPCPs should not undergo surgery without prior complex polyp MDM discussion (GRADE of evidence: Very low; Strength of recommendation: Weak)
- We suggest that primary therapeutic management of LNPCPs should be undertaken within 8 weeks of receipt of referral (GRADE of evidence: Very low; Strength of recommendation: Weak)
- We recommend that endoscopic resection should be first line therapy for the removal of LNPCPs where there is no suspicion of malignancy (suspicion of malignancy as defined in these guidelines) (GRADE of evidence: Moderate; Strength of recommendation: Strong)
- We recommend that piecemeal resection (either endoscopic or surgical) should be avoided if malignancy is suspected (GRADE of evidence: Low; Strength of recommendation: Strong)
- We suggest that in the context of significant comorbidity, conservative management may sometimes be appropriate following detailed patient discussion and documentation (GRADE of evidence: Very low; Strength of recommendation: Weak)
- **Lesion Assessment**
 - We recommend that all LNPCPs should be photographed or videoed prior to removal (GRADE of evidence: Very low; Strength of recommendation: Strong)
 - We suggest that a size estimate of LNPCPs should be made, ideally by measuring against an open snare (GRADE of evidence: Low; Strength of recommendation: Weak)
 - We recommend that the Paris Classification should be used wherever possible to describe polyp morphology (GRADE of evidence: Low; Strength of recommendation: Strong)
 - We recommend that the surface characteristics of a polyp should be described using a classification system such as the NICE NBI or Kudo Pit Pattern classification. The use of image enhancement techniques (digital or chromoendoscopic) can improve diagnostic accuracy in lesion assessment (GRADE of evidence: Moderate; Strength of recommendation: Strong)
 - We suggest that if a lesion may be amenable to endoscopic removal, biopsies should be used with caution, as there is a risk of submucosal tethering due to scarring, rendering

the lesion unresectable. Where biopsies are required because of concern of cancer, they should be targeted to the area exhibiting features indicative of cancer, avoiding flat areas and the lesion periphery. Tunnelling biopsies (biopsy through biopsy) should not be used (GRADE of evidence: Low; Strength of recommendation: Weak)

- **Endoscopic Management: Pre-Procedure**

- We recommend that adequate planning should be undertaken (including length of time booked for procedure, endoscopist and nursing staff skills and endoscopic equipment) so that prior to an attempt at advanced polypectomy, the endoscopist has a high level of confidence that complete resection can be achieved in a single procedure (GRADE of evidence: Very low; Strength of recommendation: Strong)
- We recommend that antiplatelet medications such as clopidogrel and prasugrel, and newer antiplatelet agents such as ticagrelor should be stopped at least 7 days prior to resection in accordance with BSG Antiplatelet Guidelines (GRADE of evidence: Moderate; Strength of recommendation: Strong)
- We recommend that warfarin should be stopped at least 5 days prior to resection of LNPCPs, and INR should be confirmed as below 1.5 prior to the procedure, in accordance with BSG Anticoagulation Guidelines. (GRADE of evidence: Moderate; Strength of recommendation: Strong)
We suggest that general recommendations regarding the management of newer anticoagulants which have differing properties, such as rivaroxaban and dabigatran, cannot currently be made due to a lack of evidence. Appropriate specialist advice should be sought in this scenario (GRADE of evidence: Very low; Strength of recommendation: Weak)
- We suggest that patients should be consented for the risk of thromboembolic events such as stroke and venous thromboembolism when stopping anticoagulants before endoscopic resection (GRADE of evidence: Very low; Strength of recommendation: Strong).
Advice given should be tailored to a patient's individual risk with a 'bridging regimen' of low molecular weight heparin given to high risk individuals in accordance with BSG guidelines. The risk of bleeding versus risk of thromboembolic episode should also be explained (GRADE of evidence: Low; Strength of recommendation: Weak)
- We suggest that where cessation of anticoagulants or antiplatelet medications is contraindicated due to comorbidity, or where there is uncertainty, appropriate specialist advice should be sought. If the anticoagulation/antiplatelet medication is temporary and the lesion has been adequately assessed as being of low risk for cancer, deferral of resection until after this medication can be discontinued may be appropriate (Grade of evidence: Very low; Strength of recommendation: Weak)
- We suggest that evidence for the cessation/continuation of low dose aspirin in the context of LNPCPs is weak and the decision should be individualised according to patient risk (GRADE of evidence: Low; Strength of recommendation: Weak)

- We recommend that when obtaining consent for the endoscopic resection of LNPCPs, written information in plain English should be given. Management options including endoscopic therapy, surgery and conservative management should be discussed. Regarding endoscopic therapy, patients should be informed of the potential need for subsequent check procedures and surveillance endoscopy. The risks of post-procedure bleeding (both immediate and delayed), perforation and residual polyp/recurrence should be explained (GRADE of evidence: Very low; Strength of recommendation: Strong)

- **Endoscopic Management: Peri-Procedure**

- We recommend that carbon dioxide should be used in preference to air insufflation during colonoscopy to improve patient comfort and safety (GRADE of evidence: High; Strength of recommendation: Strong)

- We recommend that the use of contrast agents such as indigo carmine or methylene blue in the submucosal injection solution may be considered to help demarcate a lesion, its resection margins, and to outline a clear submucosal plane (GRADE of evidence: Low; Strength of recommendation: Strong)

- We suggest that the addition of low concentration adrenaline to the submucosal injection solution may be considered to keep the resection field clear during endoscopic resection (GRADE of evidence: Low; Strength of recommendation: Weak)

- We suggest consideration of the use of colloidal type submucosal injection solutions in preference to normal saline lifting solution for LNPCPs (Grade of evidence: Low; Strength of recommendation: Weak)

- We suggest that endoscopists should be familiar with the range of snares available, although a single optimal snare cannot currently be recommended (GRADE of evidence: Very low; Strength of recommendation: Weak)

- We suggest that pure cutting or prolonged pure coagulation current should be avoided due to an increased risk of post polypectomy bleeding and thermal tissue injury respectively (GRADE of evidence: Low; Strength of recommendation: Weak)

- We suggest that whilst en-bloc endoscopic snare resection of lesions \leq 20mm is recommended to reduce the risk of recurrence and to enable more accurate histopathological interpretation, this practice should be used with caution in LNPCPs due to an increased risk of diathermy associated thermal injury and perforation (GRADE of evidence: Low; Strength of recommendation: Weak)

- We recommend that treatment naïve lesions that fail to lift after adequate submucosal injection should not be subject to attempted resection with conventional snare polypectomy technique (GRADE of evidence: Low; Strength of recommendation: Strong)

- We recommend that during endoscopic piecemeal resection, the snare should be used to resect a lesion completely wherever possible. Thermal coagulation techniques such as argon plasma coagulation (APC) and soft coagulation may be used as adjuncts when

snare resection of small residual fragments of polyp is not possible (GRADE of evidence: Low; Strength of recommendation: Strong)

- We recommend that careful post-procedure inspection of the resection site and photographic documentation of completeness of resection should be performed (GRADE of evidence: Low; Strength of recommendation: Strong)
- We recommend that with the exception of the rectum or caecum, a tattoo should be applied in accordance with local policy to aid endoscopic follow up or subsequent surgical resection. As tattooing can cause submucosal fibrosis, the tattoo should be placed at least 3cm from the lesion (GRADE of evidence: Very low; Strength of recommendation: Strong)

- **Endoscopic Management: Post-procedure**

- We recommend that written information about the risk of post-procedure complications (including bleeding risk for up to 2 weeks), together with recommended actions and an emergency phone number should be provided to patients (Grade of evidence: Very low; Strength of recommendation: Strong)
- We suggest that recommencement of anticoagulant and antiplatelet therapy post-polypectomy should be considered on an individual basis, weighing up the risks of post-procedure bleeding with the risks of a thromboembolic event. Further specialist advice (ideally sought prior to the procedure) may be appropriate (GRADE of evidence: Low; Strength of recommendation: Weak)
- We recommend that in the case of piecemeal EMR, initial follow-up should take place within 2-6 months (GRADE of evidence: Low; Strength of recommendation: Strong)
- We recommend that on follow-up, the scar site should be positively identified, scrutinised and photographed. Image enhancement with techniques such as dye spray and digital enhancement may aid detection of residual neoplasia on a polypectomy scar. Areas of possible residual polyp require tissue diagnosis and definitive treatment (GRADE of evidence: Low; Strength of recommendation: Strong)
- We suggest that the management of residual/recurrent polyp tissue can be challenging and should be performed by an endoscopist with complex NPCP experience (GRADE: Low; Strength of recommendation: weak).
We suggest that the management of ongoing recurrence should be discussed in a complex polyp MDM (GRADE of evidence: Low; Strength of recommendation: Weak)

- **Surgical Management of LNCPs**

- We recommend that surgical therapy should be considered where malignancy is suspected or concerns about the likelihood of incomplete endoscopic resection arise following complex polyp MDM discussion (GRADE of evidence: Moderate; Strength of recommendation: Strong)

- We recommend that laparoscopic therapy should be used in preference to open surgery in the surgical management of LNPCPs (GRADE of evidence: High; Strength of recommendation: Strong)

3.4) Agreed Statements and Voting Summary

3.4.1) Definitions and Terminology

The term '**Non-pedunculated colorectal polyp**' (NPCP) was agreed to be the clearest and most appropriate term to define sessile and flat colonic lesions. In accordance with other international series, it was agreed that Paris classification and the term 'laterally spreading type polyp' (LST) may be used to sub-classify lesions further. It was also agreed that the guidelines should focus primarily on polyps at least 2cm in size, given the increased complexity associated with their removal, and these lesions are referred to as large NPCPs (LNPCPs) unless specified otherwise. However, much of the guidance in this document may be applicable to smaller polyps.

100% agreement reached in round 2

No vote in round 1, participants asked to offer terminology suggestions

Terminology changed from 'Laterally-spreading type polyp (LST)' which was proposed in preliminary round to describe predominantly flat (Paris 0-II) and sessile polyps (Paris Is) of at least 10mm in size- marked disagreement with this term, no consensus reached.

- 1. We recommend that lesions with the following characteristics should be identified as those with as increased risk of malignancy: Lesions exhibiting; pit pattern type V, Paris 0-IIc or 0-IIa+IIc morphology, non-granular LST (laterally spreading type polyp, LST-NG), granular LSTs (LST-G) with a dominant nodule, distorted surface pattern, colour and vessels (NICE NBI type III), thick and irregular microvessels (Sano capillary pattern type III) (GRADE of evidence: Moderate; Strength of recommendation: Strong)**

Consensus Reached at Round 1: 100% agreement

Addition after preliminary round of 'LST-G with dominant nodule' and 'NICE NBI type III lesions'

- 2. We recommend that the following lesions with the following characteristics are identified as having with an increased risk of incomplete excision/recurrence: Size \geq 40mm, location involving ileocaecal valve, appendix, diverticulum or dentate line; within an inflamed segment of colitis; prior failed attempt at resection or recurrence at site of previous resection (excluding unifocal, diminutive and easily resected/ablated residual adenoma on first site check); non-lifting sign after submucosal injection; endoscopist concern about difficult location (e.g. behind flexure or fold, in stenotic diverticular disease); (GRADE of evidence: Low; Strength of recommendation: Strong)**

Consensus reached at Round 2; 92.3% agreement

Removal of '75% circumference' after round 1

- 3. We recommend that endoscopic factors associated with an increased risk of adverse events include: Caecal location, size \geq 40mm and endoscopist inexperience (GRADE of evidence: Low; Strength of recommendation: Strong)**

Consensus Reached at Round 1: 84.6% agreement

Addition after preliminary round of 'endoscopist inexperience'

- 4. Complex NPCP: We suggest this term to describe NPCPs with any of the following features: (a) increased risk of malignancy; (b) increased risk of incomplete resection/recurrence; (c) increased risk of adverse event; (d) SMSA level 4 (GRADE of evidence: Low; Strength of recommendation: Weak)**

Consensus reached at Round 2; 92.3% agreement

Consensus reached at preliminary round and at round 1. However modification (addition of 'SMSA 4') made at round 2.

Deleted after preliminary round:

- Endoscopic Mucosal Resection (EMR) – snare polypectomy with prior submucosal injection and lift (consensus reached at preliminary round but statement removed and definition described in introduction)

3.4.2) Service Provision and Management Principles

- 1. We recommend that hospitals that detect or manage LNPCPs should develop a referral pathway to facilitate their management and processes to monitor the quality of the service. The pathway should ensure that patients have access to and information about a full range of therapeutic options, including laparoscopic surgery, a provision for the management of complex rectal lesions and endoscopists capable of performing endotherapy on complex NPCPs (GRADE of evidence: Very low; Strength of recommendation: Strong)**

Consensus Reached at Round 1: 100%

Consensus reached at preliminary round and round 1. The term 'colorectal NPCPs' was used instead of 'LST'

- 2. We suggest that clinicians involved in the management of LNPCPs should have access to a multidisciplinary network such as a multidisciplinary meeting (MDM) to discuss complex cases (complex as defined in these guidelines). Membership should include at least one complex NPCP endoscopist, at least one colorectal laparoscopic surgeon and a gastrointestinal histopathologist. (GRADE of evidence: Very low; Strength of recommendation: Weak)**

Consensus Reached at Round 2; 92% agreement

Statement modified after preliminary round from 'Clinicians involved in the management of colorectal LSTs should have access to a complex polyp MDT meeting, to discuss all complex cases. Membership should include at least one complex LST endoscopist, at least one colorectal laparoscopic surgeon and a gastrointestinal histopathologist'

- 3. We recommend that all endoscopists performing endotherapy on LNPCPs should be highly experienced in standard polypectomy, should have endoscopy service approval for this work and should be subject to regular audit to ensure their key performance**

indicators are above minimum quality standards (GRADE of evidence: Low; Strength of recommendation: Strong)

Consensus Reached at Round 1: 100%

Statement modified after preliminary round from 'All endoscopists performing endotherapy on LSTs of at least 2cm in size should be subject to regular audit to ensure their key performance indicators are above minimum quality standards'.

4. **We suggest that patients with benign NPCPs should not undergo surgery without prior complex polyp MDM discussion (GRADE of evidence: Very low; Strength of recommendation: Weak)**

Consensus Reached at Round 1: 84.6% agreement

5. **We suggest that primary therapeutic management of LNPCPs should be undertaken within 8 weeks of receipt of referral (GRADE of evidence: Very low; Strength of recommendation: Weak)**

Consensus Reached at Round 2; 100% agreement

Statement modified after preliminary round from 'Primary therapeutic management of LSTs should be undertaken within 6 weeks of the detection of a colorectal LST'.

6. **We recommend that endoscopic resection is first line therapy for the removal of LNPCPs where there is no suspicion of malignancy (suspicion of malignancy as defined in these guidelines) (GRADE of evidence: Moderate; Strength of recommendation: Strong)**

Consensus Reached at Round 1; 92.3% agreement

Addition of after preliminary round of 'where there is no suspicion of malignancy' made to statement following GDG feedback.

7. We recommend that piecemeal resection (either endoscopic or surgical) should be avoided if malignancy is suspected (GRADE of evidence: Low; Strength of recommendation: Strong)

Consensus Reached at Round 1; 84.6% agreement

Statement modified after preliminary round from 'En-bloc resection techniques (either endoscopic or surgical) should be used where malignancy is suspected (such as colorectal LSTs with Paris 0-IIc morphology, central depression, type V pit pattern, fold convergence or a non-lifting sign).'

8. We suggest that in the context of significant comorbidity, conservative management may sometimes be appropriate following detailed patient discussion and documentation (GRADE of evidence: Very low; Strength of recommendation: Weak)

Consensus Reached at Round 1; 85.7% agreement

Statement modified after preliminary round from 'Conservative management may be appropriate if life expectancy is less than 5 years'

Deleted after preliminary round

- Endoscopic management of complex LSTs should be performed by experienced complex LST endoscopists who demonstrate high quality key performance indicators from continuous audit- merged with another statement

3.4.3) Lesion assessment

1. We recommend that all LNPCPs should be photographed or videoed prior to removal (GRADE of evidence: Very low; Strength of recommendation: Strong)

Consensus Reached at Round 1; 100% agreement

2. We suggest that a size estimate of LNPCPs should be made, ideally by measuring against an open snare (GRADE of evidence: Low; Strength of recommendation: Weak)

Consensus Reached at Round 1; 100% agreement

- 3. We recommend that the Paris Classification should be used wherever possible to describe polyp morphology (GRADE of evidence: Low; Strength of recommendation: Strong)**

Consensus Reached at Round 1; 100% agreement

- 4. We recommend that the surface characteristics of a polyp should be described using a classification system such as the NICE NBI or Kudo Pit Pattern classification. The use of image enhancement techniques (digital or chromoendoscopic) can improve diagnostic accuracy in lesion assessment (GRADE of evidence: Moderate; Strength of recommendation: Strong)**

Consensus Reached at Round 1; 91.7% agreement

Statement modified after preliminary round from 'Kudo Pit Pattern assessment should be used to describe the surface characteristics of LSTs'

- 5. We suggest that if a lesion may be amenable to endoscopic removal, biopsies should be used with caution, as there is a risk of submucosal tethering due to scarring, rendering the lesion unresectable. Where biopsies are required because of concern of cancer, they should be targeted to the area exhibiting features indicative of cancer, avoiding flat areas and the lesion periphery. Tunnelling biopsies (biopsy through biopsy) should not be used (GRADE of evidence: Low; Strength of recommendation: Weak)**

Consensus Reached at Round 1; 92.3% agreement

Deleted after preliminary round

- The use of image enhancement techniques (either digital or chromoendoscopic) to examine colorectal LSTs is encouraged as they can improve diagnostic accuracy.
- The use of cross sectional imaging such as MRI and CT scanning to assess for submucosal invasion and lymph node involvement may aid MDT decisions in the diagnosis, staging and management of malignant LSTs.
- We suggest that the resection of LNPCPs should not be performed at the time of discovery, unless the patient has been specifically consented for this, and the endoscopist determines they have sufficient time and expertise to do so

3.4.4) Endoscopic Management: Pre-procedure

1. We recommend that adequate planning should be undertaken (including length of time booked for procedure, endoscopist and nursing staff skills and endoscopic equipment) so that prior to an attempt at advanced polypectomy, the endoscopist has a high level of confidence that complete resection can be achieved in a single procedure (GRADE of evidence: Very low; Strength of recommendation: Strong)

Consensus Reached at Round 1; 100% agreement

2. We recommend that antiplatelet medications such as clopidogrel and prasugrel, and newer antiplatelet agents such as ticagrelor should be stopped at least 7 days prior to resection in accordance with BSG Antiplatelet Guidelines (GRADE of evidence: Moderate; Strength of recommendation: Strong)

Consensus Reached at Round 1; 92.3% agreement

3. We recommend that warfarin should be stopped at least 5 days prior to resection of LNCPs and INR should be confirmed as below 1.5 prior to the procedure, in accordance with BSG Anticoagulation Guidelines. (GRADE of evidence: Moderate; Strength of recommendation: Strong) We suggest that general recommendations regarding the management of newer anticoagulants which have differing properties, such as rivaroxaban and dabigatran, cannot currently be made due to a lack of evidence. Appropriate specialist advice should be sought in this scenario (GRADE of evidence: Very low; Strength of recommendation: Weak)

Consensus Reached at Round 1; 92.3% agreement

Statement modified from 'Anticoagulants such as warfarin should be stopped at least 5 days in advance with an INR below 1.5 prior to advanced polypectomy, in accordance with BSG Anticoagulation Guidelines' after preliminary round.

4. We recommend that patients should be consented for the risk of thromboembolic events such as stroke and venous thromboembolism when stopping anticoagulants before

endoscopic resection (GRADE of evidence: Very low; Strength of recommendation: Strong). We suggest that advice given should be tailored to a patient's individual risk with a 'bridging regimen' of low molecular weight heparin given to high risk individuals in accordance with BSG guidelines. The risk of bleeding with this regimen should also be explained (GRADE of evidence: Low; Strength of recommendation: Weak)

Consensus Reached at Round 1; 85.7% agreement

Statement modified after preliminary round from 'Patients should be consented for the risk of thromboembolic events such as stroke (up to nearly 3% in patients with increased comorbidity) when stopping antithrombotic agents before endoscopy procedures.'

5. We suggest that where cessation of anticoagulants or antiplatelet medications is contraindicated due to comorbidity, or where there is uncertainty, appropriate specialist advice should be sought. If the anticoagulation/antiplatelet medication is temporary and the lesion has been adequately assessed as being of low risk for cancer, deferral of resection until after this medication can be discontinued may be appropriate (Grade of evidence: Very low; Strength of recommendation: Weak)

Consensus Reached at Round 1; 100% agreement

6. We suggest that the evidence for the cessation/continuation of low dose aspirin in the context of LNPCPs is weak and the decision should be individualised according to patient risk (GRADE of evidence: Low; Strength of recommendation: Weak)

Consensus Reached at Round 2; 100% agreement

Statement modified after preliminary round from 'Low dose Aspirin is safe to continue prior to advanced polypectomy '

7. We recommend that when obtaining consent for the endoscopic resection of LNPCPs, written information in plain English should be given. Management options including endoscopic therapy, surgery and conservative management should be discussed. Regarding endoscopic therapy, patients should be informed of the potential need for subsequent check procedures and surveillance endoscopy. The risks of post-procedure

bleeding (both immediate and delayed), perforation and residual polyp/recurrence should be explained (GRADE of evidence: Very low; Strength of recommendation: Strong)

Consensus Reached at Round 1; 92.9% agreement

Statement modified after preliminary round from ‘When obtaining consent for advanced polypectomy, written information in plain English should be offered. Management options including endoscopic therapy, surgery and conservative management should be discussed. Regarding endoscopic therapy, patients should be informed of the potential need for repeated endoscopic procedures.’

Deleted after preliminary round

- Regarding consent for endoscopic therapy, the risk of post-procedure bleeding (both immediate and delayed; up to 7% of cases), perforation (approximately 1%), recurrence requiring additional therapy (potentially over 20%) and persistent recurrence (up to 7%) should be explained

3.4.5) Endoscopic Management: Peri-procedure

1. **We recommend that carbon dioxide should be used in preference to air insufflation during colonoscopy to improve patient comfort and safety (GRADE of evidence: High; Strength of recommendation: Strong)**

Consensus Reached at Round 1; 100% agreement

2. **We recommend that the use of contrast agents such as indigo carmine or methylene blue in the submucosal injection solution may be considered to help demarcate a lesion, its resection margins, and to outline a clear submucosal plane (GRADE of evidence: Low; Strength of recommendation: Strong)**

Consensus Reached at Round 1; 100% agreement

Statement modified after preliminary round to 'The use of contrast agents such as methylene blue in the submucosal injection solution to help to demarcate the lesion, its resection margins, and to outline a clear submucosal plane is recommended'.

- 3. We suggest that the addition of low concentration adrenaline to the submucosal injection solution may be considered to keep the resection field clear during endoscopic resection (GRADE of evidence: Low; Strength of recommendation: Weak)**

Consensus Reached at Round 1; 100% agreement

Statement modified after preliminary round from 'The addition of low concentration adrenaline to the submucosal injection solution may be considered to reduce the risk of peri-procedure bleeding'

- 4. We suggest the consideration of the use of colloidal type submucosal injection solutions should be used in preference to normal saline lifting solution for LNPCPs (Grade of evidence: Low; Strength of recommendation: Weak)**

Consensus Reached at Round 1; 92.3% agreement

- 5. We suggest that endoscopists should be familiar with the range of snares available, although a single optimal snare cannot currently be recommended (GRADE of evidence: Very low; Strength of recommendation: Weak)**

Consensus Reached at Round 1; 100% agreement

- 6. We suggest that pure cutting or prolonged pure coagulation current should be avoided due to an increased risk of post polypectomy bleeding and thermal tissue injury respectively (GRADE of evidence: Low; Strength of recommendation: Weak)**

Consensus Reached at Round 1; 92.3% agreement

7. **We suggest that whilst en-bloc endoscopic snare resection of lesions \leq 20mm is recommended to reduce the risk of recurrence and to enable more accurate histopathological interpretation, this practice should be used with caution in LNPCPs due to an increased risk of diathermy associated thermal injury and perforation (GRADE of evidence: Low; Strength of recommendation: Weak)**

Consensus Reached at Round 1; 84.6% agreement

Statement modified after preliminary round from 'En bloc endoscopic snare resection of LSTs up to 2cm is recommended, to reduce the risk of recurrence and to enable more accurate histological interpretation. En bloc endoscopic snare resection of LSTs of 2cm or greater in size should be used with caution due to increased risk.'

8. **We recommend that treatment naïve lesions which fail to lift after adequate submucosal injection should not be subject to attempted resection with conventional snare polypectomy technique (GRADE of evidence: Low; Strength of recommendation: Strong)**

Consensus Reached at Round 1; 92.3% agreement

Statement modified after preliminary round from 'Lesions which do not lift after adequate submucosal injection (with no prior intervention) should not be attempted with piecemeal endotherapy due to the risks of submucosal invasion and incomplete excision'

9. **We recommend that during endoscopic piecemeal resection, the snare should be used to resect a lesion completely wherever possible. Thermal coagulation techniques such as argon plasma coagulation (APC) and soft coagulation may be used as adjuncts when snare resection of small residual fragments of polyp is not possible (GRADE of evidence: Low; Strength of recommendation: Strong)**

Consensus Reached at Round 1; 100% agreement

Statement modified after preliminary round from 'During endoscopic piecemeal resection, the snare should be used to resect the lesion completely wherever possible. Thermal coagulation techniques such as argon plasma coagulation (APC) be used on resection

margins as an adjunct after piecemeal EMR to help achieve complete resection and to reduce recurrence, but should only be used once further snare resection is impossible.'

- 10. We recommend that careful post-procedure inspection of the resection site and photographic documentation of completeness of resection should be performed (GRADE of evidence: Low; Strength of recommendation: Strong)**

Consensus Reached at Round 1; 100% agreement

Statement modified after preliminary round from 'Post-procedure photographic documentation to document completeness of resection should be performed'

- 11. We recommend that with the exception of the caecum or rectum, a tattoo should be applied in accordance with local policy to aid endoscopic follow up or subsequent surgical resection. As tattooing can cause submucosal fibrosis, the tattoo should be placed at least 30mm from the lesion (GRADE of evidence: Very low; Strength of recommendation: Strong)**

Consensus Reached at Round 1; 92.3% agreement

Statement modified after preliminary round from 'Unless previously placed, a tattoo should be applied in accordance with local policy to aid endoscopic follow up or subsequent surgical resection'

Deleted after preliminary round:

- The colorectal LST should be positioned adjacent to the endoscope instrumentation channel to facilitate safe and effective removal
- In circumstances such as a high risk of bleeding or prior to recommencement of antiplatelets/anticoagulants, post-resection mucosal defect closure with endoscopic clips to reduce post-resection bleeding may be considered

Deleted after round 1:

- Marking of the snare handle at the point where the tip of the snare just protrudes from the sheath is recommended.

3.4.6) Endoscopic Management: Post-procedure

1. We recommend that written information about the risk of post-procedure complications (including bleeding risk for up to 2 weeks), together with recommended actions and an emergency phone number should be provided to patients (Grade of evidence: Very low; Strength of recommendation: Strong)

Consensus Reached at Round 1; 100% agreement

Statement modified after preliminary round from ‘Given the potential for complications to occur several days post procedure, patients should be given instructions should symptoms arise. This may be written in an instruction leaflet or on the endoscopy report itself which may not only be informative for a patient, but also an emergency doctor’.

2. We suggest that recommencement of anticoagulant and antiplatelet therapy post-polypectomy should be considered on an individual basis, weighing up the risks of post-procedure bleeding with the risks of a thromboembolic event. Further specialist advice (ideally sought prior to the procedure) may be appropriate (GRADE of evidence: Low; Strength of recommendation: Weak)

Consensus Reached at Round 1; 100% agreement

3. We recommend that in the case of piecemeal EMR, initial follow-up should take place within 2-6 months (GRADE of evidence: Low; Strength of recommendation: Strong)

Consensus Reached at Round 1; 92.9% agreement

4. We recommend that on follow-up, the scar site should be positively identified, scrutinised and photographed. Image enhancement with techniques such as dye spray and digital enhancement may aid detection of residual neoplasia on a polypectomy scar. Areas of possible residual polyp require tissue diagnosis and definitive treatment (GRADE of evidence: Low; Strength of recommendation: Strong)

Consensus Reached at Round 1; 84.6% agreement

Statement modified after preliminary round from 'On endoscopic follow-up, the scar site should be positively identified, scrutinised and photographed to exclude recurrence. Consideration should be given to biopsy of the scar as additional proof.'

- 5. We suggest that the management of residual/recurrent polyp tissue can be challenging and should be performed by an endoscopist with complex NPCP experience (GRADE: Low; Strength of recommendation: weak). We suggest that the management of ongoing recurrence should be discussed in a complex polyp MDM (GRADE of evidence: Low; Strength of recommendation: Weak)**

Consensus Reached at Round 1; 100% agreement

New statement created after preliminary round

Deleted after Preliminary Round

- Image enhancement with techniques such as dye spray and digital contrast enhancement may aid detection of residual neoplasia on a polypectomy scar
- Thermal coagulation techniques such as APC may be used in the management of residual and recurrent tissue of up to 1cm in size in cases of recurrence of 1cm or greater in size, the case should be discussed at a complex polyp MDT. Options such as ESD, surgical resection and conservative treatment may be appropriate
- In cases of recurrence of 1cm or greater in size, the case should be discussed at a complex polyp MDT. Options such as ESD, surgical resection and conservative treatment may be appropriate.
- Curative downsizing may be used to provide symptomatic relief

3.4.7) Surgical Management

- 1. We recommend that surgical therapy should be considered where malignancy is suspected or concerns about the likelihood of incomplete endoscopic resection arise following complex polyp MDM discussion (GRADE of evidence: Moderate; Strength of recommendation: Strong)**

Consensus Reached at Round 1; 92.9% agreement

Statement modified after preliminary round from 'Surgical therapy should be considered in the multidisciplinary setting where malignancy is suspected or concerns about incomplete endoscopic resection arise following complex polyp MDT discussions'

- 2. We recommend that laparoscopic therapy should be used in preference to open surgery in the surgical management of LNPCPs (GRADE of evidence: High; Strength of recommendation: Strong)**

Consensus Reached at Round 1; 92.9% agreement

Deleted statements after preliminary round

- The use of adjunctive surgery such as laparoscopic assisted endoscopic polypectomy (LAEP) should be considered in the multidisciplinary setting in cases where a concern over incomplete resection and/or perforation is associated with endotherapy
- TEMS may be considered as an alternative primary therapeutic option for complex rectal LSTs

3.5) Discussion

The challenge of creating of a consensus based guideline document for the management of large non pedunculated colorectal polyps was considerable. The aim of the process was to produce a document encompassing best practice and technical guidance in an evolving field, a proposed model for training in this discipline and encourage further work by the identification of important research questions still to be conclusively answered.

This is an area that the BSG had sought to offer guidance for many years but had found difficult to coordinate. Prior to commencing the process, the plan to create guidelines was shared with the Northern Region Endoscopy Research Group (NREG) with initial opinion pessimistic. The main concern cited was that there was a paucity of high quality evidence

available to support any guidance made and that the guidelines may be based mainly on expert opinion only and therefore categorised as the lowest grade of evidence. However, this concern was allayed upon conducting a comprehensive literature review guided by discussion from a BSG approved writing subcommittee with a large amount of evidence available covering many aspects of LNPCP assessment and management. The main challenge was to assess, interpret and combine evidence of a sufficient standard with expert opinion where evidence was unavailable. Another important step in ensuring the creation of a robust document was the selection of a high quality guideline development group including multidisciplinary individuals of a national and/or international standing with experience and a background of producing important evidence in in this field. This was ensured by the recommendation of GDG members by relevant bodies such as the BSG endoscopy committee, the ACPGBI and the Royal College of Pathologists with a group of clinicians aware of the best available evidence, and therefore able to add to the existing evidence base. This occurred at every stage of group consultation and resulted in a sizable and broad range of references. In addition, where recommendations were to be made in the absence of sufficient evidence, the reputation and experience of the GDG would make it more likely that they could be considered valid.

The BSG have clear guidance for the formation of a guideline development group which is likely a reflection of the fact that consensus methodology is increasingly considered as essential internationally in healthcare guideline development.

The BSG GDG criteria ensured a wide representation of disciplines involved in the management of LNPCPs allowing for the interests of all relevant stakeholders to be represented and increased applicability of the guidelines. The GDG included both expert and non-expert endoscopists, managerial staff, colorectal surgeons, a gastrointestinal histopathologist and a patient representative. Whilst consensus methodology raises a potential issue with people without specific relevant expertise being asked to vote on complex issues, for example in this case with patient and histopathology representatives voting on technical endoscopic issues. This concern was addressed by ensuring that members felt suitable were recruited and felt able to vote due to the provision of extensive relevant information in an understandable form (such as the interpretation of evidence and rationale for a recommendation, in addition to the comments of other GDG members). Ensuring patient representation was essential to ensure that patient's best interests were represented and also a mandatory feature of any BSG approved guideline.

Finding patient representatives proved difficult, especially given that this would be a time consuming process involving reviewing complex information. One patient representative withdrew from the process citing these concerns whilst also admitting that they would feel intimidated by working alongside clinicians considered experts in the field and unsure that they could make a full contribution. The BSG were however able to identify a suitable patient representative who had previous experience in this role. A vital undertaking to ensure that they felt engaged was the creation of an information document that could be interpreted by a lay person. In view of this, the format of the provisional and subsequent voting documents consisted of a summary of the evidence used to make recommendations below all recommendation statements in addition to the evidence database used. In addition, whilst it was important to communicate with and be readily available to all members on an individual basis and deal with their queries to ensure continued participation, this was particularly important with the patient representative to help to clarify any queries they may have. This involved regular email and phone exchanges and this additional interaction was important in keeping the patient representative engaged with the process.

The decision to use consensus methodology, in this case a modified Delphi technique, appeared valid as this is a complex field with a paucity of evidence and differing opinions with regards to best practice in some areas. This was apparent when reviewing comments and the views of GDG members (discussed later).

The modified Delphi process, albeit requiring significant coordination due to the availability and differing geographical locations of the GDG participants, appeared to run smoothly with all participants able to return their responses. The use of a preliminary round prior to subsequent formal voting appeared important in:

- Document enhancement- This included the suggests of new statements and removing statements and wording felt to be inaccurate or inapplicable along with areas of duplication
- Increasing robustness: Ensuring the accuracy of wording and the interpretation of supporting evidence
- Building on the evidence database- Suggestions with regards to additional references

The anonymous dissemination of voting results and comments allowed for members to give their views without fear of prejudice from other members, whilst also helping to moderate strong or outlying opinions. In addition, comments from GDG members not considered to be experts in the management of LNPCPs (e.g. patient representative, non-expert endoscopists, GI Histopathologist) indicated that access to the views of other group members improved their understanding of the issues and content in the process. When strong views were expressed it was important to be mindful of their context in relation to available evidence and the possibility of introducing bias. For example, a GDG member suggesting the use of an experimental technique that they have had a role in developing over more established techniques with a larger evidence base, or refusing to advocate a procedure that is an alternate to a modality that they provide.

The face to face meeting format of the final round of voting was invaluable in enabling consensus to be reached for recommendation statements for remaining contentious points positively or negatively and pertinent research questions. Logistical considerations included the identification of a meeting date mutually acceptable to all GDG members, ensuring the availability of anonymous keypad voting and directing queries regarding reclaiming travel expenses from the BSG. The roundtable meeting ensured that the GDG were able to interact in greater depth with discussion in addition to the ability to question and clarify issues, whilst still able to vote anonymously.

In addition, in the absence of any evidence supporting the creation of guidelines for a specific LNPCP training model, the face to face meeting allowed detailed discussion identifying potential training modalities that may be pioneered (see later).

The structure and format of the guidelines was formulated based on the literature review undertaken into LNPCP management and a review of recent international endoscopic guidelines such as ESGE, BSG Barrett's Oesophagus guidelines which favoured various sections and statements with voting outcomes and supporting evidence below. Sections were identified to cover every aspect of LNPCP management but from the available evidence base, it was clear that the majority of sections would focus on endoscopic management and associated considerations whilst it was important to pose questions about known contentious issues where it was likely consensus would not be reached to generate discussion to ensure that a clear position on these issues could be included for guideline users.

3.5.1) Definitions

Identifying suitable clear definitions was considered important to ensure that there could be universal understanding over what is considered to be a large non pedunculated lesion, and that lesions associated with increased risk of malignancy, complexity for removal and risk of complications ('complex' lesions) could be easily identified prior to any attempt at therapy. This would facilitate the discussion and referral of lesions between clinicians. This was also felt to be important in view of evidence that lesion assessment appears to vary widely even amongst experienced clinicians (263).

It was agreed that the lesions targeted by the guidelines should at least 2cm in size, given the increased complexity associated with their removal and the increased risk of malignancy in this group (17, 32). The term 'laterally spreading tumour' (LST) was originally proposed to identify large non-pedunculated polyps however this was rejected as it did not encompass all relevant lesions such as sessile lesions identified as Paris Is using the Paris Classification System. It was clear that a suitable term would need to encompass internationally validated lesion morphology classification systems such as Paris classification and LST. Other proposed terms included 'large non-pedunculated lesion' (LNL), 'large sessile colorectal polyp' (LSCP), 'large non pedunculated polyp' (LNP). However the term '**Non-pedunculated colorectal polyp**' (**NPCP**) was unanimously considered the clearest and most appropriate term to define sessile and flat colonic lesions with lesions at least 2cm in size referred to as a large NPCP (LNPCP). In accordance with other international series, it was agreed that Paris classification and the term 'laterally spreading type polyp' (LST) may be used to sub-classify lesions further. The identification of lesions with increased malignancy risk was straightforward due to strong evidence identifying subtypes with increased associated malignancy within various lesion classification systems such as Paris, Kudo Pit Pattern, Sano Capillary Pattern and LST. Not originally included, the 'NICE NBI' system that characterised lesions based on vessel and surface pattern and colour, was not well known to most of the GDG. However it was proposed by a member of the GDG who was part of the study group that had recently validated the system. In view of this there was deemed sufficient evidence for its inclusion. On a background of good evidence showing worse outcomes with certain lesions, there was almost unanimous agreement with regards to the identification of lesions associated

with increased difficulty in achieving successful endoscopic resection based on lesion location and access issues and mucosal fibrosis due to inflammation and previous therapeutic attempts. There was however, some initial contention in the identification of factors felt to be likely to increase the risk of adverse events. Whilst size was recognised as a risk factor, the evidence originally included to support the inclusion of caecal location was not felt to be of sufficient strength. This was remedied by the inclusion of a recent large BCSP study that unequivocally identified caecal location as being associated with an increased risk of perforation and bleeding. The inclusion of 'endoscopist inexperience' was also suggested by the GDG with the purpose of highlighting the need for experienced endoscopists in the management of these large lesions and additional evidence strongly supporting this assertion was also provided.

There was a query within the GDG about the need to identify 'complex NPCPs', however defining complex lesions was successfully justified as important to allow the identification of the most challenging lesions best suited to management by clinicians with the relevant skills and experience within a multidisciplinary environment and also emphasise the need for safety and good outcomes. It appeared logical that lesions with an increased malignancy risk, risk of incomplete resection and risk of adverse events should be identified as complex, whilst the term also enabled inclusion of the SMSA scoring system which was strongly supported within the GDG and had recently been validated as an accurate method of assessing the likelihood of achieving successful endoscopic resection based on lesion characteristics.

3.5.2) Service Provision and Management Principles

This section sought to focus on promoting patient safety and a uniform standard of service delivery. This included:

- Highlighting the importance that clinicians with the requisite expertise should undertake management of these challenging lesions
- Limiting exposure to unnecessary invasive procedures via careful assessment
- The provision of a full range of assessment and management options either accessible within a single centre or another centre within a referral network service.
- Ensuring that patients receive timely management without unnecessary delay

This section generated a great deal of debate throughout the consensus process as although the GDG agreed with these principles, there is limited scientific evidence to support many of the recommendations within this section. As such, the wording of such statements was felt to be important to ensure that their validity was not questioned. There was universal agreement with the statement **'We recommend that hospitals that detect or manage LNCPs should develop a referral pathway to facilitate their management and processes to monitor the quality of the service. The pathway should ensure that patients have access to and information about a full range of therapeutic options, including laparoscopic surgery, a provision for the management of complex rectal lesions and endoscopists capable of performing endotherapy on complex NPCPs (GRADE of evidence: Very low; Strength of recommendation: Strong)'**.

This statement was felt to encompass the importance of competent endoscopists, a referral pathway that can allow audit of outcomes to highlight areas for future improvement, a recognition of the special considerations required for rectal lesions and the ability to provide minimally invasive resectional surgery.

The identification of suitable endoscopists and monitoring of outcomes was cited as a challenge.

'We recommend that all endoscopists performing endotherapy on LNCPs should be highly experienced in standard polypectomy, should have endoscopy service approval for this work and should be subject to regular audit to ensure their key performance indicators are above minimum quality standards (GRADE of evidence: Low; Strength of recommendation: Strong)'

It is likely that the application of the key performance indicators (KPIs) recently agreed by the GDG with existing therapeutic endoscopists may allow this over time.

The recommendation regarding access to a multidisciplinary network such as a complex polyp MDM and its composition was not finalised until face to face discussion at the final voting round. The potential benefit of an MDM was felt to be high, especially by GDG members currently participating in them, but issues over the logistics of such a meeting were raised. It was anticipated that there may be resistance by clinicians with an already heavy schedule to another formal meeting whilst it may be perceived as increased interference in management, especially with limited current quantitative evidence to

advocate its use. In view of this, the wording of the statement was modified to specify that a multidisciplinary network, which may include a complex polyp MDM (a specialised meeting or within an existing colorectal cancer multidisciplinary team (MDT) meeting) or informal discussion, should be in place to allow clinicians access to additional expertise.

Another concern raised was ensuring that guidance was provided regarding the minimum dataset of information with regards to lesion and patient features and imaging (high quality videos or video) required for valid assessment and discussion. This was felt to be especially applicable when referrals were received by less experienced endoscopists as patients may be then subject to extra, unnecessary diagnostic assessment via colonoscopy prior to a decision on therapy. Additional work within this thesis has been undertaken to develop a minimum dataset for MDM discussion with prospective data analysis to validate its use (see chapter 6).

Given the high availability of endotherapy such as EMR and international evidence supporting the efficacy, increased safety and cost-effectiveness of endotherapy compared with surgical resection for LNCPs, there was no dissenting discussion within the GDG relating to recommending endotherapy over surgery where possible with demonstrated curative rates of approximately 90% (5, 9), reduced rates of morbidity and mortality (11) and strong economic evidence cited in cost evaluation studies (10).

These factors, in addition to data demonstrating successful endoscopic management in LNCPs initially felt to be endoscopically unresectable and originally referred for surgical management ensured early consensus for a statement recommending multidisciplinary discussion prior to undertaking surgery in LNCPs without a suspicion of malignancy. As the CARE study demonstrated, the therapeutic capabilities of different endoscopists does not appear uniform and multiple international series suggesting over 70% endoscopic success in this scenario supports a recommendation (5, 56, 67).

Whilst the GDG were keen to emphasise the importance of endoscopic management, the need to recommend caution, particularly in the context of a suspicion of malignancy was supported.

The statement '**We recommend that piecemeal resection (either endoscopic or surgical) should be avoided if malignancy is suspected (GRADE of evidence: Low; Strength of recommendation: Strong)**' was agreed on after initial discussions to discourage piecemeal

resection of suspected malignancy in accordance with established oncological principles given widespread evidence of the retrieval of suboptimal histopathological specimens resulting in:

- The potential to miss malignancy and other poor prognostic features
- An inability to comment on completeness of resection
- A higher likelihood of recurrence if used on an intention to treat basis

These factors were highlighted as important reasons to justify specifying piecemeal therapy an inadequate diagnostic and therapeutic tool in this scenario. There was however disagreement within the GDG about the benefit of recommending en-bloc endotherapy such as ESD alongside surgery as anything other than a diagnostic tool, necessitating a change from the provisional statement of **'En-bloc resection techniques (either endoscopic or surgical) should be used where malignancy is suspected'**. Whilst there was a view from GDG members practicing ESD that it could be used as a first line option due to the ability to obtain optimal histological diagnosis and the ability to comment on complete removal of malignancy in many cases, particularly in the rectum where there is a need to avoid resectional surgery, the view from the surgical representatives was that it offered insufficient assurance about complete lesion clearance if anything other than superficial malignancy was found due to an inability to sample or remove surrounding lymph tissue. In addition, with regards to rectal lesions, the surgical representatives supported the surgical option of TEMS over en-bloc endotherapy due to greater availability and the ability to offer full-thickness resection. In view of this, it was agreed that the statement should discourage piecemeal resection in this scenario whilst further individualised discussions over optimal therapy could take place within a multidisciplinary setting.

There was support for the recommendation of conservative management as a potential option in the context of limited life-expectancy due to severe comorbidity as good sense in asymptomatic patients. This was a practice used in certain cases by members of the GDG and an area not felt to be feasible to conduct further research in. There was strong agreement about the need to be able to accurately identify suitable patients on an individualised basis and to ensure that patients or next of kin could be informed of and understand the rationale for this option before it could be supported (85). Whilst LNPCPs are associated with a future risk of malignancy and may sometimes already harbour malignancy, the risk of symptomatic malignancy and cancer-related mortality is likely to be

outweighed by comorbidities such as advanced age, frailty, dementia, chronic cardiorespiratory conditions and other established malignancy. In this context, it was agreed that subjecting a patient to the additional immediate risks of endoscopic or surgical resection may not be in their best interests(86).

The rationale for supporting conservative management as a potential option was extrapolated from the results of polyp growth studies with adenoma to carcinoma transformation to a point where a lesion becomes symptomatic is likely to take years(70). In addition, the use of mortality index models was felt to strengthen stratification of individual patient risk prior to attempting invasive therapy. The Schonberg index in particular (described earlier) was cited as a model that could accurately predict patient mortality risk (85).

The greatest source of contention in this section was agreeing on what was an acceptable timeframe for management of LNPCPs and indeed whether it was appropriate to propose a timeframe at all. There was strong opposition by some for a timeframe as there was no evidence to support a specific time period and a concern that attempts to keep within the timeframe could result in inappropriate endoscopists undertaking therapy. A six week timeframe was initially proposed as being both prompt and in keeping with an NHS directive specifying that diagnostic tests should take place within six weeks. Whilst there were some members advocating a shorter time period such as 2-4 weeks due to an accepted view that over 10-15% of these lesions may harbour malignancy, specifying a shorter period such as two week pathway as with cancer was not felt to be necessary nor feasible given the likely resultant pressure on services. Following round table discussion and hearing specific views from the patient representative, the need for a management timeframe was agreed as important to ensure timely management due to the potential for LNPCPs to harbour malignancy. An amended proposal of eight weeks, although not evidence based, was felt to be more appropriate as it allowed for more time to ensure that an appropriate endoscopist would undertake therapy and was aligned with the NHS 62 day pathway. It was also accepted that increasing the timeframe to eight weeks was likely to be safe given evidence from polyp growth studies.

3.5.3) Lesion Assessment

Recommendations regarding the use of Paris morphology classification were strongly supported due to established accuracy and already widespread acceptance. Image documentation and size assessment recommendations were supported as good sense in the absence of high quality scientific evidence as they were felt to be important in the accurate assessment of lesion characteristics such as malignant potential and technical issues. Further lesion assessment based on surface characteristics was also strongly agreed on. However, the use of pit pattern recognition alone, whilst recognised as accurate, was cautioned against with GDG feedback that true Kudo pit pattern recognition relies on magnification and staining of pits with cresyl violet, with access to both extremely limited in the UK. In view of this, the recommendation was expanded to include NICE NBI classification which requires readily available NBI, given its recent validation including with inexperienced endoscopists whilst allowing for recognition of other modalities such as Sano classification, flexible spectral imaging colour enhancement (FICE) (FICE vs NBI accuracy; n=235, sensitivity: 77.7% vs 63.6, specificity: 100% vs 99.0%, FICE association with correct diagnosis of malignancy $p < 0.01$) and I-scan (diagnostic accuracy 74-94% independent of lesion size). It was however important to stress the learning curves required for its use.

Known areas of contention in lesion assessment related to biopsy practice and radiological investigation. A recommendation clarifying queries about cautious biopsy practice was felt to be important given its association with submucosal fibrosis complicating subsequent endotherapy attempts, whilst recognising its diagnostic importance in the correct circumstances. A recommendation regarding the potential use of radiological modalities for diagnostic purposes was discussed and rejected due to a lack of supporting evidence (see later).

3.5.4) Endoscopic management: Pre-procedure

Although having only limited supporting evidence, the statement **'We recommend that adequate planning should be undertaken (including length of time booked for procedure, endoscopist and nursing staff skills and endoscopic equipment) so that prior to an attempt at advanced polypectomy, the endoscopist has a high level of confidence that complete resection can be achieved in a single procedure (GRADE of evidence: Very low;**

Strength of recommendation: Strong) was strongly supported by the GDG as it was felt to assert that lesions should not be removed at the time of discovery unless time, facilities and patient consent are in place for this and also reinforce the importance of adequate planning to achieve single session resection where possible, given reduced patient exposure to invasive therapy and evidence of reduced curative resection in lesions previously attempted compared with treatment naïve lesions due to submucosal fibrosis (91% vs 74%).

Many of the statements in this section relate to anticoagulation management and consent related issues which may be complex to manage, particularly due to individual patient factors that would need to be accounted for. Recommendations regarding antiplatelet agents such as clopidogrel, prasugrel and newer agents such as ticagrelor were strengthened by relatively high quality evidence demonstrating significantly increased bleeding risk with this class of agent and well established existing BSG recommendations in their antiplatelet guidelines. Whilst less evidence was available concerning ticagrelor and similar newer agents however, in the context of pharmacological reports suggesting that modification of platelet aggregation for up to seven days, a similar period of cessation to clopidogrel and prasugrel was recommended.

With regards to warfarin, still the most common anticoagulant in use, conclusive evidence and established BSG guidance in relation to its cessation ensured a strong recommendation about its cessation (five days prior to therapy) could be made. There was an issue however with regards to making a recommendation about newer anticoagulants such as rivaroxaban and dabigatran that are increasing in use. The absence of clinical evidence related to endotherapy ensured that no recommendation other than consultation of relevant specialist advice (cardiology/haematology) prior to endotherapy was felt possible. It was recognised that the cessation of antithrombotic medication poses differing risks of thrombotic episodes to patients and in view of this, whilst evidence based recommendations such as the use of a bridging regimen for high risk individuals could be made in line with existing BSG recommendations, the potential complexity surrounding this issue meant that the GDG were keen to highlight the importance of relevant specialist input and only weak recommendations could be made.

The issue of management of aspirin prior to polypectomy has proven to be controversial with conflicting evidence reported in international literature and differing views expressed

by GDG members. Although both UK and US recommendations recommend that aspirin may be continued prior to polypectomy and no data reports aspirin as a statistically significant risk factor for bleeding, surveys of endoscopists demonstrate that a large proportion withhold aspirin. As much of the available evidence pertaining to aspirin does not refer to LNPCPs specifically, this practice was understood and supported by various members of the GDG, especially as it was felt that in many cases temporary cessation of aspirin was unlikely to be unsafe. In light of evidence provided by a BSG reviewer demonstrating no increased bleeding risk with the continuation of aspirin prior to ESD, it was agreed that the use of aspirin was most likely safe but that its management should be individualised according to patient risk and a strong recommendation could not be made.

It was considered vital that recommendations with regards to patient information and consent were comprehensive, clear and explicit to ensure the General Medical Council's policy with regards to patient consent was adhered to. This included recommending that information about all potential management options (including endoscopic, surgical and conservative and the potential benefits and risk associated with both) and the potential individualised thromboembolic risk with anticoagulant withdrawal prior to LNPCP removal were explained. This would allow patient to participate in making a fully informed decision about all therapeutic options, select a preferred therapeutic option and the timing of therapy e.g. potentially delaying therapy until a more convenient date, such as post cessation in patients on temporary anticoagulants. The statements made related to patient information and consent were strongly recommended as supporting patient autonomy and representing 'good sense'.

3.5.5) Endoscopic Management: Peri-procedure

This section sought to provide recommendations about the use of equipment and equipment settings identified in a review of evidence as potentially beneficial in achieving optimal safety and results during the actual polypectomy process, strategies during the resection process and a position on contentious areas where the likelihood of high quality scientific research findings was not considered feasible to obtain.

The use of carbon dioxide of during endoscopy is strongly supported by available evidence, including the findings of a randomised controlled trial, demonstrating improved patient comfort during endoscopy compared with air insufflation and therefore allowing for the longer procedure times required for advanced polypectomy. In addition the non-

flammable properties of CO₂ indicate increased safety associated with its use. Findings related to improved patient comfort and safety ensured that the use of CO₂ was strongly recommended by the GDG.

The use of contrast agents as part of the submucosal injection solution to lift an LNPCP prior to resection was considered as accepted standard practice by the GDG in line with international literature with strong agreement regarding improved lesion demarcation. Indigocarmine was considered the preferred agent described in international literature. However, it was noted, unlike methylene blue, that indigocarmine is not licensed for use in this country despite apparent widespread use. In view of this, the initially proposed recommendation statement had referred specifically to methylene blue. This was met with resistance from the GDG who strongly supported the recommendation of indigocarmine, primarily due to their longstanding use of indigocarmine and concerns within the group about reported association of methylene blue with potential DNA damage to colonocytes in laboratory based work, a finding not associated with indigocarmine. It was suggested that indigocarmine and not methylene blue should be included as there were no safety issues raised with the former, but the inclusion of both methylene blue and indigocarmine was accepted in the statement with a view that this recommendation may aid a change in the latter's licensing conditions.

A strong recommendation was agreed mainly in relation to aiding demarcation of serrated lesions. The CARE study demonstrated residual polyp tissue on almost half of serrated lesions where complete resection had been considered achieved, far higher than with other polyp types (20).

Recommendations regarding the use of adrenaline and colloidal type solutions in submucosal injection solutions were supported in view of evidence suggesting reduced immediate bleeding (potentially allowing clearer views during resection) and easier resection respectively. There was however no effect on delayed bleeding found and the GDG view was that a recommendation about adrenaline should specify this. Whilst a concentration of 1:10000 has been reported in various trials, many members reported using a more dilute form, primarily due to a concern about the increased risk of cardiovascular compromise with higher concentrations. In view of this, a particular solution strength was not specified but a warning about the potential for cardiovascular

compromise was included in supporting text. It was noted that the evidence for its use was primarily from small retrospective studies and that further research in this area was felt to be feasible and so the strength of recommendation made was recorded as weak. A proposed study was a prospective placebo controlled RCT assessing immediate bleeding rates with varying concentrations of adrenaline. The GDG considered the evidence to support colloidal type solutions such as succinated gelatin strong with multiple accounts of a longer lasting submucosal lift, improved procedure times and en-bloc resection rates reported when compared with normal saline, including a small RCT by an internationally renowned group (158). However, although considered beneficial, only a weak recommendation was made as the use of colloidal type solutions for LNPCP resection was not widely used by GDG members and not considered essential, especially as no improvement in patient safety was demonstrated.

Finalising recommendations with regards to specific equipment settings and configurations proved difficult with opinion rather than scientific evidence prevalent and various practices reported both within the GDG and in international questionnaires. The choice of specific snares was one such example where there are many shapes, textures and sizes available but no studies advocating the use of a particular shape or size. While it was felt that clinical trials were possible, for example assessing the effect of various snares on procedure times, en-bloc resection rates, recurrence and thermal tissue injury, it was felt that these factors were most likely to be affected by an endoscopists familiarity and comfort with a particular snare, with many GDG members reporting favoured use of different snares, and therefore it was felt that that only advising users to become comfortable with a favoured snare was appropriate in this scenario.

Formulating recommendations in relation to electrocautery settings proved similarly difficult. In addition to various types of available current such as cutting, blended and coagulation current, various voltage settings exist, in addition to manufacturer variations meaning that equivalent voltage settings may deliver differing amounts of current. As with the results of large questionnaires, the preferred configurations of electrocautery delivery varied within the GDG with recommendations based on experience rather than evidence. Observational evidence did appear to suggest that both blended and coagulation current were safer than pure cutting current with the latter identified as despite providing optimal histopathological specimens, a strong risk factor for post procedure bleeding and

questionnaire results suggested that this was understood with cutting current markedly less in use. The potential hazards of prolonged pure coagulation current were also recognised with porcine evidence suggesting increased thermal tissue injury and perforation risk with higher voltage settings and diminished haemostasis properties with lower settings. The risk of thermal tissue injury is of greater relevance in the thinner right colon and it was accepted that the use of lower settings would likely be safer in this setting. Human clinical research in this area was not considered feasible due to the ethical issues associated with assessing an outcome of thermal tissue injury. With no evidence available supporting specific settings, various manufacturer variables and more recent data supporting the use of blended current combining the properties of both cutting and coagulation current in a controlled manner the GDG felt the most valid recommendation possible was to caution against the use of prolonged cutting or coagulation current for safety reasons.

The plan to recommend technical strategy parameters was initially met with some opposition within the GDG with a concern raised that technical points did not fall within the remit of these guidelines. The majority of feedback however indicated GDG support for technical recommendations with good evidence and/or rationale suggesting improved patient safety and reduced adverse outcomes. One such recommendation referred to the risks associated with caution with the use of en-bloc snare resection for LNPCPs. Whilst recommended where possible for smaller lesions, multiple expert international authors have reported technical difficulties with this approach with LNPCPs due to reduced snare stiffness and uncertainty about the resection plane leading to a concern about perforation due lack of control of tissue volume and thermal injury due to an inability to control the cutting plane. The inclusion of this recommendation was supported with its rationale considered logical and likely to lead to improved patient safety.

A recommendation advising against the use of conventional snare resection with LNPCPs displaying the 'non-lifting sign' in treatment naïve lesions in response to submucosal injection was supported strongly due to a strong association with deep submucosal cancer by large volume case series. The wording regarding this recommendation was modified following GDG discussion to refer to 'conventional snare polypectomy resection' such as pEMR as the initial proposed wording referring to 'piecemeal endotherapy' was felt to be inaccurate by multiple expert endoscopists within the GDG. Two members asserted that some lesions may be amenable to a hybrid EMR & ESD type technique that may not be en-

bloc for the whole lesion but still result in en bloc removal of the component with difficult lift.

Recommendations about adjunctive thermal ablative techniques such as APC and soft snare coagulation in endoscopic resection were debated at length within the GDG. Despite long standing evidence suggesting a reduction of residual or recurrent tissue on follow-up surveillance with use of APC peri-procedurally on resection margins and small residual areas of polyp, more recent case series have not supported this finding. In addition, there were views within the GDG that APC was inferior to soft snare coagulation despite no current data to support the use of the latter. There were concordant views within the GDG that soft coagulation use was beneficial based on personal experience and it was recognised that a prospective RCT examining its effect was currently recruiting patients in Australia based on encouraging preliminary results. The data supporting APC use was considered more valid than more recent opposing data however, as they included an RCT and assessed the relationship between APC use and recurrence as a primary outcome, whilst opposing data was observational and reported APC efficacy as a secondary outcome. It was therefore felt that the conditions where APC was used in these case series was less likely to be controlled, such as use in unsuitable circumstances. Taking these findings as a whole the GDG were prepared to recommend thermal coagulation use, especially APC use, but to specify its applicability following a full attempt at snare resection on resection margins where no or small fragments of residual tissues remained as opposed to an alternative to snare resection in larger residual areas. The recommendation was strong given the likely benefit and lack of major safety concern with thermal ablative techniques but it was recognised that this was an area where further research was feasible. In addition to the pending soft coagulation RCT, further proposed studies included a large multicentre APC RCT with strict criteria for its use and a head to head comparison between soft-coagulation and APC.

Other initially proposed technical recommendations relating to snare handling and endoscope positioning were withdrawn due to a lack of evidence, no previous prior consensus and ongoing disagreement about their merits. Marking of the snare, prior to closure on a polyp has been advocated as ensuring an appropriate amount of tissue is ensnared, thus reducing the risk of perforation. However this practice was cited by multiple GDG members as inaccurate and potentially dangerous with certain lesions such as

flat LNPCPs and a statement relating to this practice was withdrawn. A statement proposing standardised endoscope positioning with the LNPCP adjacent to the emergence of the snare from the endoscope accessory channel was withdrawn due to criticism that it was overly prescriptive and unnecessary with no established benefit. In addition, a statement supporting the use of prophylactic clip application over the resection area to reduce the risk of post procedure bleeding that was created following a recent RCT advocating its use was rejected as there were concerns over the methodology used in the study. The bleeding incidence reported in the 'clip group' (9%), although lower than the control group, was markedly higher than reported data from other international case series (<5%).

The final recommendations in this section related to adequate visual documentation of the polyp site and allowing identification of this area on further endoscopic or surgical follow-up. These recommendations were strongly advocated as they were considered good practice and were already well established in the UK BCSP. These recommendations were also considered to have specific applicability with LNPCP management. For example, adequate visual documentation was not only considered good practice from a documentation view, it was felt that high quality imaging whether or not endoscopist resection had taken place may allow detailed discussion of further management, e.g. such as within an MDM, and optimise follow up management. In addition, whilst tattoo marking is already established practice, it was felt necessary to explicitly specify tattoo application practice in light of multiple case reports of new and follow-up LNPCP resection compromised by submucosal fibrosis from tattoo application too close to the LNPCP site. In view of this, it was agreed that tattoo marking at a safe distance away from the LNPCP site would limit the likelihood of this occurring and a distance of at least 3cm was recommended in accordance with international opinion (264).

3.5.6) Post procedure

The recommendations in this section sought to provide guidance for the period following the initial endotherapy session and subsequent follow-up. This related to post procedure management, including patient instructions and medication management, and the detection and management of potential recurrence and residual tissue.

Given evidence that patients may present with symptoms of serious complications such as bleeding and perforation over two weeks after endotherapy a recommendation regarding

clear patient information and instructions in the event of alarm symptoms was considered essential. The inclusion of an emergency contact number was also recommended in accordance with JAG guidance, and considered standard practice within the GDG as this may allow for planning for prompt remedial management.

Creating recommendations regarding the recommencement of antithrombotic medications was considered difficult, as with pre-procedure management, due to conflicting evidence regarding the safety of prompt recommencement balanced with the thrombotic risk of delayed recommencement. An example of this was warfarin recommencement which was shown as safe for same day recommencement in one study but was later strongly associated with increased bleeding risk when restarted within seven days in a larger study. In addition, there was conflicting opinion within the GDG regarding optimal timing of recommencement and an acceptance that this may vary on an individual basis. In view of this it was agreed that antithrombotic medication recommencement should be individualised according to patient risk with specialist input in complex cases ideally beforehand to ensure adequate pre and post procedural planning.

With existing international recommendations already suggesting initial endoscopic surveillance follow up post piecemeal LNCP resection within a six month period and strong evidence suggesting that recurrence levels rise markedly after this point, a similar recommendation was strongly favoured by the GDG. There was discussion about whether initial follow-up should take place after either 2-3 months, as favoured by most endoscopists within the GDG, or at six months with available data suggesting similar recurrence rates and additionally, findings of recurrence seen at six months not seen at three months suggesting that a six month period may allow all recurrence to be caught. It was felt that while surveillance endoscopy at too early a stage may not be useful due to likely ongoing inflammation, a finding of high grade dysplasia or concern about malignancy would warrant more prompt follow-up. Recommending follow-up 2-6 months post endotherapy was considered acceptable with this view further strengthened by similar American Cancer Society guidelines.

There was strong agreement regarding the need for recommendations regarding optimal assessment for and management of recurrent/residual tissue. This need was further emphasised by the publication of the CARE study just prior to the commencement of the consensus process demonstrating levels of recurrence much higher than expected in lesions

where complete resection was considered to have been achieved. The use of image enhancement techniques such as NBI, dyespray and magnifying high definition were all advocated by GDG members with evidence demonstrating superiority to conventional white light imaging to support all these modalities. There was disagreement regarding the benefit of taking biopsies from the LNPCP resection scar site on follow-up in the absence of visible recurrence, in spite of evidence suggesting that significant levels of recurrence were detected following biopsy at sites where no visual polyp tissue was observed. There were several GDG comments that the biopsy of healthy looking tissue was not justified and that post inflammatory tissue may be confused with true recurrence. However, following the publication of a large volume case series during the consensus process that recorded almost identical findings, allied to the acceptance that the quality of visual assessment appears to vary between endoscopists as witnessed by the CARE study, and the ease of obtaining biopsies in this scenario, there was eventual support to recommend biopsy assessment.

It was felt necessary to provide guidance about the management of recurrence tissue as this was considered to be a complex scenario especially with large areas of recurrence that may not be amenable to snare resection or APC ablation due to submucosal fibrosis and extensive size respectively. As previously discussed, it was considered desirable to avoid surgery where possible, especially in this scenario, with evidence that endoscopic eradication rates may be above 70% in the appropriate expert setting and reports less invasive options such as ESD may also yield success. Optimal assessment and management was felt to be more likely, with the involvement of an endoscopist experienced in complex NPCP management or preferably using a multidisciplinary network to allow assessment of all management options including endoscopic, surgical and conservative management. This recommendation was justified as being 'expert opinion'.

A preliminary round proposed recommendation regarding the use of APC on recurrent/residual tissue was removed following strong opposition. In the absence of evidence to suggest efficacy in this scenario it was felt that it should not be recommended as a sole therapy for treatment of recurrence of any size and should only be used in conjunction with resection or only after histological confirmation that there is no malignancy in the residual tissue. There was also a concern that recommending the use of APC for recurrent/residual tissue may encourage its use in inappropriate circumstances by less experienced endoscopists rather than referring these cases for more learned opinion.

3.5.7) Surgical Management of LNPCPs

Recommendations on surgical management for the management of LNPCPs were led by the ACPGBI colorectal surgery representatives and finalised by the ACPGB colonoscopy committee. This was also a section with extensive high quality evidence unlike other areas in the guidelines. Despite a preference for endoscopic management in the management of LNPCPs by all parties, it was also considered vital to highlight the importance of surgical management as a potential management option where endoscopic management was not considered technically safe or feasible or where a concern about malignancy existed. This was considered especially important for centres lacking access to more advanced and specialised treatment modalities and supported by extensive high quality evidence demonstrating the efficacy of surgery in this scenario, further strengthened by reports that the level of malignancy found post-surgery in lesions previously considered benign is vastly higher than first thought. There was also strong support by both the GDG and the ACPGBI for recommending laparoscopic surgery over open surgery where feasible in view of extensive evidence demonstrating a markedly improved patient experience terms of pain, return of bowel function, hospital stay and earlier mobility.

A statement recommending laparoscopic assisted endoscopic polypectomy (LAEP) as a management option for LNPCPs considered technically difficult to resect endoscopically was removed following opposition from multiple endoscopists within the GDG. Although thought to allow colonic manipulation for improved access for endoscopic resection, allow for immediate management of complications and malignancy, endoscopists with experience with LAEP suggested that it may in fact complicate resection due to general anaesthetic. In addition, supporting evidence was considered weak and with separate NICE guidelines regarding its use currently in development, this was initially felt to be a more appropriate setting. The ACPGBI however felt that a reference to LAEP was important, on the basis that its consideration as a management option may result in improved multidisciplinary dialogue, and due to increasing case series reporting its successful use. These views were accepted as valid by the GDG and accommodated.

The ACPGBI were also keen to emphasise the role of transanal surgery such as TEMS and TAMIS as primary management for rectal LNPCPs and wanted this described in greater detail after a proposed statement detailing transanal surgery was withdrawn following the

preliminary round. This was only felt to be possible to a certain extent. Whilst it was accepted that transanal surgery is an important management option, the evidence for use of TEMS/TAMIS in benign lesions was considered variable with very few studies showing comparable efficacy when compared with endoscopic studies. Whilst initial data on TAMIS is encouraging, it was argued that there is not as yet enough data to routinely recommend its use with only a single case series of 50 patients currently published. In contrast, EMR is more widely available, with evidence to suggest equal efficacy when allowing for repeat therapy on follow up and fewer complications (77, 217). In addition, even when allowing for repeat endoscopic sessions it is cheaper and is therefore may be considered more cost effective (56, 249). In addition, in the context of lesions where there is no suspicion of malignancy, expert opinion within the GDG was that en-bloc resection is not essential. The GDG felt that in view of these factors, transanal surgery could not be recommended routinely as first line management for benign lesions but did specify it is a viable option, especially where en-bloc resection is desirable or where lesion characteristics make successful endoscopic snare resection technically difficult, such as with extensive soft 'carpet-like' villous lesions that are difficult to adequately capture with a snare. There was a concern that the exclusion of specifying transanal surgery from the guidelines would introduce bias. Strong opposition to this modality was registered by GDG endoscopists who perform ESD, another mode of obtaining en-bloc resection. It could be argued that ESD endoscopists may receive fewer referrals by the recommendation of transanal surgery within these guidelines. It was therefore considered important to ensure that transanal surgery was specified as a management option. This was achieved with a summary of available opinion and evidence within the supporting text of an existing statement about surgical management for LNPCPs, with this approach accepted by the ACPGBI.

The ACPGBI were strongly supportive of the guidelines overall, with strong representation of their membership on the GDG. They did however raise several considerations they felt required greater attention in addition to their views on LAEP and transanal surgery. A main concern was that there was sufficient distinction between colonic and rectal lesions in view of differing surgical management in these areas and the availability of transanal surgery for rectal lesions.

This was clearly an important consideration with resectional surgical management considered less of a concern for colonic than with rectal lesions where it would be avoided if possible with benign lesions due to:

- the complexity and morbidity associated with both open and laparoscopic surgery in the rectum
- the potential for requirement of a permanent stoma (e.g. with non-sphincter saving surgery such as an abdominoperineal resection (APR) in the management of low rectal lesions)
- the potential for less invasive full thickness transanal surgery for rectal lesions.

Their final concern was the support for the use of a complex polyp MDT for lesions identified in the guidelines as 'complex'. Whilst they felt that this was an ideal scenario and that they supported discussion prior to management in this scenario, they were concerned that it may not be feasible in many centres where the infrastructure is not in place for a new meeting and clinicians may face time-pressures limiting their ability to participate in another MDM in addition to the colorectal cancer (CRC) MDT. Their position was that in this scenario the existing CRC MDT was a sufficient discussion forum as a complex polyp MDM providing a therapeutic endoscopist was in attendance. Whilst there was strong support within the GDG for a dedicated polyp meeting, primarily due to a concern that LNPCPs are often not be prioritised for sufficient detailed discussion in a CRC MDT meeting due to the absence of malignancy and the existing CRC service pressures, the ACPGBI's stance was recognised as valid, particularly as it was anticipated that specifying a complex polyp MDM would prove controversial on dissemination of the guidelines due to the concerns raised above. In view of this, a compromise was made in terms of an acceptable multidisciplinary forum for LNPCP discussion with the wording in the guidelines was amended accordingly.

3.6) External consultation process

Ensuring that these guidelines were seen as generic management guidelines as opposed to solely endoscopic guidelines was important given the various non endoscopic management options available. In view of this, the guidelines were sent for consultation by the ACPGBI at multiple stages in addition to the BSG, as their endorsement would enable this.

The initial responses from the BSG (BSG endoscopy committee and appointed reviewers) and ACPGBI were strongly positive. The consensus process was considered valid, extensive, well referenced and likely to improve LNPCP management.

More specific comments from the BSG reviewers pertained to detail felt to be missing, limited or requiring greater clarification. A response to the reviewers was required to display additional content and clarification in subsequent drafts as well as justify content in areas where the GDG did not agree with reviewer comments.

An initial observation was that the GDG panel could be perceived as 'endoscopist heavy' with more endoscopists on the GDG than from other specialties. However, BSG Guidance on guideline development had been followed with the recruitment of GDG members with a group felt to reflect the key multidisciplinary stakeholders routinely involved in the management of these lesions that are presumed benign until proven otherwise. The GDG consisted of endoscopists (both expert and referring endoscopists), management, colorectal surgeons who are also advanced endoscopists, a patient representative and a GI histopathologist. That there are a larger number of endoscopists as part of the GDG is perhaps a reflection of the fact that the majority of these lesions are managed endoscopically. In addition, a response was given that guidelines had been written in conjunction with the ACPGIB, who nominated the 2 surgeons on the panel and had no concerns over the composition of the committee. The fact that the GI histopathologist was nominated by the Royal College of Pathologists was felt to further strengthen the multidisciplinary credentials of the guidelines.

It was apparent from the feedback from the BSG reviewers that the GRADE tool used to assess the quality of a recommendation required clarification. Multiple reviewers questioned why there was often a disparity between the strength of evidence and the strength of recommendation for a recommendation statement/parameter.

However clarification that the GRADE system was now increasingly used to evaluate scientific evidence due to an ability to allow evaluation to be made based on the both strength of evidence and the strength of a recommendation, therefore allowing recommendations to be made where there appeared to be good sense in spite of the absence of high quality scientific evidence, was accepted (261).

The number of recommendations for where the strength of supporting evidence was recorded as 'low' or 'very low' was also seen as a potential weakness of the guidelines by one reviewer. However, it was countered that the nature of LNPCP management is that it is an area with a large amount of evidence from observational studies and limited evidence resulting from RCTs whilst there are many areas within this field where conducting RCTs

may not be feasible. It was argued that although many of the international series regarding LNPCP management were classified as observational studies and as such given a low strength of evidence grading, the studies were considered to be from high quality centres, were of high importance, made good sense and were unlikely to be disproved by further work and could therefore warrant a strong recommendation. It was also stated that the GRADE system was applied very strictly to emphasise how robustly available evidence was analysed and that several GRADE recordings may in fact warrant stronger evaluation scores and recommendations than originally given.

Another issue raised by the reviewers related to the role of histopathology in the management of LNPCPs which was not felt to be adequately covered in the draft guidelines. Specific questions felt to be unanswered included:

- Important histopathological reporting considerations and minimal reporting guidance for LNPCPs
- Why the use of existing histological grading systems such as the Kikuchi system were not recommended.
- The role of the histopathologist in LNPCP management, including in the multidisciplinary setting such as a complex polyp MDT/MDM

These comments were important in ensuring the detailing of important histopathological considerations in the management of LNPCPs in subsequent revisions of the guidelines. It was important to highlight that the guidelines refer to lesions presumed benign at the time of assessment and lacking histopathological evidence of malignancy. This was asserted in the introduction section with review of the ACPGBI position statement on malignant polyps and the NICE colorectal cancer guidelines advised in the event of a finding of malignancy. Discussion between the GDG took place in light of the reviewer comments, led by the GI histopathology representative, the lead author of the recent Royal College of Pathology Colorectal Cancer guidelines. Whilst important, histopathology was felt to have a less significant role in the management of benign polyps than in the management of malignant polyps. Although pathological assessment, including depth of invasion (by Haggitt level, Kikuchi level, and quantitative measures), differentiation, lymphovascular invasion, tumour budding etc. are all considered important in consideration of subsequent management of malignant regions, these features were not considered relevant in the context of benign lesions. This view was supported by the ACPGBI and the GDG considered justification for

this position strengthened by BSG recommendations for colonoscopy surveillance intervals for completely excised benign polyps, where only the number and size of adenomas influences follow-up management and dysplasia grade and villousness are not considered. This was felt to further limit the role of histopathology in the management of LNPCPs with the main histopathological considerations for LNPCPs felt to be:

- Judicious use of targeted biopsies: Recommended only when there is suspicion of malignancy in a LNPCP, to help ensure endotherapy is not compromised.
- Awareness of significant potential for under calling of malignancy in the endoscopic biopsy setting.
- In polypectomy evaluation, confirmation of the adenomatous nature of the polyp and confirmation of benignity i.e. exclusion of adenocarcinoma arising within the adenoma
- Emphasising the distinction between invasive neoplasia and so-called 'epithelial misplacement'.
- Assessment of adenoma subtype according to WHO 2010 classification as tubular, tubulovillous, villous or traditional serrated.
- Assessment of grade of dysplasia/neoplasia using a two tier system.
- Assessment of margin involvement by dysplasia, where possible, in accordance with the nature of the specimen received (en-bloc or piecemeal) and endoscopic correlation regarding completeness of excision. (253, 265)

With regards to the multidisciplinary role of a histopathologist in LNPCP management, including a complex polyp MDM, it was felt that histopathological input could be delivered equally effectively via the existing colorectal MDT meeting or during a specialised benign polyp MDM, either during, pre or post meeting in person or via other secure communication such as encrypted email or teleconferencing. The allowance for a histopathologist not to be present during a complex polyp MDM was felt to be reflective of the reduced input of histopathology when compared with malignant lesions.

A concern about the lack of reference to the use of radiological modalities was also specified. The GDG countered that whilst it was recognised that radiological input may be warranted in certain cases, such as where there is difficulty in determining whether a lesion is benign or malignant (e.g. the use of MRI for a large rectal lesion). It was also felt that the proportion of cases where radiological investigation changes management of LNPCPs was

low. In addition, it was argued that proposing routine radiological investigation in the absence of regular benefit could not be considered cost-effective and these factors supported a view that radiological input was therefore not considered essential in routine assessment but suggested for consideration on a case by case basis. It was also specified that a proposed recommendation statement regarding the use of radiological modalities was withdrawn with but it accepted that that a reference to radiological input was warranted with the GDG's position specified in content regarding multidisciplinary team management.

Additional comments advised the inclusion of more practical and technical advice for endoscopic practice in complex situations. An example included LNPCPs crossing the dentate line which were cited as potentially painful to resect due to the innervation in this area and often more difficult to remove due to the difficulty in obtaining a stable endoscopic position for resection. Instructions regarding the use of local anaesthetic (lignocaine) and using the retroflexed position were subsequently added.

A final concern was that considerations for follow-up of large lesions had not been addressed initially. Clearly this was an important consideration requiring inclusion and the GDG position that follow-up should be in line with existing BSG guidelines for polyp follow-up following specific lesion clearance assessment follow-up was subsequently recommended.

Following suitable amendments as specified above and the return of a response document outlining the GDG's responses and position on the BSG reviewers' comments, the BSG and ACPGBI formally approved the guidelines with a recommendation for submission to 'Gut' journal, the official journal associated with the BSG. The guidelines were subsequently accepted for publication. This marked the completion of a long process complicated by the need to satisfy all concerned parties. It can be concluded that these are the world's first comprehensive genuinely multidisciplinary guidelines for the management of LNPCPs. It is anticipated and hoped that these guidelines will readily provide evidence based information and expert opinion on the optimal assessment and management of large non-pedunculated colorectal polyps (LNPCPs) for all clinicians involved in their care to improve management. It is also hoped that the guidelines will act as a reference to guide further research in this field and provide a template for training in LNPCP management. The

intended target audience includes gastroenterologists, nurse practitioners, physicians, colorectal surgeons, radiologists and pathologists.

Whilst it must be accepted that there is a paucity of evidence within this field considered to be of the highest scientific quality evidence such as large multicentre RCTs and meta-analyses, these guidelines comprehensively reference and summarise the available evidence and opinion in this field and appear to be a marked improvement on previous resources for LNPCP management. This is confirmed by acceptance and publication in a high impact international journal.

Chapter 4: Development of Key Performance Indicators for the Management of Large Non-Pedunculated Colorectal Polyps

4.1) Measures of Quality in Healthcare

In light of healthcare performance considered to be substandard both nationally and internationally, a means of improving healthcare performance has been sought on a worldwide basis. The need to improve public safety and ensure cost effectiveness of healthcare services to allow continued provision is paramount, along with the objective of improving public confidence in the face of increasing expectations (266, 267)

There has been a drive for improved standards internationally following cases of substandard care. A US report estimated the incidence of mortality relating to medical error to be 44 000–98 000 cases per year whilst an Australian study found that 16.6% of hospital admissions were associated with an adverse event. In the UK, the recent reports regarding care at the Mid Staffordshire Hospitals have also been followed with calls for improved standards (268-270).

Key aims of the provision of high quality healthcare and healthcare improvement measures include:

- Improving patient safety
- Improving public confidence in healthcare
- Improving standards of healthcare uniformly to all service users
- Providing a more cost-effective service

A critical strategy in improving standards has been the creation of targets and standards across a variety of disciplines relating to both the infrastructure of services and clinical performance to enhance both efficiency and performance. The aims of targets include:

- Motivation of various centres towards a common goal
- Achieve agreement regarding the priorities and expectations of setting targets and standards
- Setting a benchmark and allowing a means to measure and monitor progress
- Communicating to stakeholders about the priorities and expectation of services
- The ability to make decision makers accountable (267, 271)

Applying standards across different regions or even internationally may prove difficult. This has been reported to be the case in countries such as the USA where healthcare may be regulated separately from state to state and provided by various private insurance companies between which competition for subscribers exists. In the UK however, where a centralised NHS service exists, a partnership to apply key targets and standards may be easier to achieve. In view of this, where widespread national and international implementation of standards is applied, clear definitions are required with standards applicable to all stakeholders (268).

Quality healthcare has been defined as care based on assessed needs using finite resources efficiently to raise standards and reduce risks associated with management whilst also being a continuous process (see below) (272)

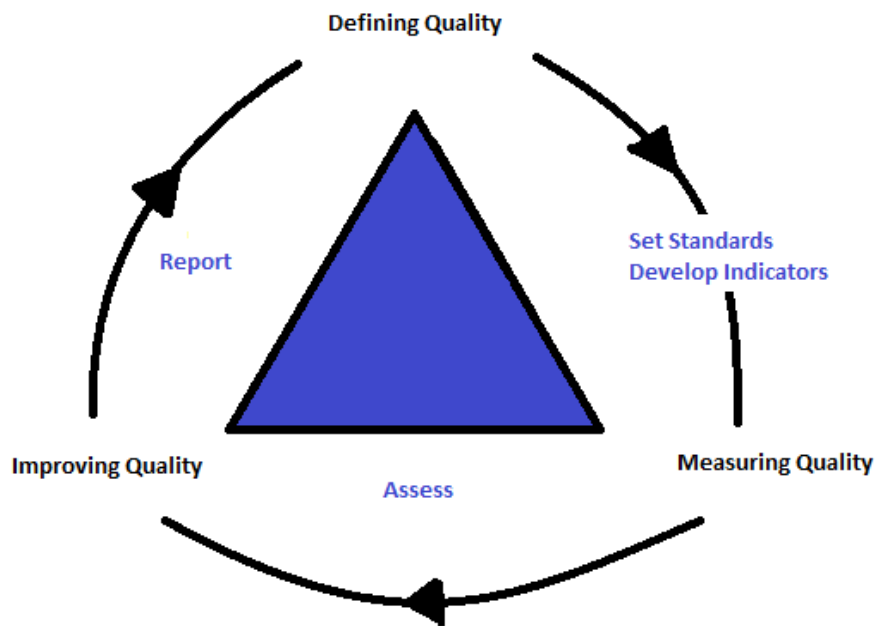


Figure 14. Quality Assurance Triangle Model (273)

Donabedian et al proposed a 3 part model of assessing healthcare quality:

- Structures- The resources of a healthcare system to the population needs
- Processes- What is done to improve care (e.g. indicators that measure compliance)
- Outcomes- The results of care such as safety and change in the quality of life (274)

4.2) Key Performance Indicators

Key performance indicators (KPIs) are specific measurable elements of care provision that can be derived from Donabedian's model, set either via evidence from a literature review or via an expert based consensus. The data used to support KPIs is standardised and the utilisation of KPIs as performance measurement tools have been proposed as a clear, defined and structured method of delivering improved health policy through the setting of targets and standards. In many cases, KPIs are considered essential in the setting of

standards, monitoring and evaluation of performance and enacting improvement in healthcare services with the benefits felt to markedly outweigh potential drawbacks (266).

The potential benefits of setting targets include:

- The collection of high quality data allowing meaningful feedback
- Setting a benchmark to aim for and encouraging improvement
- The identification of underperformance, allowing remedial measures
- The increased communication and engagement of service providers regarding key objectives
- Improving patient safety
- Improving public confidence in healthcare services

Potential drawbacks of targets include:

- Undermining confidence in underperforming centres
- Avoidance by centres in managing high risk cases to improve figures
- Possibility of overlooking the needs of stakeholders in order to meet targets (275)

The possibility of centres avoiding management of higher risk cases has been a significant concern however this does not appear to have occurred in previous examples where performance measures have been introduced (276).

A current example of the use of KPIs in the UK is in the monitoring for endoscopy standards within the NHS Bowel Cancer Screening Programme for both delivery of service and clinical outcomes (2).

Within this context KPIs have allowed high quality recording of performance data providing the public, service users and healthcare providers reliable information about current and desired standards by allowing meaningful comparison between different centres in relation to stated objectives and targets (277).

The establishment of compulsory standards may raise standards with a focus and aspiration by centres to match or better defined minimum standards or those from other centres. The ability for service users to choose a treatment centre may also act as an incentive to raise standards (278).

When defining KPIs it is considered essential to identify aspects of healthcare delivery that require measurement. These are termed 'domains of quality'. Lester and Roland asserted that these domains should incorporate the following characteristics:

Safety: The minimisation of risk to service users

Effective: The best achievable outcomes are sought

Person Centred: A focus and respect for the needs of patients

Equitable: Fair access to care based on need and addressing health inequalities

Efficient: Best possible use of resources to provide care (279)

KPIs may be subdivided as either **generic** (relevant to the majority of the population and not to a specific service user group, e.g. accident and emergency waiting times) or **specific** (relevant to a specific service user population, e.g. children's accident and emergency waiting times). KPIs may also be classified according to their function (e.g. screening, diagnostic, intervention and follow-up). Many factors may be used when considering the finalisation of a KPI (see below).

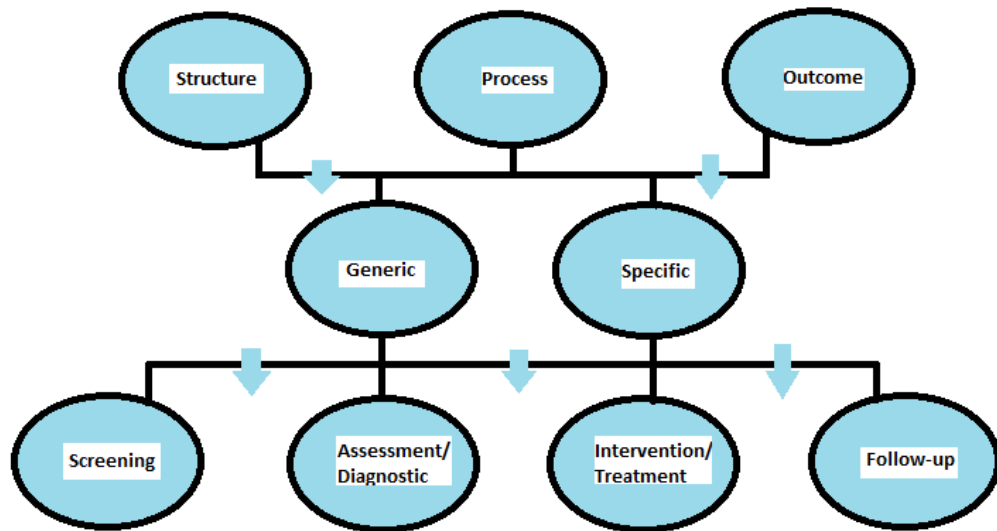


Figure 15. Factors associated with KPI development (267)

A number of additional factors appear important when developing robust KPIs:

4.2.1) Definitions and Data quality

The quality and uniformity of data collected depends on clear definitions and checks to ensure accurate data collection. If this is not the case then data will not be robust enough to set a benchmark for performance.

4.2.2) Service user profile

Variations in the profiles of patients such as sex, age and co-morbidity may affect outcomes and the design of KPIs must reflect this to ensure that these factors do not inadvertently affect outcomes.

4.2.3) Data availability

The creation of KPIs must reflect what is felt to be likely to contribute to service improvement and this may help to identify gaps in data availability. KPI should not be solely

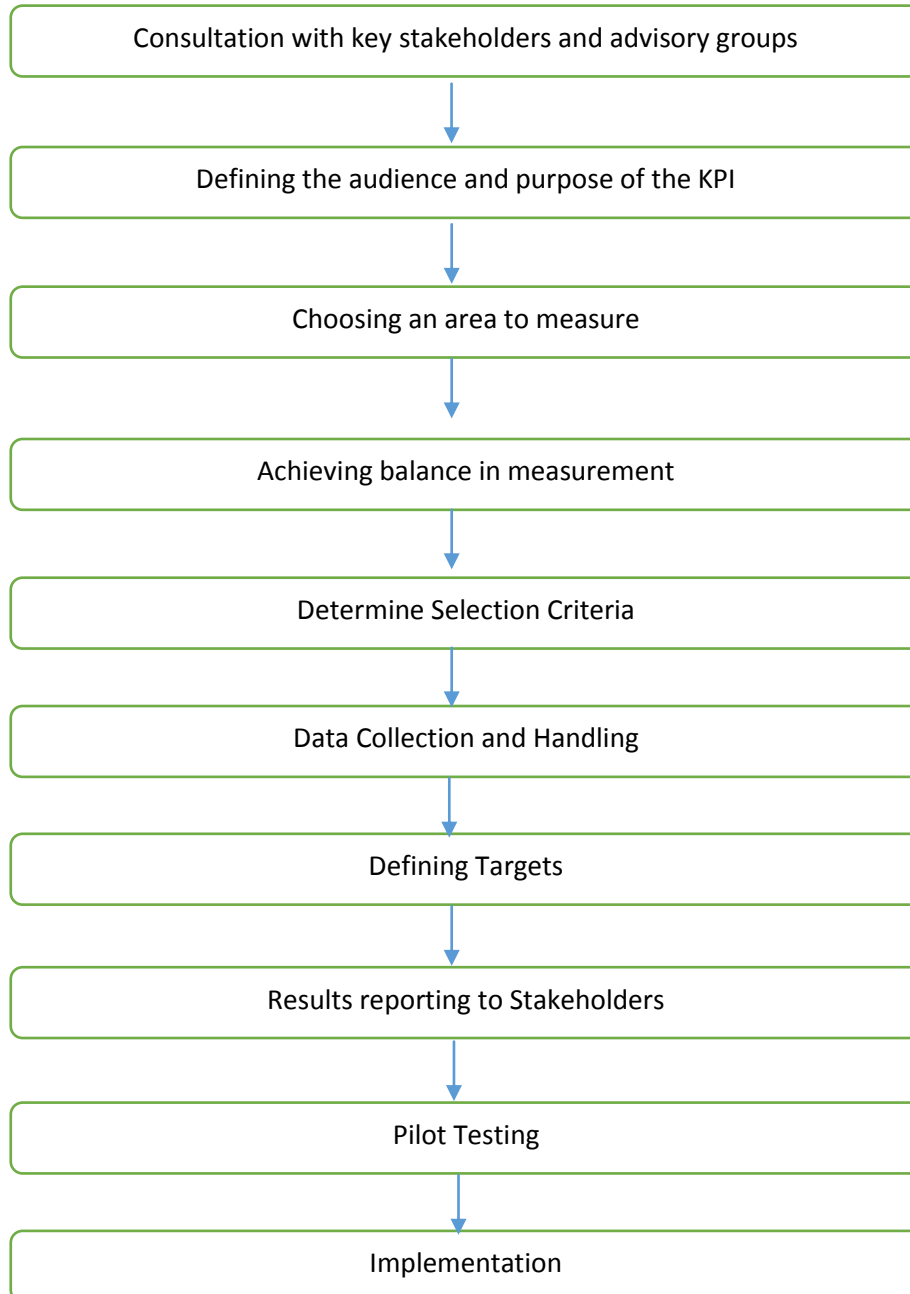
dependent on what data is available as may result in measures that do not result in improved standards.

4.2.4) Local application of KPIs

Variation in healthcare funding and provisions between different regions may affect the performance of certain centres negating the possibility of meaningful comparison and setting a benchmark. This suggests the importance of set KPIs being relevant across all regions and not diverting resources away from frontline healthcare services. Ensuring equal awareness of KPIs across various regions may also help to more uniform uptakes of new measures.

4.3) KPI development process

A proposed structure for the development of KPIs is described below(280-282):



4.3.1) Consultation with key stakeholders and advisory groups

Consultation with all key stakeholders and advisory groups using a multidisciplinary group throughout the process may help to ensure that the needs of all parties (e.g. patients and health providers) are met whilst improving the likelihood that the chosen KPI is of sufficient quality. Consultation also enables agreement to be made about particular elements of a KPI, familiarises all groups with data and standards and may improve public confidence in the standards developed (283).

4.3.2) Defining the audience and purpose of a KPI

It is important to determine what the KPI is intended to achieve prior to formulation and the audience for whom decision making will be influenced by the indicator. Selecting the appropriate domains will help to structure KPI formation and may be influenced by the target audience (283).

4.3.3) Choosing an area to measure

Patient safety is regarded as the most important domain whilst other important considerations include the importance of a particular problem, the likelihood that improvements can be made and the extent to which a variable is controllable by a healthcare provider and patient (283).

4.3.4) Achieving a balance in measurement

Kaplan and Norton proposed a 'balanced scorecard' which gives 4 factors a KPI should incorporate to ensure that it is comprehensive. These include the patient perspective, the key business factors that have been identified as necessary to provide best management, the ability to measure an organisation's ability to improve and the financial perspective to ensure management is as cost effective as possible (284).

Validity	Does the KPI measure what it is supposed to measure?
Reliability/Reproducibility	Does the KPI provide a consistent measure in the same population and settings irrespective of who performs the measurement?
Explicit evidence base	Is the KPI supported by scientific evidence or the consensus of experts? Has the evidence used been scrutinised for rigidity using a system such as the GRADE tool.
Acceptability	Are the KPIs acceptable to both those being assessed and those undertaking measurement?
Feasibility	Has feasibility analysis taken place and is it possible to collect the required data and is it worth the resources?
Sensitivity	Is the KPI capable of detecting changes in quality of care and reflect these in the results?
Specificity	Does the KPI actually capture changes that occur in the service for which the measure is intended?
Relevance	What useful decisions can be made from the KPI?
Balance	Do we have a set of KPIs that measure different aspects of the service, providing a comprehensive picture of performance?
Tested	Have previous national and international KPIs been considered? There should be a preference for indicators that have been previously tested both nationally and internationally over developing new indicators for the same purpose.
Safety	Will an undue focus on the KPI lead to potential adverse effects on other aspects of quality and safety?
Avoidance of duplication	Has consideration been given to other projects or initiatives to avoid duplicating work?
Timeliness	Is the information available within an acceptable period of time to inform decision-makers?

Table 8. WHO criteria used to assess rigidity of KPIs (285)

Another proposed framework is the '3 Es' model citing economy (using the appropriate quantity and quality of resources at the lowest cost), efficiency (providing quality healthcare with minimum cost) and effectiveness (the degree to which an organisation attains stated goals) as domains (267).

4.3.5) Determine selection criteria

KPIs formulated either by a review of evidence or expert consensus may be tested for rigidity using criteria developed by the World Health Organisation (see table 8):

4.3.6) Data Collection and Handling

Identifying data sources is a key consideration. It needs to be established whether newly created KPIs can be assessed using available data or whether additions or modifications to data collection need to be made. This is part of developing a minimum dataset (the minimum information required to adequately measure and use a KPI). There are also important issues regarding data collection and storage with the use of information governance required to ensure the legal and ethical handling and use of data whilst measures must be in place for data quality checks to verify compliance and the accuracy of the data (267).

4.3.7) Defining Targets

Defining quantitative minimum standards and targets may be determined either via a review of the evidence base or via expert consensus. Other considerations include the threshold for undertaking remedial action when standards are not met in addition to the sanctions for substandard performance (267).

4.3.8) Results Reporting to stakeholders and pilot testing KPIs

'Pilot testing' KPIs appears important before widespread implementation to ensure that there are no validity issues in relation to the KPI. These include ascertaining whether there are any data validity and collection issues, whether the KPI contributes to improved care and whether modifications need to be made.

4.3.9) Implementation

Once the previous considerations have been satisfied, the KPI may be considered for widespread implementation (267).

4.4) Why are LNPCPs suitable for KPIs?

In the absence of a framework for the management of LNPCPs there have been no clear indicators with regards to the management of these lesions both nationally and internationally. Moreover, with evidence that quality outcomes appear to vary markedly even between experienced endoscopists with larger polyps, a potential for serious harm to patients in the event of suboptimal management, and a large proportion of endoscopists lacking formal training in LNPCP management, it appears justified to hold the view that general standards are suboptimal and that this may compromise patient safety.

4.4.1) Is the problem important?

Yes, colorectal cancer is the second most common cause of cancer death in the UK with 90% of cases due to adenomatous polyps, especially LNPCPs. There is as yet no framework for their management, an issue highlighted by many endoscopists as a cause for concern in a recent large UK survey (4).

4.4.2) Are there public safety concerns?

Yes, complications related to advanced endoscopy techniques involve death, bowel perforation and haemorrhage, the latter two occurring in approximately 1% and $\geq 3\%$ respectively and commonly requiring surgical intervention (5, 9). There is strong evidence to suggest that certain lesions are associated with an increased complication rate. Surgical management is associated with 20% morbidity and 1% mortality (11).

4.4.3) Is there evidence to suggest practice is suboptimal?

Yes, the CARE study showed marked variation in outcomes between different endoscopists whilst figures from the BCSP suggested incorrect management (e.g. piecemeal resection of malignant lesions) occurred at higher levels than previously thought (17, 20).

4.4.4) Is there evidence to suggest practice can be improved?

Yes, there is evidence to suggest that careful assessment and stratification of LNPCPs with management in the appropriate setting has led to superior outcomes with fewer complications and patients undergoing minimally invasive procedures (5). There is also evidence that the use of training modules (NBI and NICE NBI) have led to improved lesion recognition, a key component of LNPCP management, even by inexperienced practitioners (128).

4.4.5) Can management become more cost effective?

Yes, there is both national and international data showing large cost savings in terms of procedure costs and length of hospital stay in the appropriate management setting (e.g. there is estimated to be a cost saving of approximately \$6000 with endoscopic resection compared to surgical removal) (10, 56).

Consideration of these factors suggest that the management of LNPCPs in an area where the development of KPIs is warranted. Access to high quality data with regards to performance will allow accurate benchmarking, encourage improvement and indicate where improvements need to be made, in a reliable consistent manner across all participating centres.

4.5) Methodology

A modified Delphi Technique was the mode of consensus methodology used. A guideline development group with a writing subcommittee created, as described in chapter 2, suggested various search terms for a comprehensive literature review as below. The term 'colonic polypectomy' was entered into the PubMed MeSH database. 5989 articles were returned. The terms 'therapy' , 'analysis', 'complications' and 'prevention and control' were used to filter the results based on relevance following which, 2716 articles were returned and scrutinised for relevant articles. Additional PubMed searches were performed using additional search terms agreed by the writing sub-committee. The search terms used were:

'colorectal laterally spreading type polyps', 'endoscopic mucosal resection', 'complex colonic polyps', 'difficult colonic polyps', 'complications related to endoscopic polypectomy', 'endoscopic polypectomy', 'recurrence post endoscopic polypectomy', 'anticoagulation in endoscopic polypectomy', endoscopic mucosal resection', 'malignant colonic polyps', 'piecemeal endoscopic mucosal resection', 'colorectal endoscopic submucosal dissection', 'key performance indicators in healthcare' 'key performance indicators in endoscopy' and 'healthcare improvement measures'

Returned abstracts and articles were reviewed for relevance with additional references obtained from cross-referencing of references and recommendations from the GDG.

Relevant quality assurance publications were searched for from groups such as the British Society of Gastroenterology (BSG), the American Society of Gastrointestinal Endoscopy (ASGE), The NHS Bowel Cancer Screening Programme (NHS BCSP) and the European Society of Gastrointestinal Endoscopy (ESGE).

Following a review of returned international literature, including the types of outcomes reported, a suitable structure was devised for the development of KPIs with regards to the development of domains and parameters suitable within these domains. Outcomes both optimal and adverse, and factors linked to improved/adverse outcomes were felt to be key in the identification of both potential domains and KPIs and reference points for review by the wider GDG were identified based on this. The agreed reference points were to focus on patient safety, quality of management, avoiding unnecessary delay in management, quality of decision-making processes and the ensuring of regular practice to maintain competency.

A preliminary round was conducted where these reference points were sent to the GDG who were asked to vote anonymously to record their level of agreement with their use to guide the development of domains and supporting parameters. At all points throughout this process, consensus was defined as GDG agreement $\geq 80\%$.

Following receipt and review of all responses, provisional domains and KPIs with supporting literature and rationale, both evidence based and reflecting GDG comments, were created and included in a formal voting document for consideration by the GDG. A summary of domains, KPIs and supporting rationale is displayed below. The full feedback was disseminated among group in an anonymised form prior to the formal voting round. The GDG were subsequently sent the formal voting document via email and were asked to vote, recording their level of agreement with the proposed KPIs using the process described in

chapter 3. A deadline of two weeks was given to GDG members to return their voting documents.

A second voting round was conducted for KPIs where consensus had not yet been reached at a scheduled group meeting in March 2014 where there was also an agenda to finalise the wording and vote on the identification and formulation of quantitative standards of agreed KPIs.

Prior to the group meeting, a full anonymised summary of voting and comments from the first formal voting round was sent to all GDG members for consideration prior to the second round of voting where they would be asked to consider their initial responses.

In addition, the GDG conducted a detailed review of outcomes relevant to the identified KPIs from available international large volume series reporting outcomes in the management of LNPCPs. These outcomes were identified with the intention of their use as a reference for formulating quantitative standards for finalised KPIs.

The group meeting took place at the BSG headquarters with Professor Rutter as chairperson and all voting taking place using anonymous keypad voting.

On finalisation of the KPIs, voting then took place for the formulation of quantitative minimum and desired standards where appropriate.

Discussion took place individually for each KPI, and where available, relevant identified outcomes from international case series (e.g. post-procedure bleeding rate of 5%) were reported to the GDG for consideration in identifying a quantitative figure. Newly created standards were to be created reflecting the fact that reference data used was from expert centres. Participants were able to set a standard of an 'auditable outcome' as opposed to an exact figure, where it was felt that there was insufficient evidence to identify a specific

standard. All voting on proposed standards took place using anonymous electronic voting. In cases where consensus had not been reached, further discussions took place prior to repeat voting until consensus was reached.

Following the finalisation of KPIs with minimum standards, a draft summary document was created outlining the domains, KPIs, standards, supporting evidence and action plans in the event of underperformance. The 2011 NHS BCSP Endoscopy Quality Assurance Standards document was referenced when structuring the document as quality standards in BCSP endoscopy are well established nationally.

The document was then circulated to the GDG for final comments before being sent to the BSG endoscopy committee and ACPBI for consultation prior to international consultation and submission to 'Gut' journal.

4.6) Results

Domain	Proposed KPIs
1. Optimal decision-making	<ul style="list-style-type: none"> • Surgery rate for LNPCPs
2. Endoscopic skill	<ul style="list-style-type: none"> • Recurrence/residual polyp at 12 months in endoscopically managed LNPCPs
3. Safety	<ul style="list-style-type: none"> • Perforation rate • Post-procedure bleeding rate
4. Timeliness	<ul style="list-style-type: none"> • Time from diagnosis to referral for definitive therapy • Time from referral to definitive therapy
5. Volume of procedures	<ul style="list-style-type: none"> • Number of procedure per endoscopist per year

Table 9. Summary of agreed domains and KPIs for LNPCP Management

4.6A) Voting Summary

4.6.1) Optimal decision making

Objective	Assessment of the appropriateness of decision-making in the management of LNPCPs
KPI	<u>Surgery rate for LNPCPs</u>
Denominator	Inclusion of all patients with NPCPs, including lesions that prove to be cancers Exclusion of patients with LNPCPs undergoing primary surgery for cancer (where no endoscopic resection has been attempted). Do not exclude patients with cancers that undergo endoscopic therapy.
Numerator	Patients with LNPCPs undergoing surgery for that lesion
Frequency	Annual
Level of Analysis	Service level
Minimum standard	No current standard defined
Aspirational standard	No current standard defined
Action	Qualitative review of each case
Evidence	Swan et al. Gastrointest Endosc 2009, 70: 1128-1136 (10) Longcroft-Wheaton et al. Dis Colon Rectum 2013, 56: 960-966 (56) Bertelson et al. Dis Colon Rectum 2012, 55: 1111-1116 (11) Lee et al. Br J Surg 2013. 100: 1633-1639 (17) Moss et al. Gastroenterology 2011. 140: 1909-1918 (5) Buchner et al. Gastrointest Endosc 2012, 76 : 255-63 (9)
Consensus Summary	<u>Level of Agreement for KPI: 91.7%</u> <u>Level of Agreement for Standard: 92%</u>

4.6.2) Endoscopic skill

Objective	Assessment of endotherapy success
KPI	Recurrence/residual polyp at 12 months in endoscopically managed LNPCPs
Denominator	Include all patients with recurrence/residual polyp at 12 month surveillance following resection of LNPCPs.
Numerator	Patients undergoing 12-15 month surveillance with endoscopic or histological evidence of polyp recurrence at the site of resected LNPCP
Frequency	Calculate annually
Level of Analysis	Individual colonoscopist and service level
Minimum standard	<10%
Aspirational standard	<5%
Action	Qualitative review of each case
Evidence	<p>Supporting Evidence: Belberbos et al. Endoscopy 2014, 46: 388-400 (146) Moss et al. Gastroenterology 2011, 140: 1909-1918 (5) Barendse et al. Colorectal Dis 2012, 11: e191-196 (77) Khashab et al. Gastrointest Endosc 2009, 70: 344-349 (199) Knabe et al. Am J Gastroenterol 2014, 109: 183-189 (200)</p> <p>Supporting Evidence for Quality Standard: Lee et al. Br J Surg 2013, 100: 1633-1639 (6%) (17) Longcroft Wheaton et al. Dis Colon Rectum 2013, 56: 960-6 (3.9%)(56)</p>
Level of Consensus	<p><u>Level of Agreement for KPI: 100%</u></p> <p><u>Level of Agreement for Standard: 100%</u></p>

4.6.3) Safety

Objective	To maximise the safety of endoscopic therapy
KPI	1) <u>Endotherapy perforation rate</u> 2) <u>Post-polypectomy bleeding rate</u>
Definitions	<p>Perforation defined as: ‘air, bowel contents or instrumentation outside the bowel lumen’ (2, 286)</p> <p><u>Post Procedure Bleeding</u> defined as:</p> <p>Rectal bleeding within 30 days of procedure resulting in any of the following:</p> <ul style="list-style-type: none"> • Minor <ul style="list-style-type: none"> - Procedure aborted - Unplanned post procedure medical consultation - Unplanned hospital admission, or prolongation of hospital stay, for ≤ 3 nights • Intermediate <ul style="list-style-type: none"> - Haemoglobin drop of $\geq 2g$ - Transfusion - Unplanned admission or prolongation for 4–10 nights - ITU admission for 1 night - Interventional procedure (endoscopic or radiological) • Major <ul style="list-style-type: none"> -Surgery - Unplanned admission or prolongation for > 10 nights -ITU admission > 1 night • Fatal <ul style="list-style-type: none"> -Death (2)
Denominator	Include all patients with LNPCPs undergoing endotherapy
Numerator	Patients with LNPCPs undergoing endotherapy who present with a perforation (definite or probable) within 30 days of endotherapy

Frequency	Calculated at least annually.
Level of Analysis	Service and Individual colonoscopist level
Minimum standard	EMR: Perforation: <2% PPB: <5% ESD: Perforation & PPB: No current standard defined
Aspirational standard	EMR: Perforation: <0.5% PPB: No current standard defined ESD: Perforation & PPB: No current standard defined
Action	Qualitative review of each case
Evidence	Supporting Evidence- Perforation: Rutter et al. Endoscopy 2014, 46: 90-97 (101) Rabeneck et al. Gastroenterology 2008, 135: 1899–1906 (66) Nivatongs. Dis Colon Rectum 1986, 29: 825-830 (287) NHS BCSP Publication 2011 (2) Lee et al. Br J Surg 2013. 100: 1633-1639 (0.5%) (17) Moss et al. Gastroenterology 2011, 140: 1909-1918 (1.3%) (5) Buchner et al. Gastrointest Endosc 2012, 76 : 255-63 (0.4%) (9) Longcroft-Wheaton et al. Dis Colon Rectum 2013, 56: 960-966 (0.45%) (56) Supporting Evidence- Post-Procedure Bleeding: Metz et al. Endoscopy 2009, 43: 506-511 (98) Sawhney et al. Endoscopy 2008, 40: 115-119 (112) NHS BCSP Publication 2011 (2)
Level of Consensus	Endotherapy Perforation Rate <u>Level of Agreement for KPI: 100%</u> <u>Level of Agreement for standard: 92%</u> Post-polypectomy bleeding rate <u>Level of Agreement for KPI: 92.3%</u> <u>Level of Agreement for standard: 85%</u>

4.6.4) Timeliness

Objective	Provide a timely service and minimise delay in cancer diagnosis and treatment
KPI	1) <u>Time from detection to referral for therapy</u> 2) <u>Time from referral to definitive therapy</u>
Denominator	Inclusions: Include all patients with LNPCPs Exclusions: Exclude LNPCPs removed at the time of detection
Frequency	Calculate annually
Level of Analysis	Service Level
Minimum standard	Time from diagnosis to referral: <4 weeks (28 days) - No current standard defined for proportion meeting this standard Time from referral to definitive management: <8 weeks (56 days) - No current standard defined for proportion meeting this standard
Aspirational standard	No current standard defined
Action	Review cases where time from diagnosis to referral is >4 weeks (28 days) Review cases where time from diagnosis to referral is >8 weeks (56 days)
Evidence	Muto et al. Cancer 1975, 36: 2251-2270(32) http://www.scotland.gov.uk/About/Performance/scotPerforms/partnerstories/NHSScotlandperformance/Cancerwaitingtimes(69)
Level of Consensus	<u>Level of Agreement for KPI: 100%</u> <u>Level of Agreement for standards: 84%</u>

4.6.5) Volume of Procedures

Objective	Safeguard to ensure that endoscopists undertake a sufficient number of procedures a year to maintain acceptable standards
KPI	<u>Number of NPCPs of 20mm or greater in size removed per endoscopist per year</u>
Inclusions	All NPCPs of 20mm or greater in size removed per endoscopist per year
Frequency	Annual analysis
Level of Analysis	Individual Endoscopist and service level
Minimum standard	No current standard defined
Aspirational standard	No current standard defined
Action	Review in conjunction with other KPIs. Consider focusing NPCP therapy on fewer clinicians to maintain and improve skills.
Evidence	Rabeneck et al. Gastroenterology 2008, 135: 1899–1906 (66) Singh et al. Gastrointest Endosc 2009, 69: 665-671 (64) Chukmaitov et al. Gastrointest Endosc 2013, 77: 436-446 (65) NHS BCSP Publication 2011 (2)
Level of Consensus	<u>Level of Agreement for KPI: 92.3%</u> <u>Level of Agreement for standard: 92%</u>

4.7) Discussion

The purpose of defining KPIs and minimum standards was driven by a desire to deliver quality assurance (QA) and cost effective management in a field associated with complex therapy and potentially serious complications. It appears logical that well defined standards would also help to improve public confidence in the clinicians undertaking LNPCP management. During initial regional consultation, there were reservations about the evidence base available to identify suitable domains and KPIs in addition to potential minimum standards that may be specified. However an important precedent highlighting the potential benefit of endoscopic KPIs are the NHS BCSP KPIs that have been credited with improving colonoscopy and polypectomy standards within this programme. There was also

a concern that the creation of KPIs may serve to limit those managing LNPCP to clinicians in expert centres, and so excluding many current clinicians, and that the minimum standards set may be unrealistic. It was important to be clear that this was not the intention and ensure that standards set were realistic based on available supporting data. The purpose of developing KPIs with defined minimum and aspirational standards, was to allow a standardised way of monitoring and auditing clinical quality outcomes. It was anticipated that KPIs may result in improved clinical outcomes by providing a benchmark and allows support and remedial action to be taken when underperformance is identified. The need for this was emphasised by poorer than expected LNPCP management outcomes such as recent BCSP data. While it was accepted that it may take time for KPIs and standards to become finalised, it was agreed that when established, endoscopists suitable for LNPCP management would be identified as those meeting minimum KPI standards irrespective of the setting (e.g. district general hospital or tertiary centre) with KPIs and standards refined over time. With much of the supporting data for the setting of minimum standards coming from expert centre case series it was recognised that recommended minimum KPI standards should be adjusted accordingly. For example if a figure of <3% was recorded for a specific parameter a more relaxed figure such as <5% may be a more realistic target for the wider endoscopic community.

Selection of the main domains as recommended by the WHO was agreed by the GDG subcommittee and subsequently the entire GDG who agreed that the priorities of the KPIs should relate to:

- Effective management
- Patient Safety
- Optimal Decision Making
- Avoiding unnecessary delays in management
- Demonstration of regular practice allowing maintenance of standards and ensuring that recorded KPI data is meaningful.

The domains selected (optimal decision-making, endoscopic skill, safety, timeliness, volume of procedures per endoscopist) were felt to fulfil these priorities. It was agreed that finalised KPIs should relate to a few parameters felt to both feasible and of the greatest importance rather than recommending a large number of parameters that may lack clarity

and be considered too prescriptive. A filtering process was conducted with several potential KPI parameters within each domain offered for review in the preliminary round to:

- generate discussion
- identify parameters in terms of appropriateness and rank in terms of importance,
- allow for suggested additional KPIs and modifications
- enable selection of the most pertinent KPIs per domain prior to formal voting.

A concern within the GDG was how data from KPIs should be interpreted and acted upon in areas of obvious discrepancy. It is intended that the use of KPIs may be considered as a monitoring system with outliers warranting further investigation/analysis. For example, if an outcome is clearly explainable, such as a skilled endoscopist tackling more complex lesions having a higher recurrence/residual rate than a less skilled endoscopist tackling more simple lesions, then this would be recognised as acceptable. If however, endoscopists tackling similarly complex lesions have widely differing outcomes with an endoscopist producing clearly inferior outcomes, the KPI may then call into question the appropriateness for that individual to be managing certain lesions. This was clearly specified in the final KPI document.

4.7.1) Optimal Decision Making

Initial GDG views indicated that scenarios considered undesirable regarding decision-making in endoscopy included piecemeal endoscopic attempts on malignant lesions and benign lesions referred for surgery. Proposed parameters were created relating to both individual endoscopists and endoscopy centres as a whole. However whilst there was an argument that the ability to manage LNCPs and these outcomes were directly related to an individual's skill and ability rather than the centre they practiced at, it was agreed that relevant KPIs could capture data for both these scenarios. Preliminary KPIs such as 'proportion of lesions managed with primary endotherapy' and 'proportion of lesions managed with primary surgery' were not felt to offer any information regarding the endoscopist decision-making process during endoscopy and were discarded. Whilst it was accepted that piecemeal endotherapy on malignant lesions and surgery on benign lesions should be limited wherever possible, this was considered a complex area as while reported numbers may be absolute, rationale may be unclear. It was also understood that these scenarios may be unavoidable and vary based on local available expertise, patient preference and technical issues. For example, it was felt important to emphasise that

surgical management has an important role and that KPIs should not coerce clinicians into attempting endotherapy on lesions that may be felt to be too large or dangerous to remove endoscopically despite being benign.

The GDG considered that an appropriate KPI related to decision making should assess the ability to both correctly determine whether a identified lesion is endoscopically removable and identify a suitable clinician for a lesion amenable to endotherapy. The use of surgery as a secondary management modality was considered to be the result of incorrect or ineffective endoscopic management, such as the use of piecemeal endotherapy with a malignant lesion. Whilst it was accepted that surgical management continues to have an important role in LNPCP management, it was felt it was only suitable as a primary therapeutic modality after careful consideration of all feasible management options. The KPI 'Surgery rate for LNPCPs, excluding primary surgery for malignant lesions' was felt to most succinctly assess decision making. There was agreement that this parameter would identify cases considered to represent incorrect management, such as cases of LNPCPs undergoing surgery where endoscopic management was feasible and cases of piecemeal endotherapy on malignant lesions. Whilst there was available data from multiple international series reporting relevant outcomes (e.g. piecemeal endoscopic attempts on malignant lesions and surgically managed benign lesions), the figures reported varied widely, compromising the ability to set specific standards. In view of this the agreed KPI within this domain was agreed as an auditable outcome.

4.7.2) Endoscopic Skill

It was felt necessary to identify a KPI to assess levels of endoscopic success. Assessing for recurrent/residual polyp (RRP) was felt to be the most appropriate way of achieving this. KPIs recording RRP at both 2-6 (early outcome) and 12 months (late outcome) were proposed to assess for completeness of initial resection and curative resection respectively. It was felt however that whilst assessing of early outcomes was not a priority performance indicator nor necessarily a marker of poor performance given an established acceptance of high RRP rates associated with piecemeal endotherapy and widespread evidence of successful lesion eradication with repeat endotherapy. The GDG considered the measurement of 12 month outcomes to be more appropriate, relating more directly to health outcomes and consistent with the standardised use of 12 month recurrence rates as an outcome of treatment success internationally. In addition, 12 month surveillance is

commonly undertaken with lesions removed both en-bloc and piecemeal and so would allow all LNCPs to be assessed in an equivalent manner. With expert centre data reporting 12 month recurrence levels between 2-6%, a minimum target of <10% was felt to be realistic with an aspiration standard similar to the reported data (<5%).

A KPI assessing compliance with a tattooing protocol was suggested but discarded as this is already a well established generic polypectomy standard.

4.7.3) Safety

Parameters related to the most common or serious potential complications were felt to best indicate patient safety. Perforation, post procedure bleeding (PPB) and mortality were proposed as fulfilling this requirement. Although desirable to record, a robust PI assessing mortality rates was not considered feasible as it was agreed that this data was difficult to collect and establish whether deaths could be directly attributed to endotherapy, particularly in patients with greater comorbidity.

Assessing perforation and PPB levels was considered both essential and feasible. However, it was accepted that these complications may both have differing definitions and varying degrees of severity. In line with other large organisations such as the ASGE and NHS BCSP, it was felt that KPIs with clear definitions and allowing delineation of severity levels were optimal. As such, perforation, in accordance with the BCSP and ASGE, was defined as 'air, bowel contents or instrumentation outside the bowel lumen'. In addition, it was accepted in relation to complex endotherapy that a perforation repaired during endoscopy, without patient symptoms, and not requiring hospitalisation was not problematic and did not require recording. PPB was classified as minor, intermediate, major and fatal as per ASGE and BCSP definitions to allow recording of PPB at all severity levels, whilst it was specified that peri-procedural bleeding successfully managed during endoscopy could be excluded.

The specification of standards for EMR was considered straightforward with a wide range of data, recording perforation and PPB levels according to agreed GDG levels as below 1% and 3% respectively. Minimum levels were agreed as <2% and <5% respectively to acknowledge the consideration of expert centre data. An aspirational target of <0.5% for perforation was set as felt achievable given BCSP data reporting perforation at this level. ESD practice in the UK and Western World was felt to be currently too limited to set minimum standards whilst separate NICE guidance covers this modality. As such, the GDG agreed that both safety KPIs

for ESD (perforation and post procedure bleeding) should currently be considered as auditable outcomes.

4.7.4) Timeliness

Whilst ensuring that management was undertaken in a timely fashion without unnecessary delay was considered a priority, the identification of KPIs within this domain proved difficult with marked initial disagreement within the GDG and consensus only reached at the final voting round after lengthy group discussion. Specifying a management timeframe drew strong opposition from some quarters with no evidence base to support a specific timeframe and a concern that it could be seen as a political rather than a clinical performance measure. In addition, there was a concern that a timeframe may result in endoscopists not suitable to undertake management performing endotherapy to meet a target.

There was a view that LNPCPs referred to a tertiary centre are subject to longer waiting times due to service demand and that a management timeframe KPI should refer to the time of receipt of referral rather than diagnosis as a delay in referral may account for a delay in management beyond the control of the receiving centre. In view of this it was felt prudent to assess time periods between diagnosis and referral as an additional KPI where applicable. A period of 4 weeks was felt sufficient for a centre to obtain supporting information such as histology or radiology and allow local multidisciplinary discussion prior to external referral. A recommendation specifying the proportion of lesions with time from receipt of referral to initial therapy in accompanying guidelines was repeated in the form of a proposed KPI. As with the guidelines a timeframe <8 weeks as opposed to <6 weeks had greater support as it was considered more achievable and appropriate, with greater time to ensure that a suitable endoscopist undertakes therapy and no data from polyp growth studies to suggest this as unsafe practice. In addition, a timeframe of eight weeks appeared to be rational as it was in keeping with the NHS 62 day management target pathway. Performance indicators related to waiting times for follow-up procedures was felt to be less of a priority.

4.7.5) Volume of Procedures

The objective of this domain was to introduce a safeguard to ensure that endoscopists undertake a sufficient number of procedures per year to maintain acceptable standards. This was considered important to assess in light of evidence associating increased procedure volume and experience with improved outcomes. In addition, there was a view that undertaking a minimum number of procedures per year to maintain acceptable standards would allow a meaningful measurement of other KPIs. The BCSP was cited as an example, with a minimum number of 150 colonoscopies per year mandated (2, 64-66). There was a strong wish to specify a minimum annual procedure number, especially to discourage inexperienced endoscopists from undertaking management of these lesions, but it was acknowledged there was no clear evidence to suggest an appropriate annual figure. In addition there was an acceptance that LNPCP incidence was dependant on the volume of colonoscopies and population catchment size, factors that may vary greatly between centres and with the annual incidence of LNPCPs unknown, and it was initially felt that an evidence based minimum number of procedures per year per endoscopist could not be proposed or estimated based on population data at present. The issue of identifying a minimum annual LNPCP management number was revisited following ACPGBI feedback that supported a provisional number to discourage inexperienced endoscopists from sporadic practice. Some members proposed setting a target in spite of a lack of evidence, feeling that it may guide centres both nationally and internationally to develop safe high output services. They cited recent BSG Barrett's Oesophagus guidelines that specified a minimum number of upper GI EMR per annum for lesions known to have a lower incidence than LNPCPs. As such, following additional voting using the secondary voting process was undertaken with the question 'should we set a minimum number of procedures per annum?' Had consensus been reached by at least the secondary process a separate vote specifying potential minimum numbers would have taken place with the majority figure agreed as a standard. However, this was not the case and the KPI 'Number of procedures per endoscopist per year' was reluctantly agreed as an auditable outcome and recommended to be related to outcomes to ascertain if volume affects the outcome without presuming that it does. It was also felt that this KPI may be refined over time to delineate between management of LNPCPs of varying sizes (e.g. 2-3cm vs >4cm).

4.8) External Consultation

Feedback from both the ACPGBI and BSG external reviewers was largely positive, especially after the opportunity to receive clarification, with the KPIs felt to be conducive to both allowing the audit of performance and the development of a large evidence base in addition to improving standards. Aside from a recommendation regarding minimum procedure numbers, the ACPGBI were happy with all aspects of the KPIs recognising the potential for them to evolve over time following the collection of data. These views were echoed by the BSG reviewers although they did raise a few issues over which they required clarification prior to formally approving the KPIs.

There was a query over the validity of KPIs and the strength of the evidence base on which the KPIs are based. There was a concern that the KPIs may not meet the requirements for NICE quality standards. It was countered that an internationally recognised framework had been followed for the identification of key performance domains and appropriate indicators and that this was an area considered important given factors including patient safety and quality outcomes which would be important to monitor.

In addition, the use of KPIs, which is well established within the BCSP, was cited as an important precedent and was widely felt to have improved standards as well as providing a means to measure performance and developing an evidence base. It was acknowledged that the evidence for the setting of certain KPIs was limited and expert consensus opinion was used where it was felt to be important (a review of outcomes reported in the international literature was a key factor). As was the case with the BCSP, it was argued that this use of qualitative methodology to identify KPIs would provide a means to identify key quantitative measures that can be monitored and targeted for improvement to provide enhanced patient care in addition to the development of a large evidence base. Clearly with a limited evidence base, it was accepted that the rigidity of the KPIs may be questioned, but in view of our use of available evidence and expert opinion, it was felt to be a significant step forward to existing measures to improve patient outcomes that could be refined and enhanced over time.

There was also a concern about the validity of identifying certain KPIs as auditable outcomes in addition to the standards specified. It was also suggested that the inclusion of an optimal

decision making KPI may reflect a lack of evidence to support endotherapy over surgery or vice-versa. The response explained that while provisional quantitative figures were agreed where possible, in reference to relevant comparable outcomes from key international literature, there were domains and KPIs where it was not currently possible to give a quantitative figure but there was a great importance to do so. It is well recognised that targets in this scenario are defined as 'auditable outcomes' with standards potentially identified following detailed audit data (288). The 'Optimal decision making' domain where the KPI standard was an auditable outcome is an important example requiring audit. For example, the audit of surgical management to identify as suitable level appears to be of great importance as it may be the result of ineffective lesion evaluation (especially with increasing evidence that the most complex LNPCPs originally referred for surgery may be managed effectively endoscopically in the correct circumstances) with robust international analysis demonstrating reduced cost-effectiveness and higher associated morbidity than with endotherapy (10, 56, 59).

Another criticism directed at the finalised KPIs was that there should be more support for users of the guidelines such as audit tools (e.g. an audit form rather than a statement of KPIs) in line with BSG guidance and good practice in other national guidelines.

Whilst it was agreed that an audit form may be of use, an explanation was accepted that audit forms may vary locally according to local trust policy and in this context it was appropriate not to be too prescriptive.

The feedback from consultation groups indicated that the KPI development process was indeed worthwhile as had been hoped for and were likely to result in improved LNPCP management. The development of KPIs allows a new opportunity to benchmark LNPCP management performance at an individual endoscopist and service level and the targeting of improved standards. This view is supported by their approval by both the BSG and ACPGBI and acceptance for publication in 'Gut' journal.

Chapter 5: Retrospective Analysis of BCSP 2011-12

Large Non-Pedunculated Colorectal Polyp Outcomes

5.1) Introduction

Evidence from national BCSP data suggests variation in the management of large non-pedunculated colorectal polyps (LNPCPs) whilst undesirable outcomes such as piecemeal endoscopic resection of malignant lesions and primary surgical resection of benign lesions appeared to occur more frequently than previously thought. In addition international evidence demonstrated a wide variation in the quality of endoscopists based on outcome data. The endoscopists performing endotherapy on LNPCPs within the BCSP are highly experienced endoscopists and it could therefore be suggested that the practice of endoscopists performing complex endotherapy outside the BCSP may vary further. When considering the reasons for variable outcomes between both endoscopists and centres, it appears likely that variation in practice is a strong determining factor and analysis of management and outcomes over a longer time period may help to determine whether this is the case, especially when analysing the performance of endoscopists who have been through the same rigid certification process such as BCSP accreditation. The BCSP mandates uniform comprehensive data recording both regionally and nationally. A BCSP central database exists that has details of all aspects of a patient's investigations, diagnosis and management related to their screening for bowel carcinoma. For example, all colonoscopies performed are recorded in great detail, including therapies performed such as polypectomy, diagnoses, comfort levels, complications and sedation dosage. It is national BCSP practice for these details to be uploaded onto the database around the time of procedure. There is a dedicated person with the sole responsibility of doing this to ensure accurate and robust data recording. In addition, details of any histological diagnoses, complex discussions (such as MDM outcomes) and other therapies such as surgical management are also uploaded. The database can be used to filter data entries where relevant and therefore allows access to a wealth of high quality information for performance analysis and outcomes. BCSP patients are asked to give consent prior to procedures for details to be securely stored and are aware that data will be used for service evaluation and development.

5.1.1) Null Hypothesis

Variation in the management of LNPCPs will not result in variable outcomes

5.2) Methodology

Prior to the commencement of the study, the North East England NHS Research Ethics Committee were approached with regards to obtaining a waiver for ethics committee approval due to the lack of patient interaction involved in the data collection and analysis required. This was duly granted with the work considered to be NHS service evaluation and development.

LNPCPs initially diagnosed within the Bowel Cancer Screening Programme (BCSP) between 2011-12 were the subject of the study. This time period was considered suitable to ensure the collection of a sufficient sample size within the available study time period that had both long term outcomes (e.g. up to 15 months post management) and was recent enough to be considered relevant to current practice. The collection and analysis of LNPCP data over 2 years was intended to assess management at each screening centre over an extended period of time to look for trends in management as opposed to snapshot analysis. Permission was obtained from Professor Rutter in his capacity as Quality Assurance chairperson to approach the NHS BCSP Central Office for access to information concerning all polyps identified within the North East of England programme between 2011-12 that were ≥ 2 cm and diagnosed as benign prior to management. A Microsoft Excel Datasheet detailing this information was subsequently provided for further analysis. In addition to specific patient information, the datasheet provided specific information regarding polyp detection dates, morphology, size and initial endoscopic and histological diagnoses

The datasheet was then scrutinised to identify and exclude any lesions that were diagnosed as pedunculated or malignant prior to therapy (endoscopic and/or histologically diagnosed) and under 20mm in size. Lesions identified outside of the 2011-12 time period were also excluded. The updated datasheet was then filtered according to each of the four screening centres and a nominated Specialist Screening Practitioner (SSP) at each centre was then asked to analyse and provide greater detail about each of the relevant cases diagnosed at their centre using available facilities such as the BCSP central database and local endoscopy and histopathology databases. The SSPs were asked to corroborate the recorded lesion and

procedure details, in addition to recording short and long term management outcomes for each case into relevant sections on the datasheet. Information pertaining to procedure practice was sought, in addition to outcomes commonly reported in large international LNPCP case series. Information sought in addition the relevant rationale is detailed below in table 10.

Information Sought	Rationale
Use of piecemeal endoscopic resection	Commonest LNPCP management modality. Identify outcomes from piecemeal resection in relation to international case series to compare LNPCP management performance (e.g. curative resection, use of modality on malignant lesions)(5)
Use of argon plasma coagulation post endoscopic resection	Area of conflicting opinion, information regarding its use available in series as recorded for each individual endoscopic procedure(5, 184)
Early/3 month residual/recurrent polyp	Assess completeness of resection(5, 9)
Late/12 month residual/recurrent polyp	Assess curative resection rate(5, 9, 17)
Endotherapy undertaken within 8 weeks of referral	Assess timeliness of management
Discovery of malignancy	Retrospectively analyse management decisions taken in view of finding of malignancy(17)
Management modality used (endoscopic vs surgical vs conservative management)	Correlate management approach to outcomes (e.g. curative resection, finding of malignancy) to ascertain whether appropriate management approach undertaken(5, 17)
Use of secondary surgical management	Assess need to correct incomplete management(17)
Adverse events	Assess safety of management(5, 9, 17)
Other notable information	Provide extra information relating to decision making process undertaken with regards to management

Table 10. Information sought from individual LNPCP case analysis and rationale

Once completed, updated datasheets were subsequently returned. A separate repeat analysis of all cases was then undertaken independently. This process of regional data collection began with the attainment of approval and permissions to analyse LNPCPs from

each screening centre clinical director. This was achieved using face to face meetings and confirmed in writing via email. A BCSP endoscopist/SSP was nominated as a sponsor at each site to facilitate access to patient identifiable data.

All relevant audit departments were contacted with requests to audit local BCSP and supporting data with sponsors included in all communications. Local audit and Caldicott approval forms, in addition to computer services access forms, were completed prior to appropriate permissions being granted.

5.2.1) Relevant information retrieved from BCSP database and corroborated with local databases

The BCSP central database was used to obtain relevant information and outcomes for each case. Further information was obtained where further clarification was required by cross-referencing cases using endoscopy reporting databases and histopathology programmes locally at each site. This process was also used to provide information for cases where details were not available or limited on the BCSP database (e.g. subsequent follow-up outside the BCSP).

Details regarding complications were provided on request by the BCSP central office in a separate Microsoft Word document. All 2011-12 BCSP North East complications were reviewed and filtered to those related to polypectomy. Complications relating to the study sample were subsequently identified by matching patient details such as NHS number, date of birth and procedure dates.

All information, including patient identifiable information was entered into a Microsoft Excel spreadsheet and transferred as required securely using NHSmail (the only approved secure connection for transfer of patient identifiable details). The database was stored on a secure, password protected computer in a locked office in the endoscopy department at the University Hospital of North Tees.

The process of double data entry was used to ensure data accuracy. Datasheets with completed patient entries for each centre were sent to the relevant SSPs originally responsible for data entry who were asked to review the entries and compare with their own datasheet. They were then asked to report any discrepancies identified (e.g. duplicated cases). The datasheet was considered suitable for detailed statistical analysis following

amendment of identified discrepancies. Multiple variables were assessed for statistical association with outcomes identified in the international literature on an individual and combined basis (e.g. lesion size + location in relation to malignancy) where appropriate (see table 11 below for full list of variables and outcomes assessed)

Variable	Outcome(s) assessed for association	Rationale
Lesion size	-Recurrence (3 and 12 month) -Malignancy -Need for surgery (Primary + Secondary)	Previous data and international consensus that increased polyp size is associated with increased malignancy risk, the need for surgery, complications and difficulty in achieving curative resection(17, 32)
Lesion Location	-Recurrence (3 and 12 month) -Malignancy	Identified risk factor for increased endoscopic difficulty and increased likelihood of need for surgical resection(6, 17)
Lesion morphology (flat vs sessile)	-Recurrence -Malignancy	Association of polyp morphology with increased endoscopic difficulty and malignancy(6, 15)
Endoscopist Procedure Volume (Average number of LNPCPs endoscopically managed per annum)	-Recurrence -Need for surgery (Secondary)	Evidence that increased therapeutic volume is associated with improved outcomes(64, 65)
Screening Centre	-Recurrence -Malignancy -Need for surgery (Primary + Secondary) -Use of piecemeal endotherapy with malignant lesions -Endotherapy within 8 weeks of referral -Adverse Events	Compare performance between regional centres over a range of important outcomes
Use of Argon Plasma Coagulation (APC)	-Recurrence at first endoscopic follow-up	Important research question, previous conflicting evidence in this area(5, 184)

Table 11. List of variables and outcomes

Detailed statistical analysis was conducted with support from Durham University, using the IBM SPSS 20 statistics programme. The Fisher's exact test was used for univariate analysis with multivariable analysis undertaken using logarithmic regression to further assess for strength of association between variables and outcomes, and for potential interaction between variables due the binary nature of the outcomes (e.g. yes vs no). A finalised,

completed Microsoft Excel sheet, confirmed by double data entry, was exported into the SPSS programme. Recently developed key performance indicators (KPIs) (see chapter 4) were then retrospectively applied to the results for further comparison between centres. Provisional results were presented and discussed at a regional BCSP meeting in March 2015 to ascertain potential explanations for outcomes and variation in outcomes between the centres.

5.3) Results

5.3.1) Summary of Results

A summary of the lesions identified and results from subsequent follow-up performed is shown below (see figure 16)

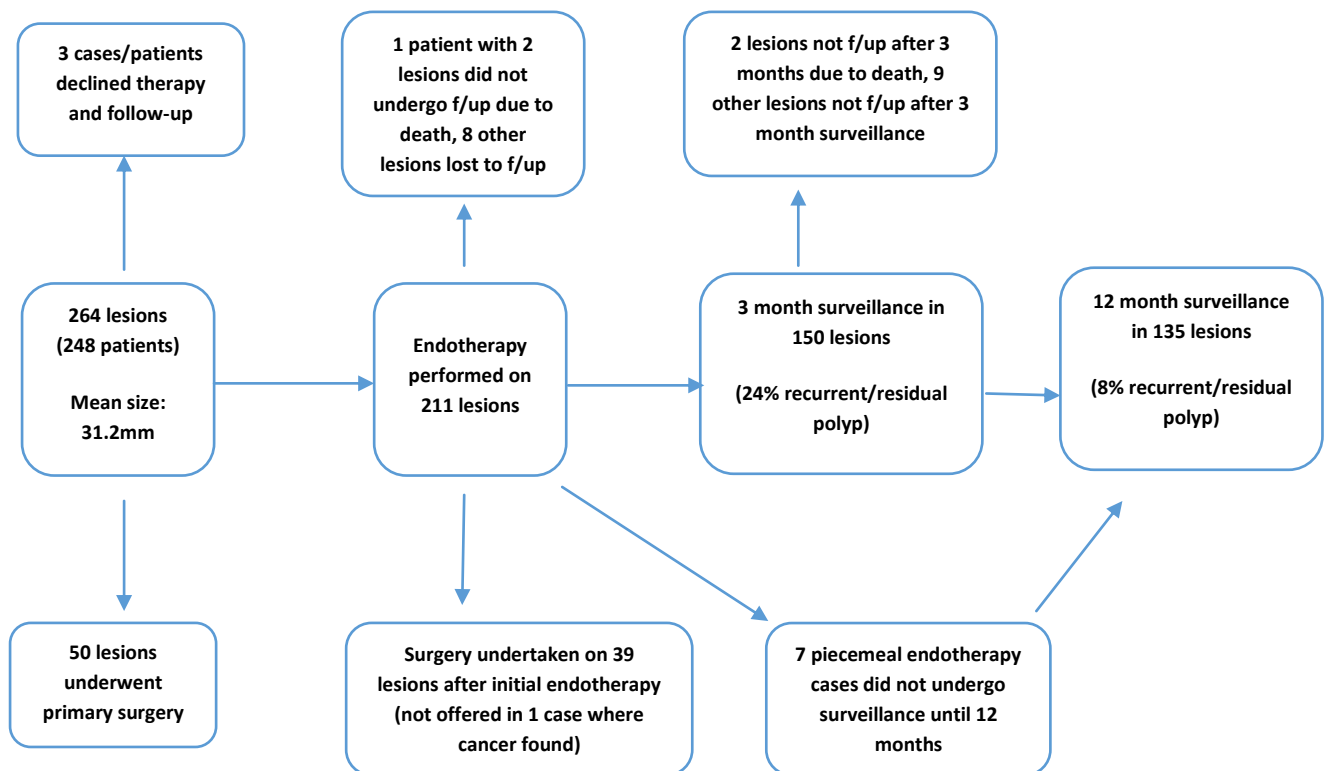


Figure 16. A summary of results and follow-up of cases

5.4) Whole Group Analysis

Malignancy was identified in 28% of all cases in the sample

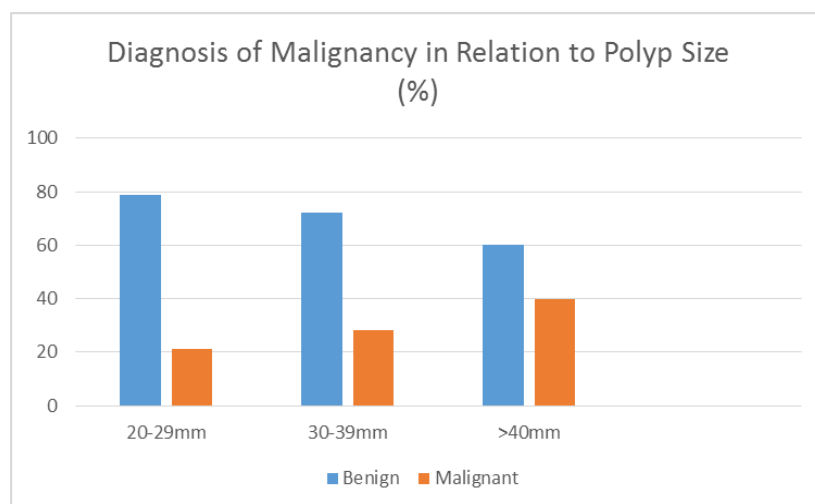
5.4.1) Polyp Size

Rationale:

- Prevalence of data indicating that increased polyp size is associated with an increased risk of malignancy, the need for surgery, complications and difficulty in achieving curative resection(17, 32)
- National BCSP data indicating that increased polyp size is associated with increased likelihood of surgery(17)
- International consensus that increased lesion size is associated with increased difficulty in achieving successful endoscopic resection(6, 56)

Finding of colorectal malignancy in relation to Polyp Size

		Malignancy (%)		Total (n)
		n	y	
Polyp size (mm)	20-29	79	21	124
	30-39	72	28	75
	40+	60	40	65
Total		72.3%	27.7%	264

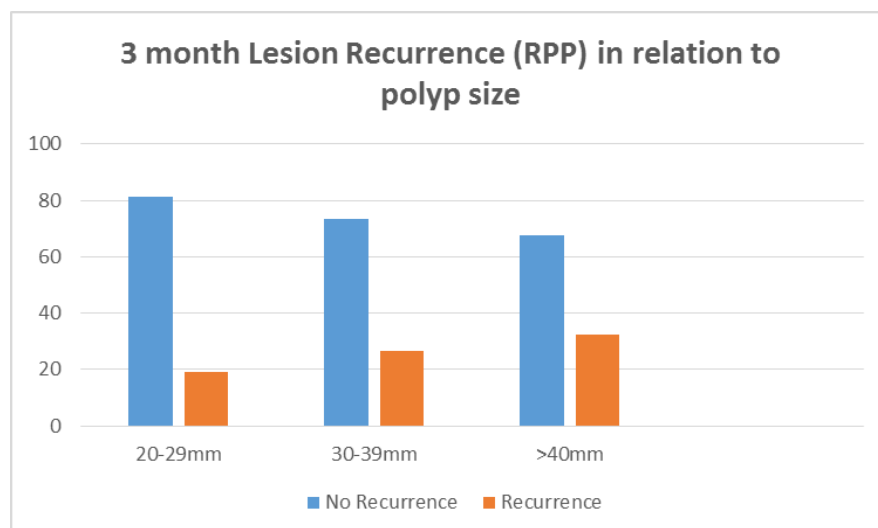


Polyp size was significantly associated with a higher rate of malignancy (p=0.023)

Lesion Recurrence in relation to polyp size

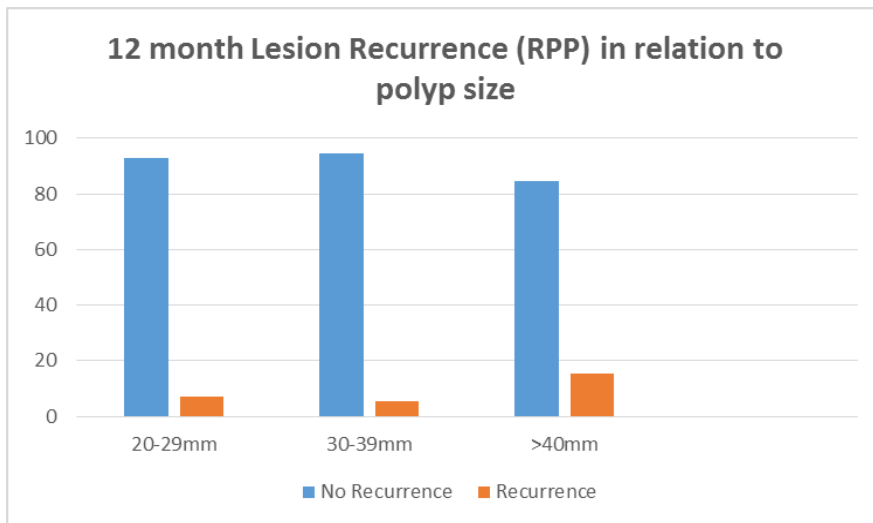
3 month Recurrent/Residual Polyp (RRP)

		3 month recurrence (%)		Total (n)
		n	y	
Polyp Size (mm)	20-29	81.1	18.9	74
	30-39	73.3	26.7	45
	40+	67.7	32.3	31
Total		76%	24%	150



12 month RRP

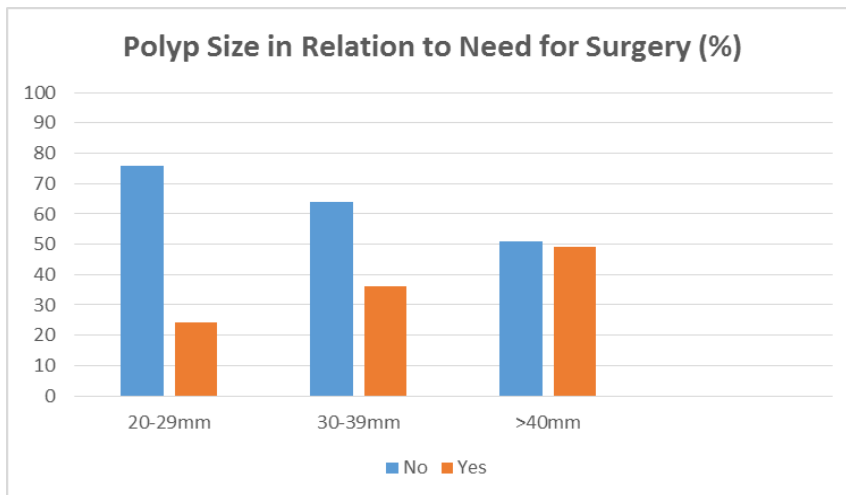
		12 month recurrence (%)		Total (n)
		n	y	
Polyp size (mm)	20-29	93.1	6.9	72
	30-39	94.6	5.4	37
	40+	84.6	15.4	26
Total		91.9%	8.1%	135



Polyp size was not significantly associated with lesion recurrence after either 3 (p=0.316) or 12 months (p=0.306))

Polyp Size in Relation to Need for Surgery

		Need for surgery (%)		Total (n)
		n	y	
Polyp Size (mm)	20-29	75.8	24.2	124
	30-39	64	36	75
	40+	50.8	49.2	65
Total			33.7	264



The association between polyp size and use of surgery was strongly significant ($p=0.002$)

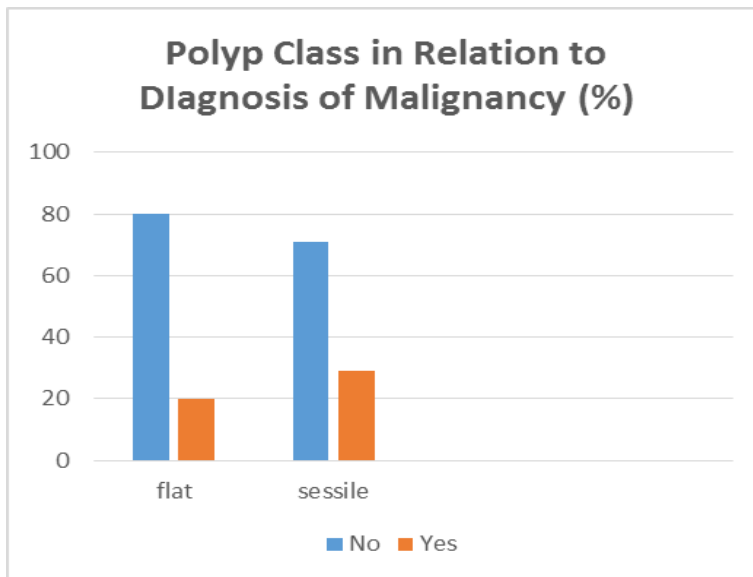
5.4.2) Polyp Morphology

Rationale:

- Prevalence of data suggesting that certain morphological classifications are associated with an increased malignancy risk(15)
- Accepted classification of flat morphology being associated with increased difficulty in achieving endoscopic resection(6)

Polyp Morphology and identification of malignancy

		Malignancy (%)		Total (n)
		n	y	
Polyp class	Flat polyp	80	20	45
	Sessile polyp	70.8	29.2	219
Total		72.3	27.7	264

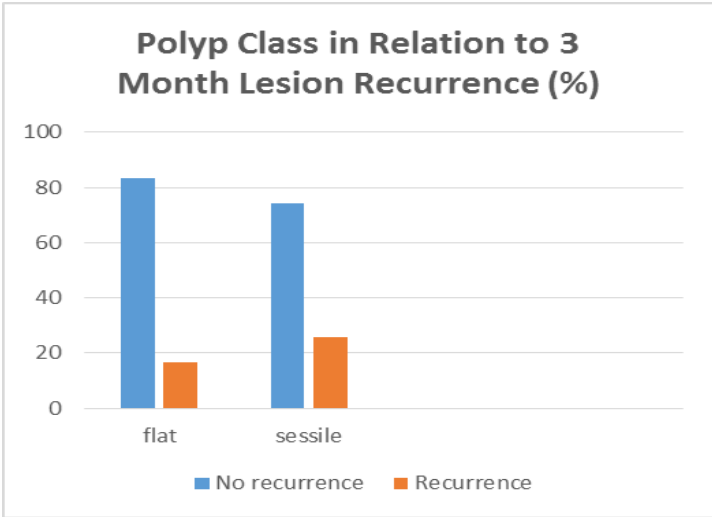


Polyp class was not associated malignancy risk (p=0.140)

Polyp Class in Relation to Recurrence

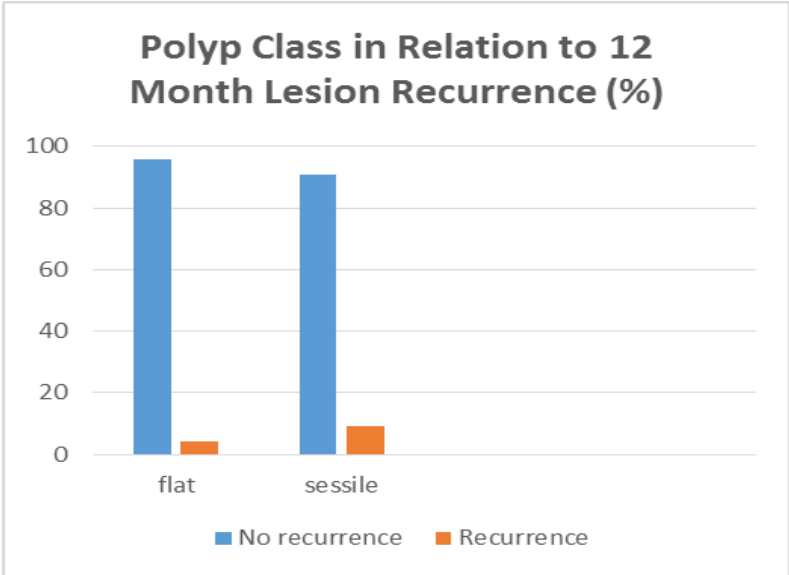
3 month RRP

		3 month recurrence (%)		Total (n)
		n	y	
Polyp class	Flat polyp	83.3	16.7	30
	Sessile polyp	74.2	25.8	120
Total		76	24	150



12 Month RRP

		12 month recurrence (%)		Total (n)
		n	y	
Polyp class	Flat polyp	96	4	25
	Sessile polyp	90.9	9.1	110
Total		91.9	8.1	135



Polyp class was not associated with RRP after either 3 (early stage) ($p= 0.211$) or 12 months (late stage) ($p=0.357$)

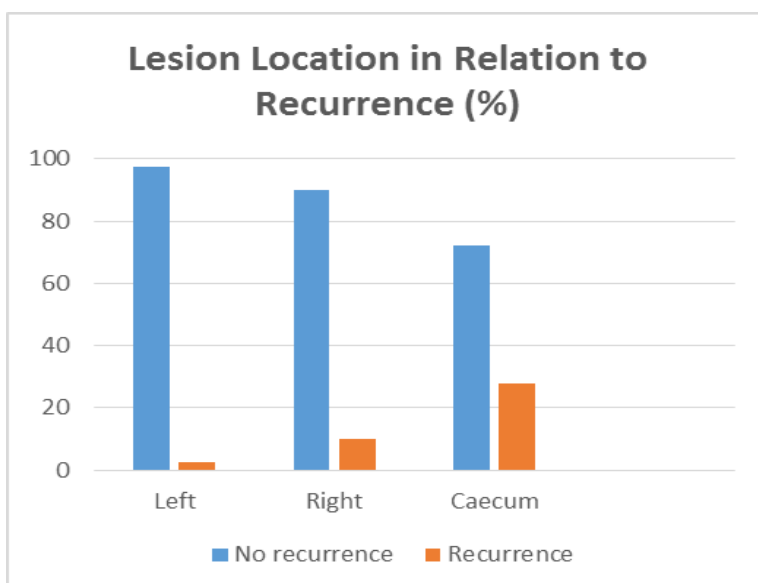
5.4.3) Lesion Location

Rationale:

- Proximal lesion location has been identified as a risk factor for increased difficulty with endoscopic removal and increased likelihood of need for surgical resection (6, 17).

Lesion Location and Recurrence

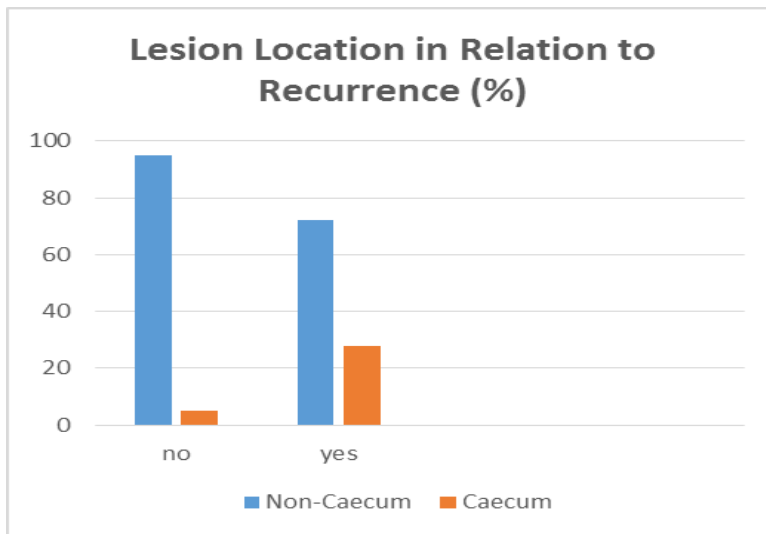
		12 month recurrence (%)		Total (n)
		n	y	
Polyp Location	Left	97.4	2.6	76
	Right (excluding caecum)	90.2	9.8	41
	Caecum	72.2	27.8	18
Total		91.9%	8.1%	135



Lesion location was strongly associated with the likelihood of 12 month recurrence (p=0.003)

Caecal Location and Recurrence

		12 month recurrence (%)		Total (n)
		no	yes	
Caecal location?	no	94.9	5.1	117
	yes	72.2	27.8	18
Total		91.9%	8.1%	135



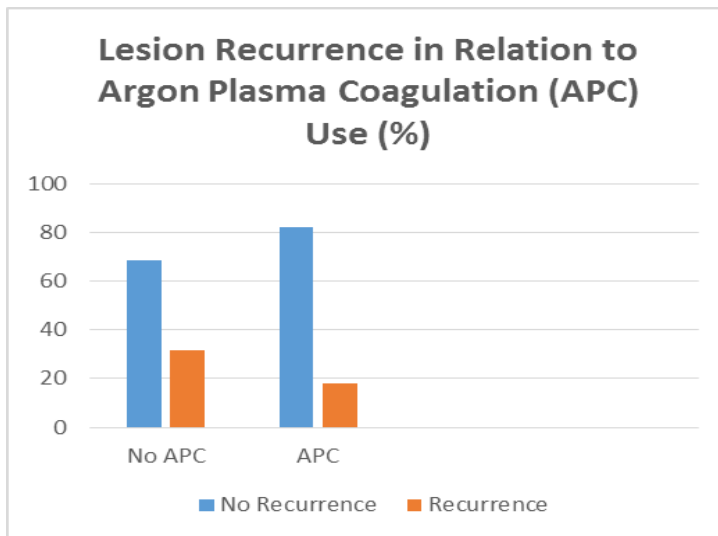
Caecal location was strongly associated with lesion recurrence (p=0.007)

5.4.4) Argon Plasma Coagulation Use

Rationale: Important research question, previous conflicting evidence in this area (5, 12, 180)

Argon Plasma Coagulation in Relation to Early Lesion Recurrence

		Piecemeal recurrence on first f/up		Total (n)
		(%)		
		n	y	
APC use	n	68.6	31.4	86
	y	82.1	17.9	67
Total		74.5	25.5	153



Statistically significant association was found between endotherapy APC use and recurrence found using 1-sided Fisher's exact t-test (0.042) but not 2 sided test ($p=0.064$). APC use was not associated with increased early lesion recurrence

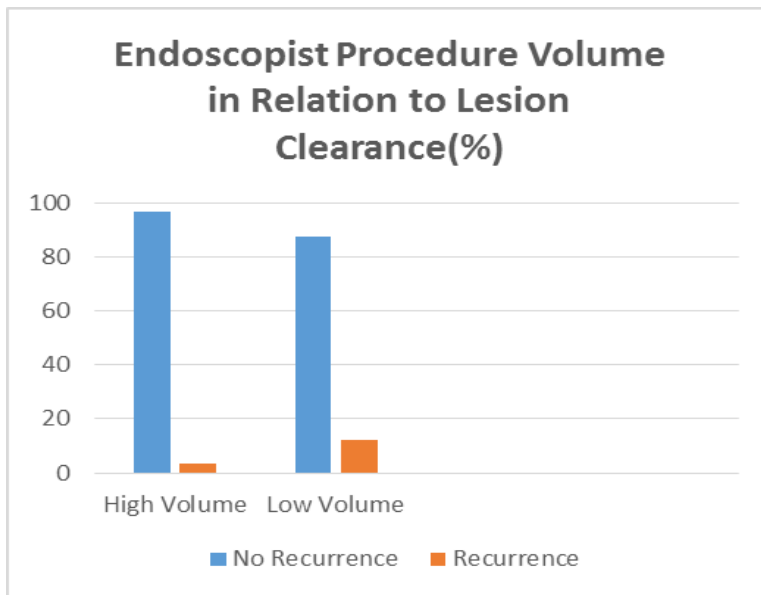
5.4.5) Endoscopist Procedure Volume

Rationale:

- Prevalence of international data demonstrating that increased endotherapy practice is associated with improved outcomes (64, 65)

Endoscopist Procedure Volume in Relation to Curative Resection

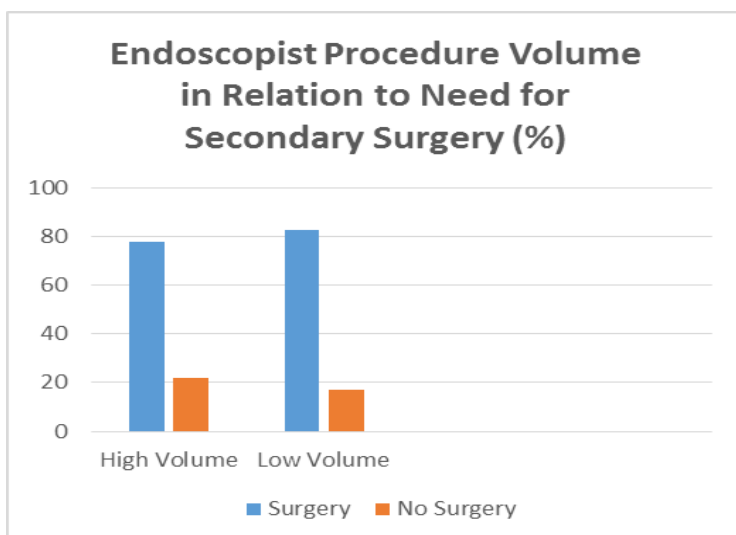
		12 month recurrence (%)		Total (n)
		n	y	
Endoscopist procedure volume	High ≥ 30	96.8	3.2	62
	Low < 30	87.7	12.3	73
Total		91.9	8.1	135



Procedure volume was not statistically associated with lesion clearance ($p= 0.050$ (1-sided)
 $p= 0.064$ (2-sided))

Endoscopist Procedure Volume In Relation to Need for Secondary Surgery

		Secondary Surgery (%)		Total (n)
		n	y	
Endoscopist procedure volume	High ≥ 30	77.9	22.1	86
	Low < 30	82.8	17.2	116
Total		124	11	202

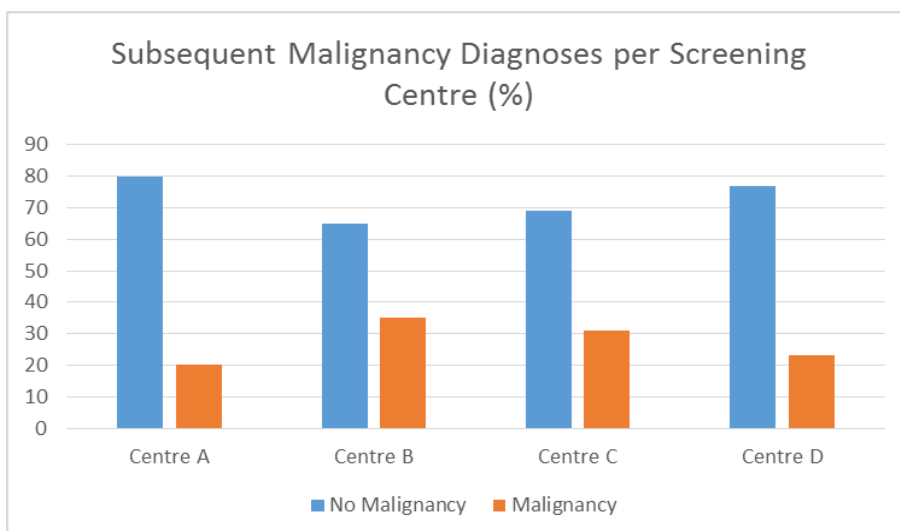


Procedure volume was not associated with a need for surgical management after initial endotherapy (p=0.243 (1-sided) p=0.471 (2-sided))

5.5) Intercentre Comparison

5.5.1) Diagnoses of Malignancy: Assessment of decision making

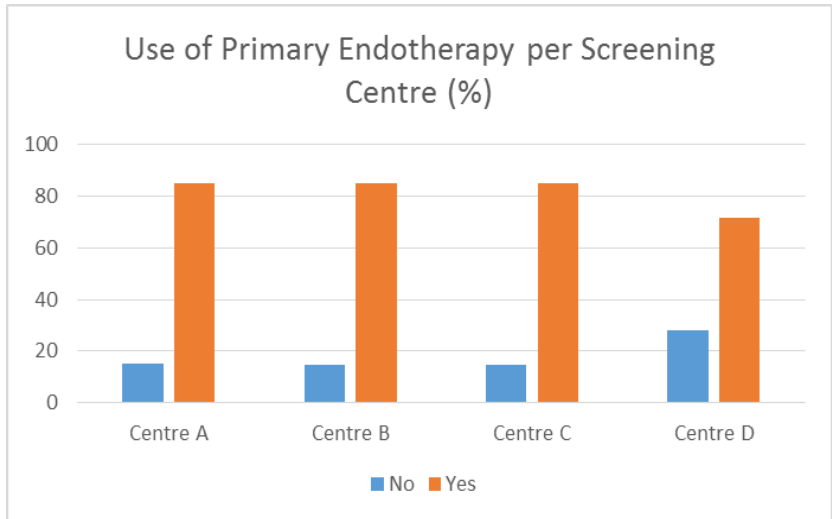
		Cancer confirmed (%)		Total (n)
		n	y	
Screening Centre	A	80	20	40
	B	65	35	74
	C	69	31	54
	D	77	23	96
Total		72%	28%	264



Malignancy found in 28% of cases of lesions initially diagnosed as benign

5.5.2) Use of Primary Endotherapy: Assessment of decision making

		Primary endotherapy (%)		Total (n)
		n	y	
Screening Centre	A	15	85	40
	B	14.9	85.1	74
	C	14.8	85.2	54
	D	28.1	71.9	96
Total		19.7%	80.3%	264

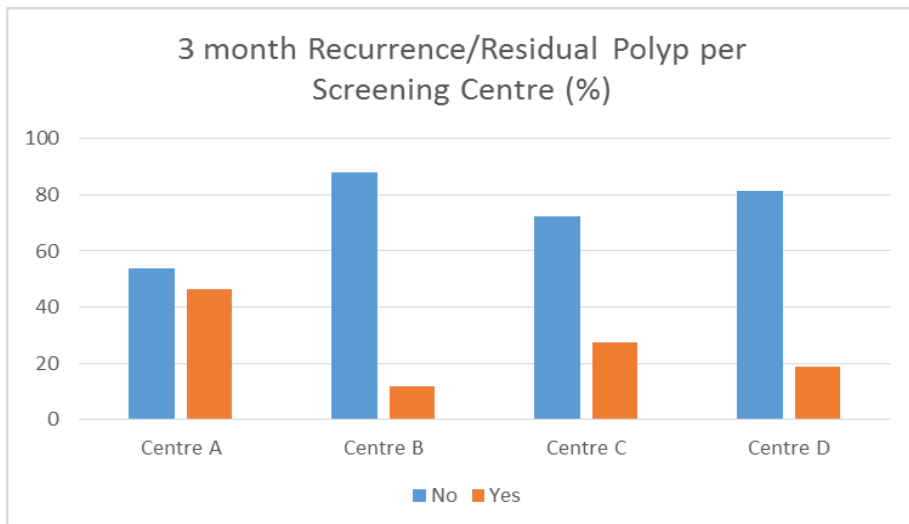


Primary Endotherapy undertaken in 80.3% of cases

The probability of Screening Centre location affecting the likelihood of primary endotherapy undertaken was not statistically significant ($p=0.097$)

5.5.3) 3 month recurrence: Assessment of completeness of resection

		3 month recurrence (%)		Total
		n	y	
Screening Centre	A	53.6	46.4	28
	B	88.2	11.8	34
	C	72.4	27.6	29
	D	81.4	18.6	59
Total		76%	24%	150

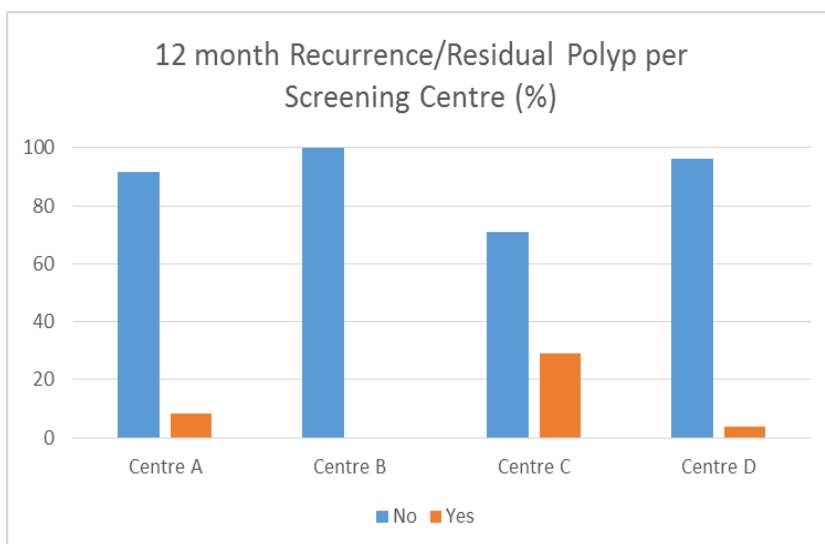


3 month recurrent/residual polyp (RRP) occurred in 24% of cases.

The probability that the endoscopic centre affected the likelihood of a finding of residual/recurrent polyp after 3 months was statistically significant ($p=0.011$)

5.5.4) 12 Month Recurrence: Assessment of Curative Resection

		12 month recurrence (%)		Total (n)
		n	y	
Screening Centre	A	91.6	8.4	24
	B	100	0	36
	C	70.8	29.2	24
	D	96.1	3.9	51
Total		91.9%	8.1%	135

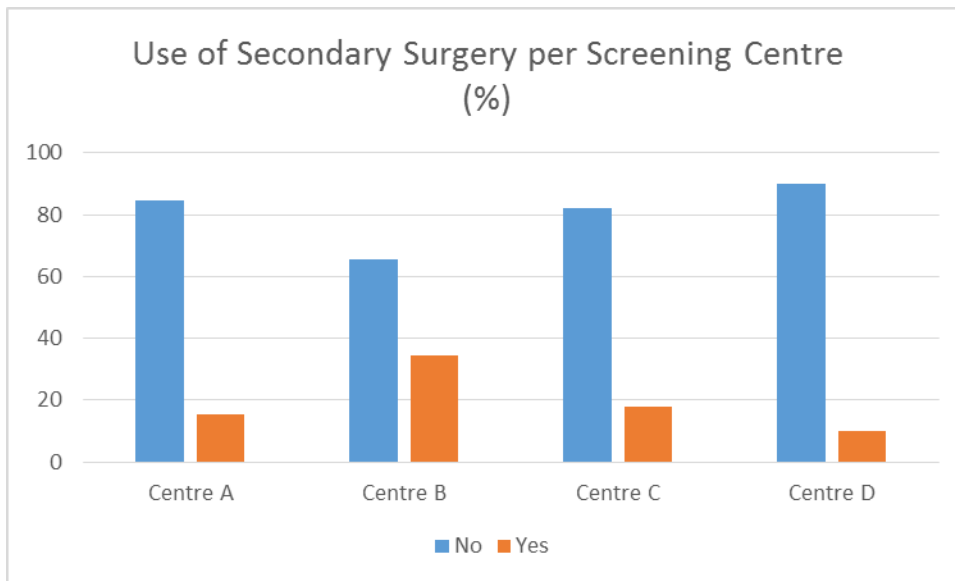


12 month recurrence occurred in 8.1% of cases.

The likelihood of finding of recurrent/residual polyp after 12 months was strongly associated with screening centre location (p=0.001)

5.5.5) Use of Secondary Surgery: Assessment of use of ineffective endotherapy

		Use of Secondary Surgery (%)		Total (n)
		n	y	
Screening Centre	A	84.8	15.2	33
	B	65.5	34.5	55
	C	82.2	17.8	45
	D	89.9	10.1	69
Total		81%	19%	202

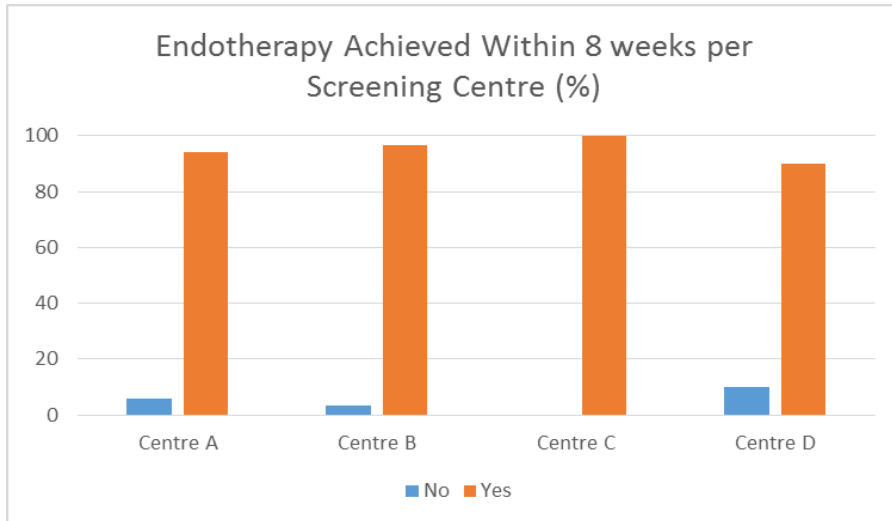


Secondary surgery was used in 19% of cases.

The probability of screening centre location affecting the need for secondary surgery was statistically significant ($p=0.008$)

5.5.6) Endotherapy within 8 weeks of diagnosis: Assessment of timeliness of management

		Endotherapy within 8 weeks (%)		Total (n)
		n	y	
Screening Centre	A	5.9	94.1	34
	B	3.2	96.8	62
	C	0	100	46
	D	10.1	89.9	69
Total		5%	95%	211

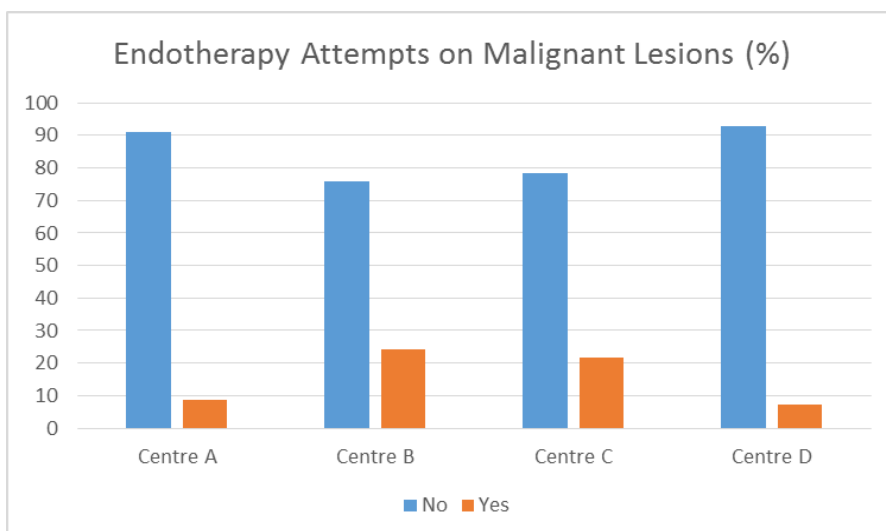


Endotherapy within 8 weeks of diagnosis occurred in 95% of cases.

The probability of cases undergoing therapy within 8 weeks of referral varying between screening centres was not statistically significant ($p=0.086$)

5.5.7) Endotherapy attempted on malignant lesions: Assessment of decision making

		Endotherapy with cancer subsequently confirmed (%)		Total (n)
		n	y	
Screening Centre	A	91.2	8.8	34
	B	75.8	24.2	62
	C	78.3	21.7	46
	D	92.8	7.2	69
Total		84.4%	15.6%	211

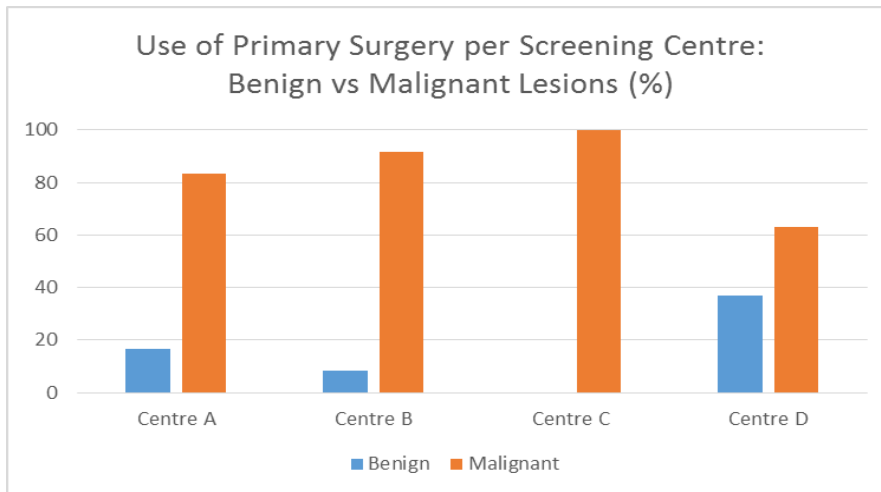


Piecemeal endotherapy on malignant lesions took place in 15.6% of cases.

The probability of undergoing piecemeal endotherapy on a malignant lesion being affected by screening centre location was statistically significant ($p=0.021$)

5.5.8) Use of Primary Surgery: Assessment of decision making

		Cancer confirmed (%)		Total (n)
		n	y	
Screening Centre	A	16.7	83.3	6
	B	8.3	91.7	12
	C	0	100	5
	D	37	63	27
Total		24%	76%	50



24% of lesions managed with primary surgery were benign.

Screening centre location was not found to be significantly associated with the use of primary surgical management on benign lesions ($p=0.145$)

5.6) Multivariable analysis:

Recurrence

Proximal location was strongly associated with an increased risk of persistent residual/recurrent polyp tissue (OR: 14.231, $p=0.003$, 95% CI: 2.491-81.283)

Malignancy

Increased lesion size was found to be strongly associated with an increased likelihood of a finding of malignancy (OR: 2.579, $p=0.005$, 95% CI: 1.333-4.990)

5.7) Complications

The complications identified are summarised below (see table 12)

Screening Centre	Complication	Number	Severity Grade	Lesion Size (mm)	Lesion Location	Intervention Required?
A	PPB	1	Intermediate	25	Descending Colon	Nil
	Perforation	0	-	-	-	-
	PPS	0	-	-	-	-
B	PPB	4	1 Major	50	Rectum	4 unit blood transfusion and surgical EUA
			3 Minor	23	Rectum	Nil
				25	Rectum	Nil
				20	Hepatic Flexure	Overnight admission
	Perforation	0	-	-	-	-
	PPS	0	-	-	-	-
C	PPB	0	-	-	-	-
	Perforation	0	-	-	-	-
	PPS	1	-	-	-	Overnight admission
D	PPB	2	2 x Intermediate	20	Rectal	Overnight admission
				30	Ascending Colon	Repeat endotherapy
	Perforation	0	-	-	-	-
	PPS	0	-	-	-	-

Table 12. Summary of North East BCSP LNPCP Complications

5.8) Screening Centre Outcomes Applied to Key Performance Indicators

Domain	Optimal Decision Making	Endoscopic Skill	Timeliness	Safety		Number of endoscopic procedures
KPI	Surgery Rate (%)	12 month recurrence (%)	Time from diagnosis to management (%)	Perforation (%)	PPB (%)	Annual Number of EMR procedures (n)
Minimum Standard	Auditable Outcome	<10%	<8 weeks	<2%	<5%	Auditable Outcome
A	17.1	8.4	94.1	0	2.9	17
B	31.7	0	96.8	0	6.3	31.5
C	16.3	29.2	100	0	0	23
D	21.5	3.9	89.9	0	2.9	34.5

Table 13. KPIs applied to North East BCSP Outcomes

5.9) Discussion

BCSP facilitates collection of a robust dataset

The method of BCSP data entry into a central database following each procedure by a dedicated practitioner ensures the attainment of a large, comprehensive and robust dataset of both endoscopic polypectomy and large colorectal polyp management. This enabled access to a wealth of information regarding all colonoscopic procedures and subsequent therapy conducted within the BCSP, in addition to documentation of decision-making prior to management. In the case of LNPCPs, this includes extensive patient details, polyp details such as size, morphology and surface characteristics and any therapeutic options taken such as the use of en-bloc or piecemeal resection, the type of electrocautery used and the use of

argon plasma coagulation. A similar level of detail is recorded on the database with information on follow up procedures, complications, multidisciplinary discussion and other therapies used such as surgery available. There is also a facility to filter cases as appropriate. For example, information regarding patients with unplanned management or lost to follow-up without planned surveillance was documented. As a result, cases of out of area management, failure to respond to appointments, cases of death and refusal of therapy could be identified. These factors ensure that the BCSP generally provides an accurate and reliable database for analysis. Another benefit of the use of BCSP data was the inclusion of only experienced endoscopists that have undergone rigid certification criteria. This allows a form of standardisation of the participating endoscopists, thus reducing the likelihood of extraneous results due to wide variation in endoscopist quality. The use of the BCSP central database ensured easier data collection, whilst the use of 'double-data entry' detailed in the methodology also further strengthened the accuracy of the data collection process and the validity of the data collection.

Logistical issues

The logistical issues with collecting and analysing data across a large geographical area such as the North East of England were considerable. Whilst there are four major centres (e.g. Tees, North of Tyne, South of Tyne and County Durham and Darlington), there are several different hospitals and NHS trusts attached to 3 of these centres. This is dissimilar to many BCSP programmes elsewhere in the country, where BCSP centres use only one hospital site. The large number of hospitals involved meant that BCSP data was entered into numerous separate endoscopy software, pathology and radiology databases. In view of this, completion of a large volume of paperwork including Caldicott Guardian approval forms and honorary contracts was required at each separate hospital site, in addition to a sponsor, before data collection could begin. The use of the central BCSP database ensured that data collection was easier than originally anticipated due to the comprehensive information it encompassed and reduced the volume of information required onsite at each hospital site to enable the retrieval of a complete dataset.

5.9.1) Whole Group Analysis

As anticipated, gender and age did not demonstrate any impact on outcomes such as recurrence and malignancy. Whilst an increased malignancy incidence is expected with

increased age, given the limited age range of BCSP patients (55-79) it was not unexpected that age was not found to be a significant factor in this series.

A 28% incidence of malignancy in this 264 lesion North East case series (range 20-35%) is significantly higher than the figure identified in a recent national BCSP case series (9.7%) of 557 patients ($p < 0.0001$). This finding appears indicative of inferior lesion assessment within the North East Region and also strongly emphasises the importance of accurate lesion assessment with LNPCPs given that initial biopsy results for all lesions in both series were benign.

Polyp Size

Polyp size was found to significantly affect the likelihood of a finding of malignancy. Malignancy was found in 21% of lesions 20-29mm in size, 28% of lesions 30-39mm in size and 40% in lesions ≥ 40 mm ($p = 0.023$). This was an expected result, given similar findings in other large case series, whilst multivariable analysis also reaffirmed this finding as the only variable associated with increased malignancy risk (Odds Ratio: 2.579, 95% CI: 1.333-4.990, $p = 0.005$)

There appeared to be a noticeably higher rate of recurrence with the largest lesions (≥ 40 mm). However, no statistical association was demonstrated between polyp size and lesion recurrence post endoscopic resection at both early (3 month: 24%, $p = 0.316$) and late stages (12 month: 8.1%, $p = 0.306$). Recurrence rates of 18.9%, 26.7% and 32.3% at (3 months) and 6.9%, 5.4% and 15.4% (12 months) for polyp sizes of 20-29mm, 30-39mm and 40+mm were demonstrated respectively. A higher rate of incomplete resection in larger lesions might be expected given that increased lesion size is an established indication of increased endoscopic difficulty (6). However, whilst the lack of statistical association may be attributed to the study being underpowered, similar findings were demonstrated in a 2014 meta-analysis(146) and national BCSP data (17). The effect of lesion size on recurrence may have been reduced by the selection of certain endoscopists considered more suitable to manage these lesions, with only 7 or the 15 endoscopists undertaking therapy on lesions at least 40mm size. Increased polyp size was associated with an increased likelihood of surgery as with national data (20-29mm: 24.2%, 30-39mm: 36%, ≥ 40 mm: 49.2%, $p = 0.002$). However, increased malignancy incidence in relation to increased lesion size appears to be a major factor in this finding with 59/89 (66.3%) of surgical cases undergoing surgery due to malignancy.

Lesion location is related to likelihood of recurrence

Whilst lesion location did not appear to impact on the likelihood malignancy, it did appear to be an important factor in recurrence with 12 month recurrence rates of 2.6%, 9.8% and 27.8% for left colon, right colon and caecal LNPCPs respectively ($p=0.003$). Further analysis of caecal lesions specifically identified caecal lesions specifically as being of the highest risk of recurrence with over a 5-fold increase in risk seen (caecal: 27.8% vs non-caecal: 5.1%, $p=0.007$ two-sided). Multivariable analysis also demonstrated this association (Odds Ratio: 14.231, 95%CI: 2.491-81.283, $p=0.003$), with proximal lesion location the only factor found to be associated with 12 month recurrence. In view of this finding, it might be speculated that proximal location would also be associated with an increased need for surgery. Although this finding was reported in national data, no statistical association was demonstrated in this series ($p=0.406$), indicating that most of these lesions were eventually cleared endoscopically (17). Whilst, the wide 95% confidence interval highlights the need for further investigation into the finding of increased recurrence with more proximal LNPCPs, the results from this series confirms the increased technical demands associated with the endoscopic resection of proximal, and especially caecal LNPCPs. In view of an increased risk of endoscopic treatment failure, in addition to the established increased risk of adverse endoscopic events, it appears justified to conclude that caecal LNPCPs may benefit from multidisciplinary discussion and should only be managed by experienced clinicians.

A finding of right sided lesions, particularly caecal lesions, being associated with increased recurrence has not previously been reported, indicating that this is a new finding. There appear to be several reasons for this finding. With large volume data identifying the removal of caecal lesions as being associated with an increased perforation and bleeding risk, it may be speculated that increased caution was used in the resection of lesions in the thinner right colon and caecum than in the left colon (101). The coagulation element of diathermy may be used more sparingly whilst the application of measures to manage potential small residual pieces such as APC may have been more limited due to the concern of perforation. In addition, it is possible that increased recurrence occurred due to these proximal lesions being removed in more numerous, smaller pieces using smaller snares than elsewhere in the colon to limit the potentially increased risk of perforation secondary to prolonged diathermy use. The results of a 2012 Japanese study ($n=222$) reporting that lesions removed in at least five pieces had a threefold increased risk of lesion recurrence

compared with lesions removed in less than five pieces ($p=0.005$) supports this theory (289). In addition, the more tangential approach required for caecal therapy, as opposed to elsewhere may have limited the ability to undertake successful therapy such as submucosal lifting (101).

Whilst the impact of this finding would likely be strengthened by corroborative data from larger case series, these results do support the rationale for citing right sided locations as more complex than those in the left colon in the SMSA scoring system (6).

Polyp Morphology

Assessment of polyp morphology was limited due to its varied reporting on both the BCSP database and on endoscopy reporting software. In view of this polyp morphology was categorised as 'flat' or 'sessile'. A finding of increased recurrence with flat lesions may have been plausible given the potentially increased technical difficulty ensnaring a flat lesion prior to resection. However, polyp morphology appeared to have no impact on the risk of malignancy with malignancy in flat and sessile lesions reported in 80% and 70.8% of cases respectively ($p=0.272$). In addition, polyp morphology did not appear to affect the likelihood of lesion recurrence at either 3 months (flat: 16.7% vs sessile: 25.8%, $p=0.348$) or 12 months (flat: 4% vs sessile: 9.1%, $p=0.689$). The limited nature of polyp morphology reporting in the BCSP may account for the lack of association seen in this series.

Interaction analysis between all variables to ascertain possible additive risk of recurrence or malignancy (e.g. polyp size + lesion location) did not demonstrate any combinations suggesting an increased risk of either of these scenarios.

Endoscopist procedure volume, seen as an important factor for analysis due to evidence that increased regular endoscopic practice leads to improved outcomes, did appear to be relevant in terms of LNPCP outcomes in terms of successful resection. When procedure volume was split into low ($n<30$) and high volume ($n\geq 30$) groups, an almost four-fold increase in 12 month RRP was seen in the low volume group (12.3% vs 3.2%, $p=0.05$ (1-sided), $p=0.064$ (2-sided)). It can be argued that the p-values, although not demonstrating statistical significance, do approach this and are a result of the study being underpowered. The results may therefore indicate clinical significance and warrant further investigation with a larger sample size. The use of secondary surgery, a marker to indicate both ineffective

endoscopic assessment and initial management did not appear to differ between the high and low volume groups however (22.1% vs 17.2% ($p=0.243$ (1-sided) $p=0.471$ (2-sided))).

5.9.2) Argon Plasma Coagulation in relation to Residual/Recurrent tissue

The use of argon plasma coagulation (APC) with piecemeal endotherapy has been debated extensively in existing literature with conflicting evidence presented with regards to its merits in reducing recurrent/residual polyp (RRP) on follow-up (182, 184). Whilst a 2002 UK study reported a marked reduction in RRP ($n= 21$, 10% vs 64%, $p=0.02$), a later Australian study identified APC use as an independent risk factor for RRP ($n= 479$, 39.5% vs 17.5%, $p=0.002$) (5, 184). The use of APC on lesions within this series could be analysed due to the recording of its use being mandatory in the 'additional therapy' section when entering details onto the BCSP database. On review of all piecemeal endoscopic cases, it was clear that its use was extremely mixed between the North East BCSP endoscopists with routine use by some, occasional use by others and lack of use by the remaining clinicians in any cases. APC was used in 67 cases with the results likely to prompt further discussion. APC use appeared to demonstrate reduced RRP on first follow-up (17.9% vs 31.4%, $p= 0.042$ 1-sided, $p=0.064$ 2-sided). While statistical significance was only seen on 1-sided chi-square analysis, the level of recurrence was over 40% lower in the APC group (31.4% vs 17.9%). It can be argued that the study may be underpowered and that the result likely indicates clinical significance. This data does not support the data from other studies indicating a possible detrimental effect of APC. Whilst the use of APC is likely to be more standardised within the BCSP, the exact circumstances of its use, such as the amount of residual tissue post snare resection remaining prior to APC use in other studies, is unclear. APC appears appropriate therapy for tiny residual polyp fragments post snare resection, as opposed to larger tissue areas. A large randomised controlled trial with a standardised protocol for APC application would add further evidence.

5.9.3) Intercentre analysis

Whilst the proportion of cases (80.3%) subject to primary endotherapy clearly identified endotherapy as first line management of LNPCPs, in keeping with numerous international case series, the level of use of primary endotherapy appeared to vary between Tees (71.9%) and the other centres (85%), although this difference in management was not statistically

significant ($p=0.097$). This difference did however indicate potential for variable outcomes between the centres based on the decision making approach with secondary surgical rescue therapy considered rescue therapy for inappropriate endotherapy in the context of malignancy or technical issues and primary surgery for benign lesions worthy of closer scrutiny.

Use of secondary surgery

Whilst the proportion of cases requiring secondary surgery after initial endotherapy in the North East series was comparable to national BCSP data (19% vs 16.1%), there was significant variation between the centres (10-1%-34.5%) with the likelihood of screening centre location affecting the likelihood of secondary surgery strongly statistically significant ($p=0.008$). Similarly, the likelihood of having piecemeal endotherapy on a malignant lesion varied significantly based on screening centre (7.2% -24.2%, $p=0.021$), although the overall proportion of 15.6% was higher compared with national data (6.7%). Piecemeal endotherapy on malignant lesions took place in 15.6% of cases. The incidence of primary surgical management varied widely (14.8-28.1%), a trend in accordance with national data (7-36%). The overall incidence of primary surgery on lesions found to be benign appeared high at almost 1 in 4 cases (24%) but did vary markedly between the North East centres, in spite of the absence of statistical significance, ranging between 0 and 37%. These results indicate continued variation in decision making and management over an extended period of time, in keeping with the shorter term national data.

Recurrence

Analysis of recurrence rates at both early (3 month) and late stages (12 month) demonstrated significant variation between the centres. Total 3 month recurrence was 24%, compared with 16.5% in the national series however this varied markedly between the centres ranging between 11.8 and 46.4% ($n=150$, $p=0.011$) indicating that the choice of screening centre was significantly associated with the likelihood of 3 month RRP. This finding may indicate inferior endoscopic technical ability in the worst performing centre but also may be due to superior endoscopic assessment for recurrence on follow-up. A similar pattern was seen with the incidence of 12 month recurrence. The regional level of 8.1% was similar to the nationally reported figure of 6% whilst individual centre outcomes ranged

between 0 and 29.2% (n=135, p=0.001) demonstrating screening centre choice as having a strongly significant association with the likelihood of 12 month recurrence . There were five cases (3.7%) of recurrence identified at 12 month where none had been reported at 3 months. Whilst these cases may be genuine cases of new 'late' recurrence, it also appears plausible that residual tissue was not detected at earlier surveillance.

12 month RRP, as an internationally recognised marker for curative resection, is considered to be a more important outcome than at 3 months. This is not least due to the widespread recognition of high early recurrence rates associated with piecemeal resection that can be effectively treated on follow-up and these figures demonstrate a strongly significant difference in the likelihood of undergoing curative resection based on the screening centre. The implications of variation in 3 month levels are worthy of consideration however, as this marker is used to assess the quality and completeness of initial endoscopic resection given that this cannot be assessed histologically with piecemeal resection specimen. It can therefore be concluded that the quality of initial endoscopic resection varies significantly between centres.

Timeliness

Ensuring a timely service is increasingly being seen as an important outcome, especially given the risk of malignancy within LNCPs. Assessment of endoscopic management time periods indicated that 95% of LNCPs were managed within 8 weeks of initial diagnosis with individual centre figures ranging between 89.9 and 100% (p=0.086) and it can be concluded that the North East BCSP had continually provided a timely service.

Endoscopist procedure volume in relation to outcomes

Whilst it was possible to record outcomes for individual endoscopists within this period, the large number of BCSP endoscopists and marked variation between endoscopists in terms of LNCPs managed meant that, while individual performance could be assessed, statistical analysis based on individual endoscopist outcomes was not feasible. It was considered desirable however, to ascertain whether increased endotherapy volume was associated with improved outcomes in LNCP management given previous data indicating improved outcomes with increased experience with standard polypectomy (65, 66). This was undertaken by dividing the endoscopists into 2 groups (high volume (≥ 30) vs low volume (< 30) endotherapy groups). No association was demonstrated between procedure volume

and early residual/recurrent polyp ($p=0.243$ (1-sided), $p=0.444$ (2-sided)), or the use of secondary surgical management following ineffective endotherapy ($p=0.276$ (1-sided) $p=0.471$ (2-sided)). In addition, no statistical association was found with persistent RRP/curative rate ($p=0.050$ (1-sided), $p=0.064$ (2-sided)). However, it can be argued that the study was underpowered and that a clinical association was demonstrated with a p-value close to statistical significance and an almost 4-fold increased rate of failed curative resection (12.3% vs 3.2%).

Complications

The overall level of complications was low with no cases of mortality or perforation, one case of PPS and seven cases of PPB (3.3%). Of the PPB cases, three were minor requiring no management, three were of intermediate severity with one requiring repeat endotherapy and one case was major requiring surgical intervention to achieve haemostasis. These figures appear comparable with national figures (see table 13).

Limitations

A major limitation identified with current BCSP data collection was the paucity of information on the database for cases where follow up took place outside of BCSP, invariably due patients falling outside the BCSP age range (55-79). Whilst information for these cases was obtainable onsite at the relevant hospitals, it would appear important to ensure that relevant surveillance information from an initial BCSP procedure is kept for all patients to allow accurate long term audit and quality analysis. In addition, whilst the list of identified cases was accurate to the best of our knowledge, a reliance on single person data entry onto the central database raises the possibility of missing LNPCPs due to details not being captured on the BCSP database at the time of endoscopy. This is unlikely however, given the fastidious nature of data entry during all BCSP procedures.

5.9.4) Analysis of outcomes and application of Key Performance Indicators to North East of England Outcomes

There appears to be marked variation in outcomes between the individual centres with a statistically significant difference in many outcomes (see table 13). The implications of these findings are of great importance as the quality of overall management received appears to vary based on screening centre location. Furthermore these results were collected within a national screening programme featuring experienced accredited endoscopists and detailed audit in an attempt to continually maintain uniform high standards.

Whilst there was a clear variation in outcomes between centres, each centre appeared to perform better in certain aspects. The application of recently agreed KPIs (developed to assess and compare performance and previously described in this thesis) was undertaken to identify the best and worst performing centres, warranting further investigation, and further specify where improvements can be made (see table 13).

The application of KPIs demonstrated that the use of surgery (secondary and primary management for benign lesions) was highest in centres B and D, the two highest volume centres due to service population, with the former using a high level of secondary surgery and the latter using primary surgery for benign lesions. These are findings that would warrant further investigation. These two centres also appeared to be the most effective endoscopically with the lowest rates of 12 month recurrence. The KPIs therefore indicate that these centres performed worse in terms of decision making but were the best in terms of endoscopic efficacy. Centre C had a 12 month recurrence rate far high than the other centres (29.2%), potentially indicating poorer overall endoscopic skill. Given that endoscopic clearance was achieved at 15 months in six of the seven cases with recurrence at 12 months, whilst complications were minimal, it might be suggested that no patient harm occurred. However, the other case of 12 month recurrence did eventually require surgery for malignancy not previously identified and it cannot be discounted that malignant transformation occurred during endoscopic surveillance. In view of this, the use of 12 month outcomes as a marker of endoscopic skill does appear valid to emphasise the importance of achieving curative resection as soon as possible to reduce the risk of adenoma to carcinoma transformation. Complication rates were acceptable in all centres whilst all centres appeared to provide a timely service.

The preliminary results were presented and discussed at a North East regional BCSP meeting in an attempt to identify the reasons behind the variation in outcomes. Whilst the quality of decision making appeared to be an important factor, it became apparent from discussion that a causative factor for high rates of endoscopic resection on malignant lesions in at least one centre (centre B) was the reticence of local colorectal surgeons to undertake surgery on lesions where malignancy was suspected without biopsy proven malignancy despite high endoscopic suspicion. This did not appear to be the case in other centres where it was reported that surgeons were happy to undertake resection based on a high suspicion of endoscopic malignancy. In addition, the availability of services locally appeared to be important. At centre D, where the use of primary surgery appeared higher than at other centres, the availability of a long- established TEMS onsite for the management of rectal lesions may explain why a number of rectal lesions underwent surgical management. In addition, it became apparent from discussion that many LNPCPs identified were not discussed with other endoscopists at the same site prior to a decision on management. For example, multiple cases were referred for surgical management without consultation with another endoscopist about the feasibility of endoscopic resection. This practice did not appear to occur at the other centres. Another potentially important factor was that the mean lesion size in centres B (37.6mm) and D (35.5mm) was larger than in centres A (32mm) and C (31.8mm). Increased size was found to be statistically associated with an increased likelihood of both requiring surgery and a finding of malignancy (with the former related to a finding of malignancy in many cases) and this may also explain the higher use of surgery in these centres.

The higher level of 12 month recurrence at centre C was also discussed. A potentially important factor was that endoscopic surveillance in certain cases (including the case where malignancy was eventually seen) where RRP was found at 3 months and subject to repeat therapy, no further surveillance took place until around 12 months. This approach differed to other centres where repeat assessment/therapy frequently took place on at least a 3 monthly basis until clearance was considered achieved. This indicates the importance of frequent endoscopic assessment of residual tissue until clearance is confirmed. In addition, repeat therapy appeared to be undertaken by a different endoscopist to that undertaking initial therapy more frequently in centre C. Whilst this is likely to be a result of service demands, it was considered an important principle that the initial endoscopist also undertakes surveillance and it can be speculated that a lack of endoscopic continuity may

have contributed to this result. Although proximal lesion location was strongly associated with lesion recurrence, this does not appear to have influenced the outcomes at centre C with centres A and B both having a higher proportion of right sided lesions managed endoscopically (Centre A: 20.6% caecal lesions, 52.9% right sided lesions; Centre B: 6.8% caecal location, 35.1% right sided location; Centre C: 11.1% caecal location, 37.3% right sided location; Centre D: 14.5% caecal location, 49.3% right sided location).

In addition, whilst all services provided a timely service, centre D had the lowest proportion of cases managed within 8 weeks. It is likely that this was a result of fewer endoscopists undertaking LNPCP removal compared with other centres.

Further discussions about techniques used during endotherapy indicated wide variation. In addition to variable use of APC, it was apparent that various type of snares were used in addition to the types of lifting solutions, lifting techniques (e.g. total lesion lift vs sequential piecemeal lift and resect) and the choice of diathermy type and settings.

5.9A) Summary

The outcomes from this series indicate safe, high quality overall management within the North East BCSP over a sustained time period, with an endoscopic curative rate of almost 92% at 12 months and almost all cases with recurrence at 12 months reported as having successful subsequent eradication without the need for surgery. In addition, there was a very low level of complications with no cases of perforation or mortality (see table 12). These figures are comparable with outcomes from various international case series (see table 14). Despite this, this series demonstrates a variation in management between BCSP centres over a sustained period, supporting the finding from national data over a shorter time period. In addition, there was a markedly higher level of piecemeal endoscopic resection of malignant lesions (approximately three times higher), a lower level of single session complete endoscopic resection and a marginally higher need for secondary surgery in this series. These findings suggest inadequacies within the North East region with the decision making processes taken during colonoscopy and highlight the need for enhanced decision making modalities such as a complex polyp multidisciplinary team meeting (MDM).

A key benefit of analysing regional data with closely aligned centres was the enhanced ability to discuss findings and to identify potential causative factors for important findings. Whilst national analysis may be more reliant on findings from the BCSP database, regional analysis allowed for discussion of findings in person and closer scrutiny of details using local endoscopy databases. Given the variation in decision making and endoscopic technique identified along with statistically significant variation on outcomes over a sustained time period, it can be concluded that variation in management does appear to result in variable outcomes in the management of LNPCPs. In addition, this is the first case series where the application of KPIs has been undertaken. The ability of KPIs to assess both performance areas warranting further scrutiny appears accurate and indicates their feasibility as a continued performance monitor of LNPCP management and performance.

	North East BCSP	Moss et al (2011)	BCSP (Lee et al, 2013)	Buchner et al (2012)	Longcroft-Wheaton et al (2013)
Number of NCPCs managed endoscopically	211	479	436	308	187
Mean size (mm)	31.2	35.6	29.5	23	41.5
Cases with complete resection considered achieved after single session (%)	84.4	89.2	Not assessed	91	90%
Malignancy in resection specimen (%)	15.6	6.9	6	4.4	5.9
Need for surgery (%)	18.5	16.3	16.1	10	9
3 month recurrence (%)	24	20.4	16.5	27	14.5
12 month recurrence (%)	8.1	2	6	16.3	3.9
Delayed Bleeding	3.3	2.9	3	7.2	2.7
Perforation	0	1.3	0.5	0.4	0.45

Table 14. Comparison of NE BCSP LNPCP Outcomes with International Series

Chapter 6: Establishment of a Multidisciplinary Network for the Management of Large Non-Pedunculated Colorectal Polyps

6.1) Introduction

The use of multidisciplinary team management and networks has long been established as standard practice for the management of malignancy with the intention of improving cancer outcomes with NICE guidelines mandating their use (290). The use of this collaborative care has been credited with helping to deliver a more coordinated and standardised service for patients nationally and in view of this, there has been a drive to provide a multidisciplinary team based approach for chronic and complex conditions (280). The combined expertise of various specialists is considered superior to that of single clinician or single specialty care, mainly due to the increased likelihood of all potential therapeutic options being considered (23). A central component of multidisciplinary care is the use of multidisciplinary team meetings (MDT) where clinicians from various relevant specialties discuss patient details such as comorbidity, diagnosis, histological and radiological factors, treatment options and other potentially important factors. The interaction in these meetings is seen as key to delivering effective holistic care. As previously discussed, there have been positive examples of MDT use related to complex gastroenterological conditions and complex endoscopic therapy such as early rectal cancer and the use of therapeutic endoscopic retrograde cholangiopancreatography (ERCP) for hepatobiliary disorders respectively. For example, the use of an MDT approach with the management of early rectal cancer was associated with a reduced level of invasive surgery, thereby exposing patients to reduced morbidity (23). A prospective case control study demonstrated that MDT input prior to undertaking therapeutic ERCP was associated with a marked reduction in patient complications in (n=1909, MDT: 6.9% vs No MDT: 12%, p<0.001) (24).

The use of multidisciplinary based care appears suitable for the management of large non-pedunculated colorectal polyps (LNPCPS) and other complex polyps (see table 15). Data from the Bowel Cancer Screening Programme (BCSP) has demonstrated that variation in practice and management exists even amongst the most highly experienced endoscopists (17). In addition, suboptimal outcomes such as the piecemeal endoscopic management of malignant polyps and surgical resection of benign lesions are more commonplace than previously thought, whilst data reported in this thesis appears to confirm that variation in

management leads to different outcomes (20). The consequences of incorrect management are significant with surgery more costly than endoscopic therapy and more hazardous with 1% mortality and 20% morbidity reported (291). Endoscopic therapy in certain circumstances may be insufficient and hazardous, exposing a patient to additional invasive procedures and increased morbidity. Another compelling reason for the discussion of complex polyps in a multidisciplinary setting is the increase in diagnostic and therapeutic tools and expertise in delivering these modalities. For example, access to centres with superior endoscopic equipment such as HD imaging and video recording may provide improved diagnostic information. In addition, it could be argued that increased engagement with clinicians proficient with minimally invasive surgical techniques such as transanal surgery and other endoscopic options such as endoscopic submucosal dissection (ESD) not universally available may lead to an increased number of patients undergoing less invasive diagnostic and therapeutic procedures with associated reductions in patient morbidity and cost.

Issue	Justification	Evidence
Evidence of uncoordinated suboptimal management?	Yes, no current management framework in place. BCSP data has demonstrated wide variation in practice with a higher than expected rate of cases with management considered to be suboptimal whilst variation in practice appears to result in variable outcomes	Lee et al, 2013 Unpublished BCSP data in this thesis
Serious consequences with incorrect therapy?	Yes, surgical therapy is associated with increased procedure cost and associated hospital stay in addition to increased morbidity and should be avoided in the case of endoscopically resectable lesions. Inappropriate endoscopic therapy may result in increased complications and exposure to further invasive procedures	Bertelson et al, 2012 Swan et al, 2011 Longcroft Wheaton et al, 2013 Ahlenstein et al, 2014
Complexity associated with treatment options?	Yes, advanced endoscopic techniques such as EMR and ESD are associated with potentially life threatening complications, especially when conducted by clinicians without the requisite expertise. Transanal surgery, although less invasive than resectional surgery is a complex procedure and may take several hours. In certain circumstances, a combined endoscopic/laparoscopic surgical approach may be desirable	Rutter et al, 2014 Albert et al, 2013 Barendse et al, 2012 Franklin et al, 2009
Availability of multiple treatment options?	Yes, in addition to EMR and resectional surgery (open and laparoscopic), there is increasing evidence that advanced techniques such as ESD and transanal microsurgery may be used for many colorectal lesions with improved histological diagnoses and treatment outcomes	Saito et al, 2011 Albert et al, 2013 Arezzo et al, 2014
Limited availability of complex treatment options?	Yes, options such as ESD and transanal microsurgery are commonly only available in tertiary referral centres. Establishing a regional network may increase knowledge and access of these treatment options	-

Table 15. Factors suggestive of MDM suitability in LNCP management

The information in table 15 indicates that applying a multidisciplinary approach may better coordinate and improve LNPCP management. There is an increasing appetite for this approach with complex polyp meetings in existence for at least 2 years at Cardiff University NHS Trust Hospital, Queen Alexandra Hospital NHS Trust (Portsmouth) and the Wolfson Endoscopy Unit, St Mark's Hospital (London). However, these are predominantly single expert centre meetings, potentially dealing with only a small selection of referred cases and not concerned with the coordinated decision-making and management across a geographical region, with little participation from a referring centre.

There have been a number of issues reported that have made the establishment of an MDM more prohibitive. An important consideration is that the ability to make robust decisions is strongly based on the information offered to the MDM panel, and this suggests the need for a standardised minimum dataset to ensure that the requisite patient and lesion information is obtained prior to MDM discussion. Other reported issues are the logistics of running a new meeting. In addition to finding a time and venue suitable for all key stakeholders, encouraging enthusiasm and cooperation by individuals already busy with other commitments has been cited as a potential difficulty (292). A pilot study may determine whether the establishment of a regional multicentre complex polyp MDM is both beneficial and sustainable in spite of these factors.

6.1.1) Null Hypothesis

The implementation of a complex polyp MDM will not result in improved LNPCP management outcomes.

6.2) Methodology

6.2.1) Initial Planning

The development of a complex polyp MDM was intended as a preliminary study. Initial consultation took place with centres in Cardiff and Portsmouth, where polyp MDMs were already established, with regards to the identification of key factors required for robust case discussion. This information was subsequently used to identify potential key assessment parameters that were subsequently forwarded to an expert panel for consideration. As described in chapter 2, consensus methodology using a modified Delphi technique was then

used to determine finalised parameters on a complex polyp MDM proforma datasheet that would allow a structured discussion during an MDM.

6.2.2) Consensus methodology use

A BSG sanctioned working party (GDG) of 13 individuals, with a steering group subcommittee, consisting of multidisciplinary key stakeholders in a potential MDM was created in the process described in chapter 3. The panel, featuring nominations by the BSG endoscopy committee, the Association of Coloproctology of Great Britain and Ireland (ACPBI) and the Royal College of Pathology, consisted of key stakeholders in a multidisciplinary process including, endoscopists (expert and referring), colorectal surgeons, a gastrointestinal pathologist and a patient representative. Identified individuals were then approached via email to enquire about their interest and availability in participating in the consensus process. A literature review was conducted as described in chapter 2 and, combined with the input obtained from the Cardiff and Portsmouth centres, a minimum dataset proforma was created containing features felt vital with regards the comprehensive complex polyp discussion. The GDG were then asked to vote via email their level of agreement with included parameters on a 5 point scale from 1-5 (1=strongly agree, 5 = strongly disagree) in addition to their comments including suggestions for other potential parameters. A minimum of 80% agreement was required for consensus to be considered achieved. A second round of voting was conducted via email for remaining parameters where consensus was not yet reached with participants allowed to see anonymised comments and scores from the group for the previous round. Plans for a third round of voting during a scheduled group meeting were in place if required. Following the consensus process, the final agreed proforma was reviewed by the GDG for final comments prior to use.

Following finalisation of the proforma, a proposed framework for MDM meetings was formulated. The MDM was implemented within the BCSP due to the large volume of lesions encountered within the programme, the high quality of endoscopists who have passed strict certification criteria and the infrastructure already in place that ensured comprehensive documentation of procedures and clinician collaboration. However, it was agreed that the meeting should provide a forum for discussion of both BCSP and non-BCSP cases to increase both the intended benefit and sample size. A framework discussion document was sent for

consultation to all members of NHS BCSP North East (Clinical Directors, endoscopists and specialist screening practitioner nurses (SSPs)) and all were invited to participate. Each screening centre was asked to nominate at least 2 colorectal surgeons to regularly participate in MDM process with the intention of increasing the potential management options (e.g. laparoscopic surgery and transanal surgery) to the MDM. National expert centre endoscopists were approached from the GDG to provide a 'national expert pool' for cases where an MDM recommendation could not be made, such as areas with ongoing disagreement or where local expertise was not considered to be available.

6.3) Organisation and Implementation of Regional Complex Polyp Multidisciplinary Meeting

6.3.1) Logistical Issues and Solutions

Discussions took place at a BCSP regional meeting in May 2014 to discuss the logistics regarding the provision of a regular complex polyp MDM. There was a stated desire to reduce both the use of surgery for benign lesions and piecemeal endoscopic management of malignant lesions whilst reducing the variation in management seen between different centres.

Potential difficulties cited included potential limitations of participant availability. It was felt that the extra time demands on participants with an already busy schedule may limit enthusiasm for full participation and there was an initial unwillingness by some BCSP endoscopists to become involved in the process. Professor Rutter was able to mandate participation by the North East BCSP unilaterally in his capacity as Quality Assurance (QA) chair. This included the mandatory referral of all LNPCPs fulfilling specific criteria. In addition, ensuring both a feasible and robust method of allowing participant communication was an issue. It was not possible to hold a physical meeting in a single centre given the large number of screening centres and geographical area covered by the North East BCSP. In addition, the technology available to different centres in the area varied widely, an example included access to videoconference facilities. The lack of a single centre meeting also raised difficulties about ensuring that participants had access to relevant information such as patient and lesion factors, and imaging (such as high quality photos and videos) that allowed for valid input and robust decision making. More specifically, a method of sharing large file videos was required, whilst it was vital to ensure that the transfer of patient identifiable

information between participants was conducted in a secure manner approved by all involved NHS trusts. Other crucial considerations were the identification of key multidisciplinary stakeholders required for the meetings and obtaining agreement about which lesions required MDM discussion, with a need to ensure that the MDM did not delay the management of routine lesions and that there was sufficient time to discuss cases thoroughly. In addition, meetings needed to be held regularly enough to ensure that management was not delayed unnecessarily due to waiting for MDM discussion.

An MDM terms of reference document detailing meeting proposals such as meeting format, information transfer and indications for mandatory referral was then sent to all relevant persons including BCSP endoscopists and SSPs. This was routinely re-sent on a monthly basis along with separate reminders about meeting times and mandatory referral criteria to increase awareness about the MDM process.

Polyps defined as 'complex polyps' during the formulation of large polyp management guidelines in chapter 3 (see figure 17) were identified as suitable for discussion in the MDM. There was also agreement that all benign lesions being considered for surgery warranted referral whilst endoscopists were encouraged to refer any lesions that they felt warranted discussion from both within and outside of the BCSP (see below).

Inclusion criteria

- Any benign lesions planned for surgical management
- Any lesions $\geq 40\text{mm}$
- Lesions classified as complex in accordance with BSG Guidelines:
 - **increased risk of malignancy** - Pit pattern type V, Paris 0-IIc or 0-IIa+c morphology, non-granular LST (laterally spreading type polyp, LST-NG), granular LSTs (LST-G) with a dominant nodule, distorted surface pattern, colour and vessels (NICE NBI type III), thick and irregular microvessels (Sano capillary pattern type III)
 - **increased risk of incomplete resection/recurrence** - Size of at least 40mm; involving ileocaecal valve, appendix, diverticulum or dentate line; within an inflamed segment of colitis; prior failed attempt at resection or recurrence at site of previous resection (excluding unifocal, diminutive and easily resected/ablated residual adenoma on first site check); non-lifting sign after submucosal injection; endoscopist concern about difficult location (e.g. behind flexure or fold, in stenotic diverticular disease);
 - **increased risk of adverse event** - Caecal location of 20+mm; elsewhere a size of at least 40mm
 - **SMSA level 4**
- Any lesion felt to warrant inclusion by endoscopist

Figure 17. Mandatory referral criteria for LNPCPs identified within BCSP

An email survey was conducted to identify participant availability with clinicians asked to indicate their availability during the week to participate in addition to obtaining their views on the frequency of meetings. Fortnightly one hour meetings (case permitting) on alternate Thursdays at 5pm were agreed based on voting indicative that this time and frequency would ensure maximum participation. It was agreed that the fortnightly format may be reviewed depending on the demand for the service whilst the meeting day was flexible depending on potential changes in participant availability. Key multidisciplinary stakeholders required for the meeting and for as required input were identified according to the disciplines identified in the development of BSG guidelines. These included BCSP endoscopists, laparoscopic colorectal surgeons, advanced endoscopists, gastrointestinal histopathology (input as required) and gastrointestinal radiology (input as required).

Audio teleconferencing was proposed as the communication modality of choice for the MDM. This allowed participants to dial in at any location, facilitating easier participation, as opposed to attempting to physically convene clinicians in one room. In addition, the need for videoconferencing facilities, not available to all centres, was negated. A case document

detailing cases for discussion along with relevant media (still images/videos) was circulated to an MDM mailing list approximately 48 hours before meetings. This would allow those unable to attend but wishing to participate to give input, thereby maximising the potential for participation. All participants were required to obtain an NHSmail account as this is the only approved method by NHS trusts for transferring NHS patient identifiable information between different NHS sites at the time of MDM establishment. MDM outcomes were sent to the mailing list 24-48 hours post MDM discussion to allow comments on management plans reached from those unable to attend to ensure that decisions made were as robust as possible, as well as providing an educational resource to participants.

The MDM proforma, agreed using consensus methodology as described earlier was designed with the intention of ensuring that all relevant information pertaining to both patient and lesion factors would be shared. Video files of referred lesions were identified as the preferred media as this allowed for more robust image assessment by MDM participants. However, high quality images were also encouraged in view of a variation in the availability of video recording facilities across the region. The ability to obtain and disseminate high quality imaging was considered as not only important in guiding case discussion, but also to reduce the need for repeat endoscopy for diagnostic purposes which had been an issue previously. Videos could not be sent routinely using NHSmail due to a size limit of 20 megabytes per email as this limit would only allow for videos of a few seconds. Videos were thus sent via the NHSmail secure file transfer application which allowed for transfer of files up to one gigabyte in size and password access to both send and receive files. Instructions were also sent to participants on the mailing list on how to set up and use the NHSmail secure file transfer application

Editing of videos was undertaken using 'RealPlayer' computer software with the attainment of high quality still images from the videos also possible using the provided image capture software. This ensured best possible imaging in scenarios where video transfer/playback was not possible. Following discussions with the North Tees and Hartlepool NHS Foundation Trust information technology department about suitable media playback platforms on NHS computers, the 'VLC video player' and 'JPEG' imaging modalities were used for viewing images across the region.

The meetings discussed new cases in addition to re-discussion of cases that had undergone management and or follow-up management. Professor Rutter chaired meetings in his

capacity as the BCSP QA chairperson and an expert endoscopist whilst I undertook the role of MDM scribe and coordinator. A nominated deputy chairperson (Dr Jamie Barbour) was also available for both chairing and scribing duties if needed. Essential participants at the meetings included core participants (chair and deputy chairpersons and coordinator), referring endoscopists and at least one laparoscopic colorectal surgeon. Participants were encouraged to make parallel referrals to existing colorectal cancer MDTs in cases with a strong suspicion of malignancy to ensure no delay in potential cancer management due to a wait for complex polyp MDM discussion, whilst also enabling continued detailed radiological and histological input for these cases. With regards to the complex polyp MDM, gastrointestinal radiological and histological input was obtained by nominated specialists at each centre on an as required basis in advance of case discussions at meetings. A pool of external endoscopists considered national experts were secured to provide expertise in cases with ongoing regional conflict or where potential suitable therapies were not available within the North East region.

A Microsoft Excel Database of all cases discussed was kept securely on a password protected trust computer in a locked room with the intention of building a prospective polyp MDM database and serving as a reminder to chase follow-up case outcomes. Data transfer was only conducted via secure NHS email accounts. The database was also used as a means of a reminder for re-discussion of cases with outcomes.

Compliance with the MDM process was assessed on a 3 monthly basis. A datasheet with all identified complex lesions in this period was obtained from BCSP central database. This datasheet was readily available to Professor Rutter in his capacity as QA chairperson and was compared with our database to assess compliance. Details about non-referred cases and reminders about the MDM referral criteria were sent to non-complying endoscopists and centres.

After seven months, data was analysed to assess for any benefit from the meeting, such as an improvement in regional performance and reduced variation in practice.

Feedback was also sought via an email questionnaire and in person at a regional BCSP meeting scheduled around the pilot endpoint to ascertain whether participants considered the MDM to have resulted in improved LNPCP management.

6.4) Results

6.4.1) Identification of Parameters for Inclusion in MDT Minimum Dataset Proforma

A. Patient details

1. Significant drug history (e.g. warfarin)

Consensus reached at round 1: 100% Agreement

2. Other pathology in the colon, e.g. IBD

Consensus reached at round 1: 100% Agreement

3. Patient wishes/preference?

Consensus reached at round 1: 100% Agreement

4. Significant comorbidities (including ASA status)

Consensus reached at round 1: 100% Agreement

5. Patient Symptoms

Consensus reached at round 1: 100% Agreement

B. Polyp details

1. Site

Consensus reached at round 1: 100% Agreement

2. Size

Consensus reached at round 1: 100% Agreement

3. Paris morphology/description

Consensus reached at Round 1: 100% Agreement

4. Polyp Surface Characteristics (e.g. Pit Pattern(s), Sano Capillary Patterns, NICE NBI Classification)'

Parameter modified from 'Pit Pattern(s) after round 1. Consensus reached at round 2: 92.3% agreement

- 5. Features indicating high risk of cancer (pit pattern v, depressed or ulcerated features, LST-non-granular, non-lifting sign)**

Consensus reached at round 1: 92.3% Agreement

- 6. Issues regarding endoscopic access (proximal aspect of fold, previous difficult/poorly tolerated colonoscopy)**

Consensus reached at round 1: 100% Agreement

- 7. Features suggesting high risk of recurrence/incomplete excision (40+mm, >75% lumen, dentate line, ICV, appendix, diverticulum, anastomotic suture line, previous failed attempts)**

Consensus reached at round 1: 100% Agreement

- 8. Available photos or video**

Consensus reached at round 1: 100% Agreement

6.4.2) Final Complex Polyp Minimum Dataset Sheet (Figure 18)

Patient details: NAME :		NHS NUMBER:
DoB/Age		
Gender		
Endoscopist+ Centre		
Any significant comorbidity/ASA score		
Any significant drug history (e.g. warfarin)		
Patient Symptoms		
Any other pathology in the colon? e.g. IBD		
Does patient have any particular wishes/preference?		
Polyp details		
Site		
Size		
Paris morphology/description 0-IIC or 0-IIa+c?		
Polyp Surface Characteristics (e.g. Pit pattern(s), Sano Capillary Pattern, NICE NBI Classification) Pit Pattern V/Sano CP III/NICE NBI Type 3		
Any other polyp features indicating high risk of cancer (depressed or ulcerated features, LST-NG, LST-G with dominant nodule non-lifting sign)?		
Any access issues (proximal aspect of fold, previous difficult/poorly tolerated colonoscopy etc.)		
Any high risk of recurrence/incomplete excision (40+mm, >75% lumen, dentate line, ICV, appendix, diverticulum, anastomotic suture line, previous failed attempts)		
Known Histopathology/Radiology		
Please provide photos or video (if providing photos please include full lesion margins and chromoendoscopic imaging)		
Previous management?		
Question for MDM :		

6.4.3) Cases Discussed

1) 62 year old male with 60mm hepatic flexure LNPCP

This LNPCP had been removed during a BCSP colonoscopy prior to MDM referral with piecemeal endoscopic mucosal resection (pEMR) and application of argon plasma coagulation (APC) to the resection margins. Complete resection was considered to have taken place but a referral was made to discuss whether endotherapy was considered by others to be the correct treatment and agree on further follow up. Histology was benign with the LNPCP reported as a tubular adenoma with low grade dysplasia. Video assessment of the lesion was available and there was unanimous agreement that endotherapy was the correct decision. 3 month surveillance was suggested which confirmed lesion eradication and 12 month repeat surveillance was agreed at repeat MDM discussion. In this case the MDM was felt to have helped to reassure the endoscopist regarding their assessment and decision making approaches used, in addition to ensuring an educational element with discussion between participants to discuss their decision making approaches during colonoscopy. In addition, as the first case discussed it was the first opportunity to test the rigidity of the BSG agreed MDM minimum dataset proforma and the use of photo and video imaging modalities in guiding discussion and recommendations.

2) 70 year old male with 40mm ileocaecal valve LNPCP.

The lesion concerned was a 40mm laterally spreading type polyp (LST) identified during a BCSP colonoscopy involving the ileocaecal valve and described as having a 'non-granular' surface (LST-NG). It's classification as an LST-NG indicated an increased malignancy risk whilst the detecting endoscopist was unable to ascertain lesion margins with a concern that it invaded the ileocaecal valve and involved the terminal ileum. The detecting endoscopist did not consider themselves suitable to attempt endotherapy as assessment of the lesion using the SMSA system defined it as a level 4 lesion and therefore being of the greatest complexity in terms of achieving successful endoscopic resection. The concerns about potential malignancy, unknown margins, ileal involvement and endoscopic complexity prompted the referrer to question whether endoscopic resection was preferable to surgical resection where en-bloc resection would be guaranteed. The patient concerned had no comorbidities but preferred endoscopic resection. The MDM opinion was that the images

provided made a definitive decision difficult and that expert endoscopic assessment was needed. It was agreed that both endoscopic and surgical options should be explained to the patient. In addition, it was suggested that if the patient was agreeable and the full lesion margins could be ascertained, an attempt at lifting the lesion with a submucosal injection could be attempted with subsequent resection. Repeat endoscopic assessment was successful with successful endoscopic resection taking place and subsequent histology benign. 3 month endoscopic assessment confirmed complete eradication and 12 month surveillance was suggested. The referral to MDM in this case was considered beneficial as it ensured robust endoscopic assessment, identified a suitable endoscopist to conduct successful endotherapy, and resulted in the avoidance of surgery for a benign lesion.

3) 84 year old male with 60mm rectal polyp

This gentleman was found to have a large lumen filling sessile lesion in the upper rectal region following a colonoscopy for fresh rectal bleeding. The endoscopist, considered an expert endoscopist, commented on poor views stating that he was unable to ascertain whether there were 2 small lesions or one large one, in addition to being unable to accurately comment on polyp morphology. The poor views were considered to significantly impact on the ability to achieve successful endoscopic resection. In addition, review of the images during the MDM led to the opinion that the likelihood of malignancy was high despite initial histology reporting a tubulovillous adenoma with low grade dysplasia. In addition, an MRI scan reported T2 invasion suggesting malignancy but as the lesion was in the upper rectum the scan was considered suboptimal. In this context, en-bloc excision was considered desirable but the inability to fully assess the extent of the lesion was a reason as to why transanal surgery had not yet been considered for this purpose. There was concern that the lesion could extend into the sigmoid colon and in this scenario, transanal surgery would not be able to reach the more proximal area of the lesion. In addition, in the context of multiple comorbidities, the patient was not considered fit for resectional surgery. This was considered to be an extremely complex case. The referring endoscopist had considered an attempt at endoscopic management and the possibility of conservative management was also raised although this was established to be unacceptable to the patient. The MDM opinion was that endoscopic resection was not appropriate in this case due to likely malignancy and limited lesion access and that en-bloc resection was needed if possible. It was agreed that assessment for transanal surgery should take place with excision to be

undertaken if the lesion margins could be ascertained and the proximal aspect reached with transanal surgery apparatus. This gentleman subsequently underwent successful transanal surgery with histological confirmation of malignancy (T2) and establishment of complete lesion removal. The patient was subsequently discharged to primary care. This was considered an excellent outcome with safe successful management in a complicated scenario and the avoidance of inadequate endoscopic resection due to a perceived lack of alternatives.

4) 62 year female with 100mm rectal LNPCP

The case was referred through the BCSP with what was felt to initially be a 50mm rectal laterally spreading tumour with a granular surface pattern (LST-G). Initial histology was benign with the LNPCP reported as a tubular adenoma with low grade dysplasia. In addition CT and MRI scanning did not suggest malignancy whilst the referring endoscopist felt there were no endoscopic features suggestive of malignancy such as depression, surface characteristics or a dominant nodule and favoured endoscopic resection. The images submitted were considered to be inadequate but based on the information given, both endoscopic resection and transanal surgery with TEMS were considered appropriate. The endoscopic representatives favoured the former whilst surgical counterparts favoured the latter and it was recommended that both options should be discussed with the patient prior to a decision on therapy. The patient favoured endoscopic resection and subsequently underwent this modality. During resection the lesion was found to be approximately 10cm in size, substantially larger than on first assessment but complete pEMR was considered achieved with subsequent histology benign. A small area of recurrence (3-4mm) seen on 3 month assessment was treated with APC with lesion eradication confirmed 3 months later. This case was notable with the patient able to choose a preferred treatment modality with more than one suitable modality.

5) 62 year old male with 15mm ileocaecal valve LNPCP

This gentleman was diagnosed with ileocaecal valve LST-NG over 18 months prior to the commencement of the complex polyp MDM. He had previously been deemed unsuitable for the colorectal cancer MDT due to the absence of established malignancy and had 4 colonoscopic assessments prior to MDM discussion. He had refused any therapeutic intervention citing concerns about the morbidity associated with surgery due to his chronic

obstructive pulmonary disease (COPD) (ASA 3) and the possibility of needing a stoma subsequently. He was also reticent to consider endotherapy stating that only 50% chance of endotherapy success had previously been quoted to him. As such, he would only agree to colonoscopic surveillance to assess for malignant change. No change in lesion characteristics were described whilst histopathology reporting described the lesion as benign (TVA with LGD) from biopsies on 3 occasions. He was referred from a general gastroenterology clinic to identify a definitive management strategy in view of the risk of eventual malignancy and was reported as being willing to consider management options recommended from expert opinion within the MDM. The images provided were of high quality whilst 2 of the MDM participants had undertaken colonoscopy on the patient meaning that the lesion and case could be described in detail. It was agreed that given the lack of malignant change up until this point and the small size of the lesion that an attempt at endoscopic therapy would be preferable to surgical resection however there was concern that the margins of the lesion were difficult to identify during colonoscopy whilst multiple biopsies over a long time period would render endoscopic lift and resection of the lesion difficult due to submucosal fibrosis. It was felt that an attempt at endotherapy should be undertaken by an expert endoscopist and that surgical resection should ideally only be offered if this was unsuccessful but would be offered as primary therapy if the patient still considered endotherapy unacceptable. It was agreed that both options were considered low risk in terms of morbidity and mortality in his case and that the likelihood of requiring a stoma was negligible. The patient was seen in clinic and subsequently agreed to endotherapy which was successful with no recurrence seen on follow-up. In this case it was felt that the MDM provided an expert forum and robust management plan for a complicated case where there had been almost 2 years of a stasis in management and a risk of preventable malignancy.

6) 62 year old male with 90mm rectal LNPCP

This gentleman was diagnosed with a rectal LST-G estimated to be between 50-60mm. High definition video recording of the LNPCP was available and the opinion of the MDM was that the lesion appeared benign. Endoscopic resection was felt achievable by all the participants however the colorectal surgical opinion was that the use of TEMS to achieve en-bloc resection would also be appropriate, especially as the histology demonstrated high grade dysplasia, a precursor for cancer, increasing concern about this lesion being malignant.

Endoscopic resection was attempted but the lesion much larger (90mm) than originally estimated and complete resection not possible with a posterior component considered to be fibrous and probably malignant. Histology confirmed malignancy and the patient subsequently underwent surgical resection. The video was retrospectively analysed by an external clinician, without prior knowledge case details, who correctly diagnosed malignancy. This case was an example of an incorrect MDM decision despite detailed discussion between several clinicians considered polyp experts. The consequence of this was that the patient underwent unnecessary invasive therapy and had a delay in receiving definitive surgical treatment. MDM reflection from this case was that in spite of the use of high quality media allowing robust assessment in this case, there was insufficient expertise within the existing MDM group with regards to rectal lesions and this was corrected by the inclusion of a surgeon specialising in transanal surgery for all referred rectal lesions.

7) 87 year old woman with advanced dementia with 30mm sigmoid colon LNCP

A 30mm sigmoid colon LST-G was detected during a colonoscopy following rectal bleeding. Histology results suggested that the lesion was benign (TVA with LGD). The question posed to the MDM was whether any therapy was appropriate as opposed to conservative management. The use of a validated life expectancy scoring system (Schonberg Index) suggested that the patient's risk of mortality within 5 years was over 50%, irrespective of the LNCP diagnosis. This was felt to be far more significant than the likelihood of mortality or morbidity from this lesion whilst there was unanimous opinion that attempting therapy would expose the patient to the unnecessary risk of a complex invasive procedure. This opinion was shared with the patient's next of kin who was in full agreement and conservative management was undertaken. The MDM was felt to have been invaluable in a complex and sensitive scenario, providing a robust consensus based decision which single clinician decision making would not have permitted.

8) 68 year old female with 60mm sigmoid colon LNCP

This LST-G was identified during a BCSP colonoscopy. Initial histology results reported the lesion as benign (TVA with LGD) whilst high definition video imaging was available. Endoscopic resection was recommended and considered successful however the histology results, although benign, suggested that the lesion was precancerous with high grade dysplasia (HGD). In view of this, prompt follow-up within 2-3 months was recommended to

reduce the risk of malignant transformation. Surveillance endoscopy confirmed successful eradication. The availability of video imaging was considered to have allowed more detailed lesion discussion than was previously possible prior to the establishment of the MDM with high confidence in the recommendation made. This case was also notable as regional agreement on endoscopic surveillance for lesions with HGD was agreed following its discussion.

9) 70 year old male with 40mm mid transverse colon LNCP

The lesion, classified as an LST-G, was identified during a BCSP colonoscopy. There was strong endoscopist suspicion that the lesion contained a malignant focus. Histopathology reporting did not confirm malignancy as expected but did report HGD. The MDM reached the same conclusion following video assessment that the lesion was likely to be malignant and that colorectal cancer MDT referral and surgical resection was the best management option. Surgical resection demonstrated malignancy, confirming the correct decision had been made. This case was noticeable as the MDM was considered to have provided a robust, multidisciplinary recommendation to ensure an inappropriate endotherapy attempt was not enforced as in the absence of proven malignancy, a scenario considered common prior to the complex polyp MDM.

10) 62 year old male with 50mm LNCP in distal transverse colon detected on BCSP colonoscopy.

This lesion was referred following an attempt at endotherapy. It was initially thought to be a 20mm polyp. However, after lifting and an attempt at resection, the lesion was found to be substantially larger (50mm) and traversing a fold. The latter factor ensured reduced lesion visibility and increased complexity associated with removal. The lesion was considered to have been completely removed but the endoscopist accepted that residual tissue was possible due to poor visibility and that resection of such a large lesion at that time was unplanned and would not have occurred if the full lesion margins had been identified initially. Histology identified HGD, necessitating prompt follow up in 2-3 months. A large area of recurrence was seen on follow up (15mm) with further snare resection and APC advised to achieve eradication. Eradication was confirmed at endoscopic surveillance 3 months later. This case was considered notable the first where MDM input was sought for guidance about the clearance of complex recurrent/residual tissue. In addition the case was

considered to have important educational value as it was felt to emphasise the importance of undertaking LNPCP assessment and resection in a meticulous, planned and controlled manner.

11) 78 year old female with 120mm rectosigmoid lesion.

This lesion was referred following a colonoscopy arranged following a change in bowel habit. This lesion was described as a diffuse circumferential lesion LST-G with a dominant nodule occupying almost all of the rectosigmoid junction. Histology did not detect malignancy (TVA with LGD). The sheer size of the lesion meant that endoscopic resection was not considered feasible whilst the lesion was also thought to be too proximal to be suitable for transanal surgery. The presence of a dominant nodule also indicated increased risk necessitating the need for en-bloc resection. The patient refused surgery having been told the risk of requiring a stoma was significant and wanted endoscopic resection despite being advised that it would probably be unsuccessful and the referring endoscopist hoped for advice on how to proceed. Video imaging was available and there was agreement that both endoscopic resection with EMR and transanal surgery were not suitable in this case, that surgery may be required and that assessment regarding further non-surgical modalities was not available within the region. The lesion was therefore referred out of region to an endoscopist considered an international expert in advanced endotherapy such as endoscopic submucosal dissection (ESD). This assessment was conducted with a colorectal surgeon present and concurred that whilst the lesion was considered benign, endotherapy was not feasible. However, rectal sparing surgery was considered possible. This case was notable for the use of a national network to ensure a robust management recommendation that improved patient confidence following initial disagreement with local opinion.

12) 78 year old female with 60mm anorectal lesion

This patient underwent a colonoscopy following a complaint of loose stools and was found to have a 60mm LST-G in the anorectum with a dominant nodule. The dominant nodule raised a concern about potential malignancy whilst the position of the LNPCP meant that endoscopic resection would need to be undertaken in a retroflexed and unstable position. It was felt that successful endotherapy would be technically difficult whilst transanal endoscopic microsurgery (TEMS) was available at the same centre and considered achievable with the benefit of enabling en-bloc resection (which was desirable in the context

of the dominant nodule). En-bloc resection was achieved using TEMS with complete resection achieved and malignancy excluded. This was the first large rectal lesion discussed since a previously incorrectly managed rectal LNPCP and the first with a transanal surgical specialist present. This case was highlighted as an example where endotherapy may have been recommended prior to the MDM despite low endoscopic confidence regarding successful resection. In addition it was considered an example of improvement in the evolving MDM process, whilst there was confidence by all participants that the MDM was now of sufficient quality to discuss complex rectal lesions.

13) 68 year old woman with 120mm rectal lesion

This LST-G was identified during a BCSP colonoscopy with histology benign (TVA with LGD). Video assessment was available. The lesion was estimated to be approximately 55mm in size on endoscopic assessment. Two MDM members were worried that a small area looked irregular and that malignancy could not be excluded. In view of this, an attempt at en-bloc resection with transanal surgery was preferred over pEMR as the treatment of choice to ensure optimal histological assessment. The lesion was considerably larger than previously considered at 120-130mm in size and although 1 large piece, approximately 120mm in size was retrieved, separate pieces of tissue at the margins were also taken for macroscopic complete resection to have taken place, signifying piecemeal resection. Post resection histology identified the lesion as a traditional serrated adenoma with no malignancy. In addition, no residual tissue was seen at 3 month surveillance. Although en-bloc resection was not possible and pEMR was feasible in this case, it was felt that the principle to attempt en-bloc specimen retrieval in the context of a concern about malignancy was sound. This case was also noted as being reflective of the increased acceptance by endoscopists to consider non-endoscopic management where available.

14) 62 year old male with 60mm rectosigmoid lesion

This lesion, described as a 35mm LST-G with benign histology (TVA with LGD) by the referring team, was referred with only limited images. The lesion was considered benign and amenable to endoscopic resection by the referring centre, but the photos suggested that the lesion appeared larger and more complex than described. An MRI scan was reported as a suboptimal scan offering no information about possible malignant invasion. The referring endoscopist did not participate in the MDM and it was felt that the lesion

required reassessment prior to a definitive management decision. The referring centre opted for endotherapy locally with unsuccessful endotherapy due to the finding of malignancy and a subsequent need for surgery. This case was notable as the MDM recommendation was not followed, likely resulting in an undesirable outcome. The case also highlighted the importance of adequate visual imaging in the assessment of LNPCPs and the potential to suggest incorrect management in the absence of sufficient information.

15) 75 year old male with 55mm rectal LNCP

This gentleman was found to have an LST-G with a large dominant nodule near the anorectal margin during a colonoscopy following a history of rectal bleeding. Histology reported the lesion as a TVA with mixed LGD/HGD. Whilst there was an opinion within the MDM that endotherapy was feasible, there was sufficient concern from examination of surface characteristics that the lesion may harbour malignancy and transanal surgery with TEMS was recommended to ensure en-bloc resection for optimal histopathological assessment. En-bloc resection from TEMS confirmed early malignancy (T1) with complete resection removal confirmed as a result of optimal histopathological specimen retrieval. In this case the patient successfully underwent successful minimally invasive removal of malignancy and this case was considered to highlight the improvement in the MDM process, especially with regards to the management of rectal lesions that had previously been highlighted as a weakness.

16) 68 year old male with 40mm mid transverse colon LNCP

This sessile lesion identified within the BCSP was felt to be benign at the time of discovery with biopsy results also suggestive of this (tubular adenoma with low grade dysplasia). This view was supported at the MDM following a review of video imaging and endoscopic resection was subsequently undertaken successfully, confirming no malignancy and no recurrence on follow-up endoscopy. With surgery avoided, the subsequent MDM recommendation was for endoscopic surveillance at 12 months.

17) 79 year old female with 50mm rectosigmoid colon LNCP

This patient was referred to the MDM following the discovery of a LNCP thought to be approximately 30mm in size. It was also considered benign with biopsy results defining the

lesion as a tubular adenoma with LGD. No video imaging was available for the MDM discussion but the images provided suggested that the lesion was indeed benign but larger than first considered. The recommendation made was for repeat expert endoscopist assessment with endotherapy at that time if there were no technical or malignancy concerns. The lesion was found to be approximately 50mm in size but with no other concerns, pEMR with APC application was subsequently undertaken with complete resection considered achieved and the lesion to be confirmed as benign. Video imaging of the endotherapy process was available during follow-up MDM discussion with agreement that endotherapy appeared successful. With surgical resection avoided due to the selection of an appropriate endoscopist, lesion eradication was confirmed at 3 month surveillance and further surveillance at 12 months was agreed.

18) 73 year old male with 120mm rectosigmoid LNPCP

This gentleman with a history of rectal bleeding had subsequently undergone transanal surgery for this lesion prior to referral to MDM. The lesion was felt to occupy over 75% of the bowel wall circumference and considered too extensive for endoscopic therapy using EMR. In addition the sheer size of the lesion was considered a risk factor for malignancy in addition to a histological finding of high grade dysplasia. The patient was reluctant to agree to resectional surgery and transanal minimally invasive surgery (TAMIS) was undertaken with the intention of achieving en-bloc resection. The TAMIS procedure was unsuccessful with only piecemeal resection possible and the proximal extent of the lesion not reached by the TAMIS apparatus, leaving a large portion of residual tissue (40mm) and subsequent fibrous bowel narrowing (stenosis) in this region. The case was referred to the MDM for advice on how to manage this case in the context of complex recurrence/residual tissue complicated by previous therapy. Following review of the case details and videos it was agreed that the decision to undertake transanal surgery has been incorrect as the lesion was too proximal to allow successful eradication and it had not been established that the proximal portion was accessible prior to commencement of therapy. In addition, it was also agreed to feed this back to the referring centre. In this case, an attempt at resection complicated further management but the patient still did not wish for resectional surgery due to the risk of requiring a stoma. Whilst surgical resection was considered to be a likely outcome, it was agreed that an attempt at EMR on the residual polyp should be made with surgery recommended to the patient if successful EMR was not possible. It was felt that had

the lesion been referred prior to an attempt at management, the patient would have not been exposed to incorrect invasive therapy. An attempt at EMR was considered largely effective given the circumstances with the vast majority of the residual polyp removed, however it was felt that there be remaining fragments of tissue within the stenosis less accessible but potentially suitable for APC ablation in the future.

This case was notable as first referral seeking advice for salvage therapy following complex recurrence and inappropriate therapy. The importance of MDM discussion was also felt to have been emphasised as a similar case to this that had been referred prior to therapy had been referred externally for a second opinion with a robust management plan delivered. There was also felt to be an important educational component to this case with regards to the applicability of transanal surgery and the management of complex recurrent tissue.

19) 68 year old male with 40mm sigmoid LNCPC

This gentleman was found to have a 40mm sigmoid lesion during a BCSP colonoscopy that the endoscopist felt was a likely malignancy requiring surgery. However the histopathology results were unexpected with a report stating that the biopsies taken could not be distinguished between bowel wall prolapse and malignancy although the former was favoured. A second histopathology opinion was sought which supported the initial finding. In addition, detailed CT imaging did not demonstrate evidence of malignancy. Whilst there was a wish to avoid surgery in a lesion without confirmed malignancy there was sufficient agreement that malignancy could not be excluded based on endoscopic features. It was felt that only surgical resection could guarantee total lesion clearance and optimal histological analysis and negate the possibility of leaving residual undetected malignancy. In view of this the patient underwent surgery and was found have malignancy.

This scenario was cited as a previous source of conflict prior to the establishment of the MDM with surgeons unhappy to operate in some cases in the absence of biopsy proven malignancy despite endoscopist concern with inappropriate endotherapy reluctantly undertaken. In this case the strength of recommendation from interdisciplinary discussion the MDM was considered sufficient to make a decisive management decision. This was also the first case where additional detailed histological input was required prior to the agreement of a management strategy. Although there is no regular histopathology representative during MDMs and it was agreed that histopathology input obtained on an as

required basis fed back to the MDM was sufficient and did not compromise the strength of discussion. In addition, this case was also felt to demonstrate the validity of the detailed endoscopic lesion assessment encouraged by the MDM, even in the absence of supporting histological and radiological findings.

20) 66 year old gentleman with 10mm NPCP encircling appendiceal orifice

This gentleman was referred for an opinion regarding optimal management following the discovery of a lesion encircling the appendiceal orifice during a BCSP colonoscopy. Although the lesion was small and there was no concern of malignancy (TVA with LGD), there was concern from the referring centre that endotherapy may not be sufficient due to the probability of a portion of the lesion involving the appendix and therefore being endoscopically inaccessible. They reluctantly queried whether surgical resection was appropriate to provide definitive management. Opinion within the MDM membership was divided over the choice of endoscopic or surgical therapy and in view of this the case was referred for consultation by the national expert pool. Their opinion was that a high risk of appendiceal involvement rendered endotherapy inappropriate and that a laparoscopic surgical option (laparoscopic extended appendicectomy) would be both minimally invasive and provide definitive therapy. This option was accepted by the MDM membership and the patient underwent successful surgery. This case was noticeable for the use of the national expert pool to reach a robust management decision where opinion had been divided, whilst a precedent was set for similar lesions subsequently recommended.

Case	Patient Details	Lesion Details	Initial Management prior to MDM referral?	Specific Concerns	Outcome	Correct decision considered reached?	Outstanding Issues
1	62 year old male	60 mm transverse colon hepatic flexure sessile LNCP	Initial pEMR with additional APC use	Was initial decision correct? Did resection look complete?	Initial decision considered correct with complete resection considered achieved No recurrence seen at 3 month follow-up	Yes	Confirm eradication at 12 months
2	70 year old male	40mm ileocaecal valve flat LNCP	None	Unable to assess full lesion margins, felt to be technically difficult to remove, concern over potential malignancy risk due to LST-NG morphology	Successful endoscopic resection undertaken with no evidence of malignancy and no recurrence seen on follow-up	Yes, surgical resection avoided	Confirm eradication at 12 months
3	84 year old male	60mm sessile rectal polyp	None	Unable to assess full lesion margins. Lesion considered technically difficult to remove and concern over potential malignancy. Frail patient not suitable for rectal surgery	En-bloc resection using transanal surgery. Malignancy identified with successful removal confirmed	Yes, definitive removal of malignant lesion with avoidance of complex rectal surgery	None
4	62 year old female	100mm rectal laterally spreading polyp	None	Large lesion- MDM advice sought with regards to lesion assessment to exclude malignancy and an opinion on whether lesion was endoscopically resectable	Patient offered choice between pEMR at referring site and transanal surgery at neighbouring centre. Patient opted for EMR- lesion felt to be substantially larger than first thought). Small area of recurrence seen on initial follow-up treated with APC with clearance seen on further follow-up	Yes, lesion eradicated 6 months after initial resection whilst patient given preferred treatment	Confirm eradication at 12 months
5	62 year old male	15mm ileocaecal valve flat LNCP	None	Lesion diagnosed over 2 year prior to MDM discussion. Patient concerned about likelihood of endotherapy failure and risk of stoma	Discussion in clinic regarding endotherapy attempt by expert endoscopist, for surgery if failure of endotherapy preferred to primary surgery.	Yes, avoidance of surgery	Confirm eradication at 12 months

				associated with surgery	Successful endotherapy undertaken with no recurrence seen on follow-up		
6	62 year old female	90mm rectal flat polyp	None	Assessment about suitability for endotherapy and exclusion of malignancy	Endotherapy abandoned due to discovery of malignancy. Patient underwent resectional surgery.	No- piecemeal endotherapy attempt on malignant lesion with surgery required as definitive management	None
7	87 year old female	30mm sessile rectal LNPCP	None	Patient with advanced dementia, unable to consent for treatment. Assessment about whether therapy suitable	5 year mortality rate estimated >50% using Schonberg Index with therapy considered not likely to improve prognosis. Conservative management opted for with agreement of next of kin	Yes-avoidance of risks of invasive procedures	None
8	68 year old female	60mm sigmoid colon sessile LNPCP	None	Assessment for suitability for endotherapy, exclusion of malignancy and selection of appropriate endoscopist	Successful endoscopic resection undertaken with lesion eradication confirmed at 3 month endoscopic surveillance	Yes, avoidance of surgery	Confirm eradication at 12 months
9	70 year old male	40mm mid-transverse colon sessile polyp	None	Strong endoscopist concern that lesion was malignant- felt not suitable for endotherapy despite lack of biopsy proven malignancy	Patient underwent surgical resection- malignancy found	Yes, high quality visual assessment resulted in avoidance of piecemeal endotherapy on malignancy despite equivocal histology	None
10	62 year old male	50mm distal transverse colon sessile LNPCP	Unplanned piecemeal endoscopic resection undertaken after inaccurate lesion margin estimation	To ascertain whether complete resection had taken place and advice regarding appropriate follow-up	Early (2-3) month surveillance advised in view of likely recurrence. Large area (15mm) of recurrence seen requiring repeat EMR and APC with eradication confirmed at next surveillance	Yes, advice given regarding management of complex recurrence with successful lesion eradication	Confirm eradication at 12 months
11	78 year old female	120mm rectosigmoid flat lesion	None	Preference for en-bloc resection due to dominant nodule increasing risk of malignancy, size of lesion precluded suitable endotherapy	Patient referred out of region for consideration for ESD, by international expert- lesion considered not endoscopically resectable but suitable for	Yes, detailed lesion assessment with full consideration of all potential management options undertaken and improved patient	Await result of surgical management

				within North East region. Patient refused resectional surgery and lesion not suitable for transanal surgery due to proximal location	rectal sparing surgery- not yet undertaken	confidence in advice given locally	
12	78 year old female	120mm anorectal LNPCP	None	Preference for en-bloc resection as lesion LST with dominant nodule. In addition anorectal lesion meant that piecemeal resection was technically difficult due to unstable position	TEMS elected	Yes, successful resection with optimal histology specimen	Confirm eradication at 12 months
13	68 year old female	120mm rectal LNPCP	None	Lesion identified as granular LST (LST-G)- concern about small focus within lesion	Concern about small focus in lesion shared by MDT, unable to confidently exclude malignancy with en-bloc resection preferred to obtain optimal histological specimen- TEMS undertaken. Lesion estimated at 12-130mm rather than 55mm as initially estimated at endoscopy and only piecemeal resection achieved. No residual tissue at 3 month check	Principle underpinning decision considered correct. En-bloc specimen retrieval permitted confident exclusion of malignancy whilst resectional surgery avoided	Confirm eradication at 12 months
14	62 year old male	60mm sigmoid sessile LNPCP	None	Lesion considered benign and suitable for endoscopic resection MDM opinion sought to corroborate this prior to management decision	Image quality considered suboptimal with lesion appearing more extensive than described (35mm). Recommendation for reassessment by more experienced endoscopist advised. Endotherapy attempt favoured by local centre with unsuccessful attempt due to finding of malignancy.	Yes, undesirable outcome likely due to MDM advice not being followed	None

					Surgery required		
15	75 year old male	55mm rectal polyp	None	Laterally spreading polyp with dominant nodule and initial histology showing high grade dysplasia -suspicion regarding malignancy	En-bloc resection favoured due to malignancy risk- TEMS undertaken with early T1 malignancy found and complete resection confirmed	Yes due to retrieval of en-bloc specimen and certain successful removal of malignancy in minimally invasive fashion.	Confirm eradication at 12 months
16	68 year old male	40mm mid transverse colon sessile LNPCP	None	Lesion considered benign and suitable for piecemeal endotherapy- MDM opinion sought to corroborate	pEMR undertaken with no residual or recurrent tissue seen on follow-up	Yes, avoidance of surgery	Confirm eradication at 12 months
17	79 year old female	50mm rectosigmoid sessile LNPCP	None	Lesion considered benign and suitable for piecemeal endotherapy- MDM opinion sought to corroborate	pEMR undertaken with no residual or recurrent tissue seen on follow-up	Yes, avoidance of surgery	Confirm eradication at 12 months
18	73 year old male	120mm rectosigmoid LNPCP	Previous attempt at transanal surgery	Unsuccessful transanal surgery- incomplete piecemeal resection with proximal 40mm of lesion not reachable with apparatus. In addition, bowel wall narrowing (stenosis) from further complicating situation	Resectional surgery felt to be most likely to be successful but had been refused by patient. Agreement regarding salvage attempt at EMR. EMR considered successful	Yes, removal of residual polyp	Confirm eradication on 3 monthly basis until clear
19	68 year old male	40mm sigmoid sessile polyp	None	Endoscopist concern about malignancy but equivocal histology unable to delineate between bowel wall prolapse changes and malignancy	Given malignancy concern en-bloc therapy considered preferable with resectional surgery undertaken- malignancy identified at surgery	Yes, accurate endoscopic assessment resulted in correct therapy and minimal patient risk despite conflicting information	None
20	66 year old male	10mm flat appendiceal orifice lesion	None	Lesion encircling appendiceal orifice with concern that there was appendix involvement limiting feasibility of endotherapy	Following split opinion within region between endotherapy and surgical resection, national panel consulted for opinion- minimally invasive surgical option favoured as definitive therapy	Yes, although malignancy not suspected, avoidance of endotherapy where there was low confidence of successful resection and identification of minimally invasive surgical option	None

Table 16. Summary of Complex Polyp MDM Cases Discussed

6.4.4) A Summary of Participation by North-East England BCSP Centres

A summary of cases referred to the MDM and details of non-referred cases mandatory for referral are described in figure 19 and table 17 respectively

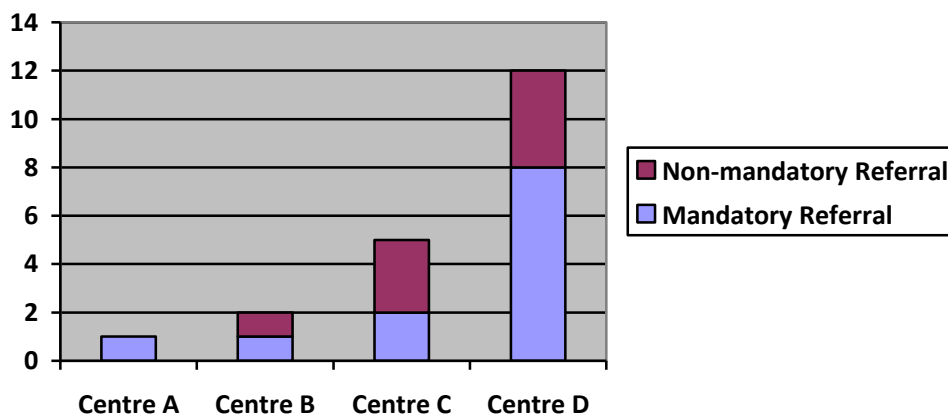


Figure 19. A summary of cases referred by centre

Centre	Case Details	Outcome	Reason case not referred
A	71 year old male with 40mm sessile caecal LNPCP	Removed piecemeal at time of detection, no recurrence described on follow-up but documentation of 40mm ascending colon lesion not previously reported	Case not deemed necessary for referral by endoscopist
A	67 year old male with 30mm flat caecal LNPCP	Removed piecemeal at time of detection, 3mm recurrence detected at 3 months, with eradication confirmed at 6 months	Case not deemed necessary for referral by endoscopist
B	71 year old male with 40mm rectal sessile LNPCP	Removed piecemeal at time of detection, eradication confirmed at 3 month surveillance	Case not deemed necessary for referral by endoscopist
C	68 year old female with 20mm sessile caecal LNPCP	Removed en-bloc at time of detection, complete resection confirmed histologically	Endoscopist unfamiliarity with referral criteria
C	75 year old male with 40mm sessile rectal LNPCP	Removed piecemeal at time of detection. Eradication confirmed at 3 month surveillance	Endoscopist unfamiliarity with referral criteria
D	71 year old male with 25mm sessile caecal LNPCP	Cancer detected elsewhere in colon, patient underwent surgery	Referral to benign lesion meeting not deemed appropriate by endoscopist in view of malignancy elsewhere

Table 17. Summary of cases not referred during first 3 months of MDM pilot

6.5) Discussion

The modified Delphi consensus process used to identify and finalise a minimum dataset proforma ensuring consideration of all information relevant to ensuring robust LNPCP assessment and management was straightforward, with a second voting round required for only one parameter and 100% agreement for almost all parameters. The identification of all relevant patient and lesion factors was essential to ensure that management decisions were safe, feasible and did not ignore important considerations such as patient wishes, comorbidity and medication issues which could impact on management outcomes. In addition, the minimum dataset ensured discussion and/or exclusion of features that could compromise successful endoscopic resection such as size, morphology, location and features suggesting increased complexity (increased malignancy risk, failure to achieve resection and likelihood of adverse events). The only parameter requiring a second round of voting related to the assessment of polyp surface characteristics. The initial parameter specifying only the mandatory documentation of pit pattern with regards to polyp surface characteristics was considered dated, insufficient and potentially inaccurate given the availability of other validated polyp surface assessment systems and the limited availability of cresyl violet staining and magnifying endoscopy essential for true pit pattern assessment in the UK. In view of this, the amended parameter allowed for the inclusion of any validated polyp surface assessment system such as the NICE NBI and Sano Capillary Pattern classification systems and was unanimously approved. The inclusion of various classification systems was also considered important to update and educate clinicians about the latest systems available.

It had been anticipated that potential new parameters or considerations may be identified when the minimum dataset was piloted during the complex polyp MDM. The need to discuss patient symptoms was subsequently identified as an important factor in determining management recommendations in certain scenarios such as the discovery of an LNPCP in elderly, frail patients where a lack of symptoms may justify conservative management as appropriate over therapy. The proposal to include patient symptoms as a parameter was unanimously agreed. In addition, the need to specify the extent of imaging required by photographic imaging where video recording was unavailable was identified following cases where insufficient imaging limited the ability to assess and issue strong recommendations on

lesions. Instructions related to minimum imaging information and standards were also subsequently added with full approval following which the minimum dataset proforma was considered both comprehensive and complete of all factors related to LNPCP management.

Although the MDM was not aimed solely as BCSP cases, the existing infrastructure of the BCSP with regionally audited data and close clinician collaboration (with regular formal meetings) ensured access to a multidisciplinary network and the ability to monitor and discuss regional outcomes. In addition, the ability of Professor Rutter to mandate the establishment of the MDM and referral of relevant lesions for quality assurance purposes in his position as QA chair ensured the viability of the meeting.

6.5.1) Initial Concerns

An initial concern was the reliance on clinicians to comply with MDM protocol and ensuring that BCSP nurses were also fully aware of the mandatory lesion referral criteria to maximise participation. There was initial opposition to the establishment of an MDM with a mandatory referral system with criticism that the measure was unproven, unnecessary and too prescriptive. There was also a concern that the meeting would lead to an increased workload for clinicians who already had a busy work schedule. The measure was justified however by the presentation of regional BCSP data suggesting evidence of discordant management, a higher level of suboptimal management than previously thought (see chapter 5) and an accepted need to improve standards and develop a more coordinated management approach within the region. In addition, there was support from a number of colorectal surgeons within the region who felt that LNPCPs were often not prioritised or discussed in sufficient detail within existing colorectal MDT meetings given the burden of colorectal cancer cases, the absence of biopsy proven malignancy in these lesions and the common lack of an advanced endoscopist. Whilst the MDM had been mandated, it was appreciated that cooperation from all parties was needed to increase the likelihood of a successful process. As a result, a pilot study over 6-7 months was agreed to ascertain the feasibility and impact of a complex polyp MDM with a view to permanent establishment if considered successful. In addition, only lesions identified as complex based on fulfilling the evidence based criteria in recent BSG approved guidelines (see chapter 3) were mandatory for referral whilst fears over a concern about potential delays in management of malignancy were allayed by the encouragement of parallel referral of lesions with strongly suspected malignancy to the existing colorectal cancer MDT as before, which also ensured detailed

radiological and histological input. It was also agreed that MDM outcomes were not binding and were recommendations only, in line with established NHS MDM policy.

6.5.2) Overcoming Logistical Issues

The initial logistical issues associated with the creation of a regional complex polyp MDM whilst numerous, were mostly anticipated in advance and factored into the methodology process. For example, it was clear that teleconferencing would be required as a single venue was not feasible for a multicentre meeting covering a large geographical area. Audio-teleconferencing, preferred to video teleconferencing due to widespread availability, appeared to facilitate participant involvement as participation was possible from anywhere. Patient and lesion information using the BSG approved minimum dataset proforma could be disseminated securely via the NHSmail email system along with high quality images and video recordings. These factors ensured a meeting format allowing structured and comprehensive discussion that was reproducible nationwide. As expected, it was not possible to choose a regular meeting time and pattern suitable for all clinicians. With a core pool of BCSP endoscopists available on a regular basis, the meeting time was chosen around the availability of surgical and rectal expertise to ensure a multidisciplinary component at all meetings. The decision to disseminate case information to a BCSP mailing list including all BCSP endoscopists and nominated surgeons 48 hours prior to meetings was successful in encouraging participation from clinicians unable to attend. This format was vital in ensuring multidisciplinary input for all cases, especially where teleconference attendance was limited. For example, on the few occasions where a surgical presence was not possible, detailed pre-meeting input was obtained and considered to have strengthened discussions during the teleconference. Email and text message reminders about meetings also appeared to ensure regular participation was maintained. The proposed fortnightly one hour meeting schedule agreed by the BCSP endoscopists via questionnaire was frequent enough to ensure that no cases suffered a delay in management awaiting an MDM outcome whilst it was not considered too onerous by participants with other significant clinical commitments.

Engagement with the MDM process varied across the region. Figure 19 demonstrates that the bulk of referrals came from centres C and D. Whilst an increased number of referrals compared with centres A and B may simply be reflective of the number of suitable LNCPs, increased engagement is suggested by the both centres referring multiple non-mandatory cases (e.g. cases not meeting referral criteria or discovered outside of BCSP). Access to the

BCSP database enabled assessment of each centre's compliance with the mandatory referral criteria for BCSP cases. Six mandatory referral BCSP cases were not referred in the first 3 months of the meeting (2 from centre A, 2 from centre C, 1 from centre B and 1 from centre D) (see figure 17). The reasons given for non-referral of cases at centres A and B was a belief that referrals were not necessary. With regards to centre C, it was asserted that non-referral was a result of endoscopist unfamiliarity with the referral criteria whilst in the case of centre D, referral was not deemed appropriate due to the discovery of a malignancy elsewhere in the colon. The benefit of using the regional BCSP to pilot the MDM was the closely aligned service meaning that the issue of non-referred cases could be addressed at frequent regional BCSP meetings and by liaising with relevant SSPs. Participation improved as the meeting became more established, with no mandatory cases not referred in the final 3 months of the MDM pilot.

6.5.3) Comprehensive Follow-up of Cases

Ensuring that all referred cases remained subject to follow-up within the MDM process was achieved by the use of a regularly updated Microsoft Excel spreadsheet with all discussed cases. This was made available to all MDM participants to capture and record updated details such as therapy and surveillance outcomes to assess longer term outcomes of all discussed cases. This spreadsheet recorded all management decisions (e.g. endoscopic, conservative and surgical management), specific procedure information (e.g. use of piecemeal or en-bloc removal, use of argon plasma coagulation with piecemeal endotherapy etc.) and outcomes (e.g. complications and findings of incomplete resection at early and late stages). A major intention of the use of the spreadsheet was to provide a growing prospective database to allow subsequent quantitative and statistical analysis of MDM cases.

6.5.4) Feedback

Positive Feedback

Feedback was obtained via group discussion at regional BCSP meeting coinciding with the end of the pilot study and via an emailed survey. All parties regularly involved with the MDM process had largely positive opinions, with the MDM considered to have aided management across a wide variety of cases. The meetings were seen as a valuable resource in improving assessment and decision making processes taken in LNCP management, with comments that there was greater cooperation and co-ordination within the region. In addition, it was noted that there was greater agreement within the region about how to manage certain lesion types (e.g. high grade dysplasia or appendiceal location). It was considered that LCPCPs were subject to more comprehensive and structured discussion than previously, providing clinicians with support and guidance with complex cases in a format that was reproducible using existing NHS resources. A cited example was case 5, where almost two years of a stasis in management posed a subsequent risk of malignancy that was considered entirely avoidable. The ability to deliver a robust collective recommendation that resulted in a positive outcome was seen as a particular example of where the role of the MDM was important.

There was also increased confidence in the management recommendations made due to improved interdisciplinary cooperation as a result of the establishment of the MDM. This was seen in cases 9 and 15 where surgical therapy was recommended and subsequently undertaken as first line management based on endoscopic suspicion of malignancy due to lesion surface characteristics in spite of initial benign histological findings from biopsies. This appears to be an improvement on previously reported scenarios within the region where piecemeal endotherapy was undertaken with malignant lesions despite a strong endoscopic suspicion of malignancy because surgical therapy had been refused based on a lack of biopsy proven malignancy. Whilst piecemeal resection of malignant lesions did occur in 2 cases (cases 6 and 14), one case (case 6) was early in the MDM process and led to more extensive MDM membership (e.g. a TEMS performing surgeon), whilst in the other case (case 14), the MDM recommendation of repeat assessment prior to management was not followed. It was also considered that the increased dialogue generated from the meetings led to a more coordinated management approach for most complex lesions within the region. This included the selection of conservative management in an elderly and frail patient where on

balance the risks of therapy were felt to outweigh the potential benefit (case 7). Discussion of the cases managed also prompted agreement that increased regional collaboration enhanced patient choice and experience. For example, there were cases where patients were offered treatment modalities such as transanal surgery that were not available within their immediate area and as a result may not have previously been considered. In addition, with varying levels of expertise with LNCP management within the region, MDM discussion enabled the selection of endoscopists considered suitable to undertake therapy in cases where endotherapy was preferred thus avoiding unnecessary surgery. Collaboration also allowed clinicians to utilise contacts of other participants and expand their network of contacts out of the region to the benefit of patients. Evidence supporting this view was seen in case 11 where the patient was unhappy with the local recommendation for resectional surgery and there was lack of expertise within the region to provide an assessment for advanced alternative therapies. Referral to a recommended external contact resulted in the patient receiving assessment for ESD that is only available in limited UK centres. Whilst an alternative to surgery was ultimately not considered possible, the patient was happy that all treatment options had been explored prior to agreeing to surgery and that adequate assurances had been given regarding the low likelihood of requiring a stoma.

Negative Feedback

It was accepted that there were enough cases to support the importance of the MDM as a modality and the MDM process was extended to at least 12 months. The main criticism cited regarding the MDM format was that its scheduling meant that it was not possible for all clinicians to participate in the meeting during the teleconference and as such it was felt that not all clinicians were able to benefit from the educational aspect of the meeting. This comment was made by one of the MDM's biggest original sceptics, suggesting that they did feel that the meeting had value but that an inability to participate in the audioteleconference was their main issue. It was also suggested that a face to face meeting format with discussion of cases at the regional BCSP endoscopist meetings would be preferable. It was countered that the scheduling of the meeting was based on the preferences of the majority of clinicians in response to a questionnaire regarding their availability, including surgical representatives whose presence was essential to ensure a truly multidisciplinary process. In addition, the dissemination of meeting information pre and post MDM was accepted as a solution, albeit a limited one. Whilst a face to face single location meeting was desirable, in addition to clinician availability and geographical issues

being limiting factors, the regional BCSP meetings took place every few months only and were therefore too infrequent. This approach would have resulted in a delay in management in many cases whilst awaiting MDM recommendations. There were also concerns amongst a few clinicians that the purpose of the MDM was to centralise advanced polypectomy to only certain individuals within the region rather than providing management support. A reason given for this opinion was interpretation of some of the wording of MDM feedback given to referring centres. For example, recommending endotherapy at the local centre only if suitable expertise was available and identifying other regional endoscopists willing to take on the case was seen as patronising and casting aspersions on the ability of the referring centre's endoscopists. Whilst neither this nor the centralisation of services was intended, this criticism was acknowledged as a disadvantage of referring individuals not being part of the teleconference and it was agreed that the wording of MDM recommendations would be more considered in future. The perceived advantages and disadvantages of the complex polyp MDM are summarised in table 18 (see below).

Central Meeting Components	Perceived Advantages	Perceived Disadvantages	Mitigation of Perceived Disadvantages
Establishment of virtual meeting using teleconferencing and email	Able to remotely connect clinicians across region with face to face single centre meeting not feasible Greater coordination between specialties and more robust lesion assessment and decision making	Lack of face to face interaction Concern about potential for delay in management whilst awaiting MDM outcome	Use of BSG approved minimum dataset to ensure standardised and comprehensive discussion of patient and polyps factors Fortnightly meeting format to ensure prompt MDM discussion
Use of NHSmail for transfer of all patient media	Secure, approved method of transfer of patient identifiable information nationally	1 gigabyte file limit for media/video transfer	Use of video editing and compression to facilitate large file transfer
Regional format with national expert group	Enhanced management options for patients- access to modalities not available locally Expert advice available for cases where MDM consensus not reached	Concern that LNPCP management may become more centralised as a result of MDM- potential for reduced participation as a result	Commitment in terms of reference that MDM outcomes are recommendations only and non-binding- in line with established NHS MDM protocol
Educational role	Improves knowledge base of participants	Reduced educational role for clinicians unable to attend teleconference	Outcomes, feedback and other educational points disseminated to group post meeting Discussion of cases and important issues at regional BCSP group meetings
Use of digital imaging for multi-clinician lesion assessment (video and still images)	High quality imaging allowed detailed multi-clinician visual assessment and management recommendation without need for repeat diagnostic endoscopy	Visual appearances central to decision making. Variation in availability of high quality media recording within region (e.g. video recording, high definition imaging). Potential for poor quality images to limit decision making	Guidance detailing recording of quality and comprehensive images
Standardised meeting day and time	Allows familiarity with and establishment of meeting format	Meeting time not suitable for all participants	Dissemination of cases 48 hours before and MDM outcomes 48 hours post MDM to maximise input

Table 18. Perceived Advantages and Disadvantages of MDM

6.5.5) Imaging

The quality of LNPCP images captured was considered as essential in facilitating adequate LNPCP assessment and of greater significance than with other specialist MDM meetings, given the strong established relationship between visual polyp characteristics and malignant

potential and feasibility of endoscopic resection. Strong recommendations could not be made in many cases where image quality was considered poor, resulting in either equivocal recommendations or a need for repeat diagnostic assessment by an additional clinician in some cases. The use of video imaging with referrals, although not uniformly available within the region, was considered to greatly enhance MDM discussion and increase the likelihood of robust recommendations when compared with photographic imaging. Video assessment was reported to allow detailed examination of lesion characteristics such as surface patterns, full margins and precise location and was therefore considered comparable to being present at the relevant colonoscopy itself in terms of enabling image assessment. This reduced the need for repeat diagnostic assessment in many cases with a decision on whether a specific therapy was possible from review of the video. For example, it was agreed that decisions on whether transanal surgery was likely to be successful in the management of rectal lesions based on full lesion accessibility and the exclusion of sigmoid colon involvement could confidently be made from video imaging. This was particularly relevant when considering case 18 where a decision on therapy had been made outside of the MDM setting without repeat diagnostic assessment with endoscopy or video recording resulting in a lesion undergoing unsuccessful transanal surgery despite being in an unsuitable location and further complicating the likelihood of successful management. Radiological imaging modalities such as CT and MRI scanning whilst recommended on a case by case basis were not found to change management outcomes in any of the cases discussed.

6.5.6) Refinement of Meeting Format

It was recognised that given the preliminary nature of the MDM process, issues and limitations of the meeting format would be identified with the strength of the MDM process evolving and improved over time. For example, given the importance of visual assessment in LNPCP management, in many cases it was considered that the quality of photographic images provided with referral was suboptimal and provided limited information in cases where video imaging was not available. This subsequently impacted on the strength of recommendation considered possible. The response to this was the addition of guidance on the MDM referral proforma relating to the minimum level of imaging required. This included recommendations regarding image clarity and ensuring that full lesion margins could be ascertained and this measure was credited with improved image quality with

subsequent referrals. In addition, whilst consultation of histopathology and radiology services was available on an as required basis, including through the colorectal cancer MDT where malignancy was strongly suspected, suspicions that the initial member composition of the MDM lacked the requisite expertise with regards to complex rectal lesion cases were confirmed by the outcome in case 6 where despite detailed lesion assessment featuring high quality video by a number of experienced clinicians, a finding of malignancy was missed resulting in an inappropriate endotherapy attempt and subsequent resectional surgery where less invasive transanal surgery would have been appropriate as first line therapy. The use of a pool of national experts for areas with continued conflicting opinion was considered to strengthen the process whilst addition of a rectal surgical specialist was considered essential. The outcome of case 15 in which there was successful assessment and management of a complex rectal lesion using TEMS following a concern over increased malignancy risk and conflicting opinion on management was seen to demonstrate a marked improvement in the MDM's ability to assess and manage complex rectal cases.

6.5.7) Educational Role

The complex polyp MDM was also widely seen to have been beneficial in providing an important educational role in LNPCP management to its membership. Participants were able to test their assessment skills by reviewing cases prior to therapy and subsequently receiving feedback with the dissemination of outcomes. The opportunity to share expertise and knowledge was considered invaluable with improved confidence in lesion assessment ability reported due to an increased awareness of image classification systems. In addition, exposure to complex scenarios encouraged exposure to potentially new and valuable resources. An example was the application of the Schonberg index, a validated but not widely known classification system in case 7 to predict mortality risk in an elderly patient in whom an LNPCP had been found, resulting in conservative management. This case was credited with improving awareness of individual patient morbidity and mortality risk.

6.6) MDM Role in Decision Making- Application of Optimal Decision Making Key Performance Indicator

The ability to apply key performance indicators (KPIs) to the pilot MDM data is limited by both the small sample size and the lack of long term outcomes (e.g. 12-15 month outcomes). However, an assessment of optimal decision making using the 'use of surgery' KPI (use of surgery as secondary management (e.g. following endoscopic management of malignancy) and as management of benign lesions) was possible. Applying the KPI criteria, the surgical rate for this sample was 30%. Whilst this figure is higher than the average surgical rate recorded within the region in the retrospective data described in chapter 5 (21.7%), an important consideration is that the lesions included in the MDM cohort are considered amongst the most complex as identified in the guidelines in chapter 4. As opposed to the retrospective BCSP sample that includes any non-pedunculated lesion at least 20mm in size, this complex sample includes lesions that are:

- Very large (some up to 120mm in size)
- Identified with an increased suspicion of malignancy,
- Subject to previous management
- Assessed as having other technical considerations (e.g. difficult location) potentially compromising endoscopic removal

The use of surgical management, which took place in four of the six 'surgical KPI' cases, appears appropriate despite an absence of malignancy, given the higher likelihood of failed endoscopic therapy compared with the retrospective series. For example, surgical management was recommended for a benign lesion in one case by a clinician considered a world expert in advanced endotherapy. In addition, of the two cases where piecemeal endotherapy was used on malignant lesions (11 cases of primary endoscopic management), the MDM recommendation was ignored in one case suggesting that an inappropriate recommendation was made in only one of the MDM cases (e.g. use of piecemeal endotherapy on malignancy: 10% (MDM sample) vs 15.6% (retrospective BCSP sample). Despite the limited sample size of this series, it appears that the decision-making KPI requires enhancement, at least in regards to the use of surgery in complex LNPCPs, to capture suboptimal decision making in this population.

6.7) Conclusions

The findings from this pilot study appear to confirm the validity of the minimum dataset proforma in ensuring structured and comprehensive LNPCP discussion.

In addition, whilst single centre complex polyp MDMs are already in place, this is the first reported example of a multicentre approach. The development and establishment of a complex polyp MDM appears feasible, with its use indicating improved decision making in LNPCP management and a more coordinated approach with improved patient outcomes and potentially more cost effective management. However at this stage outcomes are qualitative only with longer term outcome data needed. The complex polyp MDM may also be seen as an educational tool and has a reproducible format using the BSG approved proforma and existing NHS technology that may be best implemented within an existing regional infrastructure such as a regional BCSP. The complex polyp MDM may also complement existing colorectal services and be used to provide guidance and robust recommendations with regards to:

- Optimal primary therapy and more robust decision making
- Obtaining feedback about management strategy undertaken
- Consideration of full range of therapeutic options
- Widening of clinicians' regional and national network resulting in increased treatment options for patients
- Improved inter-specialty relationships
- Complex scenarios such as extensive lesion recurrence and the consideration of conservative therapy

Chapter 7: Discussion and Overall Conclusions

The findings of this thesis confirm the hypothesis that current management of large non-pedunculated colorectal polyp (LNPCPs) varies widely and is uncoordinated, leading to suboptimal outcomes. This is reflected by the long term regional data from the Bowel Cancer Screening Programme (BCSP) detailed within this thesis, a programme shown to manage a large volume of LNPCPs by multiple large volume series (17, 101). The work undertaken, including the development of a structured framework encompassing assessment and management guidelines, key performance indicators (KPIs) and a decision aid model offers solutions with regards to improving management in this field.

7.1) Findings and achievements

Work undertaken as part of this thesis has resulted in the following.

- A retrospective analysis of large non-pedunculated colorectal polyp (LNPCP) management confirming that variation in assessment and management of LNPCPs results in significantly different outcomes
- The development of comprehensive evidence based and expert opinion LNPCP assessment and management guidelines earning both BSG and ACPGBI approval and publication in 'Gut' journal
- The development of BSG and ACPGBI approved 'Key Performance Indicators' (KPIs) to allow auditing, monitoring and comparison of LNPCP outcomes with subsequent publication in 'Gut' journal
- The application of KPIs to retrospective data to ascertain the validity of KPIs
- The development of a regional complex polyp multidisciplinary team meeting resulting in more robust and coordinated LNPCP management
- The development and validation of a minimum dataset proforma detailing features relevant to LNPCP assessment and management, allowing comprehensive and structured discussion

- The identification of pertinent research questions to improve the evidence base relating to LNPCP management

7.2) Implications of this research

Prior to undertaking this thesis, the development of a LNPCP management framework including guidelines and performance, had not previously been achieved. This was in spite of a strong desire within the international endoscopic community to do so, with opinion prevalent that there were insurmountable challenges precluding it. Professor Rutter (BSG large polyp working group chairperson) was approached by the BSG in 2006 to undertake work in this field. Indeed, there was a great deal of scepticism within the Northern Region Endoscopy Group (NREG) when the plan to develop an LNPCP management framework was discussed, with a widely held view that there was an absence of evidence to suggest that variation in management contributed to variable and suboptimal outcomes. There was also a belief that there was a paucity of evidence to help create both guidelines and KPIs. Despite this, the use of extensive available evidence and multidisciplinary consensus opinion has resulted in the production of the world's first internationally peer reviewed guidelines and standardised performance measures (KPIs). These were warmly received by both the BSG and ACPGIBI who indicated that they greatly improved the support available to clinicians involved in LNPCP management and were likely to contribute to more coordinated and improved outcomes. As a result both groups were happy to endorse them. This work also satisfies the demand for structured guidance in LNPCP management reported in recent national surveys.

- **British Society of Gastroenterology (BSG)/ Association of Coloproctology of Great Britain and Ireland (ACPGIBI) Guidelines**

The BSG/ACPGIBI guidelines, devised as part of this thesis provide evidence based information and expert opinion on the optimal assessment and management of large non-pedunculated colorectal polyps (LNPCPs) for clinicians. It is also anticipated that the guidelines will act as a stimulus for further research in this field and provide a template for training in LNPCP management. The intended target audience includes gastroenterologists, nurse practitioners, physicians, colorectal surgeons, radiologists and pathologists.

- **Key Performance Indicators**

The development of KPIs provides a new and standardised opportunity for both clinicians and centres to audit, monitor and compare outcomes in LNPCP management and set a benchmark for minimum standards of practice internationally. This will allow the identification of underperformance and remedial action to improve standards. Whilst the scientific basis for their development may be argued, there is a clear precedent within the field of endoscopy for the improvement of standards using KPIs for example, for colonoscopy services in the BCSP. The use of qualitative methodology to identify KPIs provides a means to identify key quantitative measures that can be monitored and targeted for improvement to provide enhanced patient care.

- **Regional complex polyp multidisciplinary team meeting (MDM)**

Whilst single centre complex polyp MDMs are already in place, this is the first reported example of a regional, multicentre MDM. Its use was considered to improve LNPCP management by its participants whilst the model used to develop and establish the meeting is reproducible using existing NHS resources in other regions. This intervention allowed greater coordination and robustness of decision making, with improved patient satisfaction and outcomes and potentially more cost effective management. The complex polyp MDM may also be seen as an educational tool with the opportunity to learn from experience and other participants' expertise. The complex polyp MDM may also complement existing colorectal services and be used to provide guidance and robust recommendations with regards to the following:

- Optimal primary therapy and more robust decision making
- Obtaining feedback about management strategy undertaken
- Consideration of full range of therapeutic options
- Widening of clinicians' regional and national network resulting in increased treatment options for patients
- Improved inter-specialty relationships
- Complex scenarios such as extensive lesion recurrence and the consideration of conservative therapy

The development of an evidence based and validated minimum dataset for LNPCPs may enable improved management in situations where a complex polyp MDM is not feasible, for example where the absence of a network of colleagues results in a clinician working in isolation. The structured format of the proforma can serve as a checklist to ensure that features suggesting or precluding particular management options are not missed whilst enabling structured and comprehensive discussion, for example when referring lesions to tertiary referral centres.

7.3) Limitations

Retrospective analysis

The analysis of established practice within this thesis has identified wide variation in endoscopic practice and decision making as having a significant impact on outcomes. The relatively small sample size of the regional series compared with other similar international series appears to be a limiting factor in the impact of these findings. For example, whilst findings related to argon plasma coagulation use and endoscopist procedure volume indicated clinical significance, it cannot be discounted that statistical association was not accurately proven or excluded due to an underpowered study. Limitations were also apparent in certain aspects of BCSP polyp data collection. In addition to the lack of information regarding surveillance therapy on BCSP patients discharged from the programme (mainly due to being out of the age range), there was a paucity of information in relation to detailed polyp morphology such as Paris and LST classification, with sufficient information only to classify lesions as 'flat' or 'sessile'. Given the established accuracy of detailed polyp morphology in identifying LNPCPs with higher malignancy risk, the insufficient relevant information appears to have affected the validity of findings related to polyp morphology in this study. In addition, a main reliance on the central BCSP database for the retrieval of outcomes does not preclude inaccuracy based on potential data entry errors. However, the likelihood of this is reduced by both the fastidious nature of BCSP data input and the use of double data entry where all cases were also checked on the relevant sites to ensure accuracy.

Guideline development

There is a paucity of evidence in this field of the highest scientific quality such as large multicentre randomised controlled trials and meta-analyses to formulate guidelines. Many of the recommendations and findings pertaining to LNPCP management are drawn from the findings of observational studies, the quality of which would be classed as 'low' rather than 'high' when using systems designed to assess the strength of scientific evidence. It can be argued that the nature of LNPCP management renders the ability to conduct large human trials as not feasible in certain areas such as the determination of the level of tissue damage in response to varying degrees of diathermy, an area where porcine models have previously been used. This issue is similar to many other healthcare fields in this respect and may have led to increased uptake of the GRADE assessment tool that includes a separate 'strength of recommendation' process, allowing for recommendations after detailed consideration of variable factors as opposed to the study design solely. In addition, it appears that in many areas of the evidence base for LNPCP management, the recommendations and findings derive from multiple large volume papers from high impact journals and are unlikely to be changed by further research. The work undertaken for this thesis comprehensively references and summarises the available evidence and expert opinion in this field and appears to be a marked improvement on previous resources for LNPCP management. It can also be argued that the identification of several potential research areas (see later) increases the likelihood of improving on the current evidence base and strengthening the robustness of recommendations made from this research.

Key Performance Indicators

A lack of evidence deemed to be 'high quality' may also call into question the validity of certain KPIs identified as auditable outcomes, in addition to the standards specified. However, the use of established KPI healthcare strategy, with the identification of domains and subsequent KPIs related mainly to patient experience and safety, as well as consideration of outcomes widely considered by international literature as measures of quality, appears sound. In addition, whilst an attempt has been made to set realistic minimum standards based on findings from international literature, there are many KPIs for which a standard has not been set and are therefore identified as 'auditable outcomes'. It can be argued that the KPIs are currently incomplete because of this. This factor, allied to a

limited evidence base in some areas, may provoke resistance to their uptake. It will also likely take time to obtain enough data to validate and enhance the KPIs and finalise standards such as those currently defined as auditable outcomes. However, it was felt important not to set unwarranted standards without any appropriate justification as this would damage the credibility of the finalised KPIs. This scenario is well recognised in KPI development in that such parameters are defined as 'auditable outcomes' with standards likely identifiable following detailed data audit (288). In addition, whilst the decision making KPI does appear to accurately identify centres with a higher use of surgery, it appears apparent that optimisation is required for use with complex LNPCPs. An increased use of primary surgery may be anticipated in this sample and likely considered more acceptable due to limitations of endotherapy in providing curative resection. However, the development of KPIs is a dynamic process and will likely be enhanced when applied to a growing sample size. Despite the limitations of KPI development, as discussed previously, the use of qualitative methodology to develop KPIs provides an opportunity to provide a large quantitative evidence database.

Regional complex polyp multidisciplinary team meeting

Whilst the regional MDM development process was considered a success, limitations were identified. The associated logistical issues confirmed that commitment from an established network of clinicians, such as those within regional BCSP services, is required to ensure the ongoing viability of the meeting, in addition to facilitating access to relevant data sources such as ongoing case information. In addition, the ability to mandate case referrals from within the BCSP where endoscopists are subject to individual data audit was essential in ensuring the ongoing viability of the process in its early stages, prior to more widespread acceptance, a modality that is not likely to be as readily available outside of the BCSP.

The need to use NHSmail emailing for security purposes appeared to limit initial uptake of MDM compliance as it was apparent that many clinicians did not use this email account regularly and would thus miss meeting details. The use of reminders sent to clinicians' main trust email accounts, in addition to text message reminders did increase participation. An upgrade in NHSmail security during the MDM process allowing patient identifiable data transfer from NHSmail to NHS trust accounts enabled larger participation and engagement but this crucially did not allow for video imaging transfer. Given the importance of imaging

with regards to lesion assessment, the disparity in imaging technology available to different centres within the region did appear to impact on the strength of MDM recommendations made. For example, video recording, considered vastly superior to still photographic images, was only available in limited centres meaning that the strength of the MDM recommendations offered seemed to vary based on the location of the referring centre. Another issue was the ability to transfer a maximum file size of one gigabyte via secure file transfer. This resulted in the need for video editing in many cases. Whilst this was not considered to impact on decision making ability in the cases described, the increased availability of higher definition recording requiring larger file sizes may pose an issue with the file size limit. Whilst there may be an initial financial cost associated with the procurement of video recording equipment, it may be argued that this cost can be recouped over time from a reduction in diagnostic procedures required to reassess LNPCPs where initial imaging was inadequate. In addition, video recording, despite being a relatively new standard is increasing in availability in the UK meaning that image quality will likely become a less prominent limiting factor.

It may also be argued that the small MDM case volume limits the significance of its findings. The limited time period available reduced the ability to increase the case series size, however, the decision to extend the MDM process will allow collection of a larger sample size. In addition, at present there is a lack of longer term outcomes, such as 12 month surveillance outcomes, due to the limited timeframe. It may be argued that this impacts on the significance of the findings of this pilot study, especially in view of other case series reporting a finding of 'new recurrence' at 12 months where complete eradication had previously been considered. However, it appears that the findings from 12 month surveillance are highly unlikely to result in new findings in many of the cases detailed, such as endoscopic cases with complete clearance already established, with this phenomenon only having been described in very limited cases and likely in part to be the result of inadequate lesion assessment at earlier surveillance. In addition, 12 month findings are just one outcome, with this pilot primarily focused on more acute parameters (such as decision making outcomes and subjective opinion). Whilst analysis of this case series is ongoing meaning that longer term outcomes will soon be available for analysis, the major limitation of this pilot study is that the main findings are mainly qualitative (e.g. perceptual improvement) with a lack of quantitative outcomes.

7.4) Inability to create guidelines for advanced polypectomy training and accreditation

Whilst the GDG discussed ways to improve training in the management of LNPCPs and were keen to create guidelines in this area, this was not felt possible due to an absence of evidence. In view of this, a reference model was devised with key points as described below:

- **Entry requirements for training**

There was agreement that reaching a minimum number of diagnostic colonoscopy procedures was required to allow development of essential basic colonoscopy and therapeutic skills before entering advanced polypectomy training. There was broad opinion that handling and decision making skills develop after around 250-350 colonoscopies with further development following an extensive period of independent practice. Evidence that increased endoscopic experience is associated with improved performance and a reduced rate of adverse events reinforced this view. A minimum number of 500 independent (post certification) colonoscopies was felt to be a suitable number to ensure that adequate experience has been achieved in both observed and independent practice. There was unanimous opinion that snare polypectomy experience and skill were the key identifiers of endoscopists suitable for advanced training and that competency in snare polypectomy of smaller lesions (up to 20mm) needed to be established. This may be assessed with a formal assessment tool such as the DOPyS assessment tool (293). In addition to formal assessment, evidence of regular snare polypectomy experience with lesions greater than 1cm in the preceding year was considered desirable, in addition to performance data for all colonoscopy practice in that period.

- **Training Programme**

An apprenticeship programme such as a dedicated fellowship in a recognised advanced endoscopy centre was considered to be the preferred model for delivering advanced polypectomy training to trainees whereas non-trainees such as consultants wishing to develop advanced polypectomy skills would require a period of mentorship. The availability

of fellowships in specific regions may be linked to population demands. An agreed appropriate learning curve commences with a trainee continuing to develop individual colonoscopy skills whilst watching and assisting their mentor resect large lesions. During this period, trainees may gain significant experience and develop their technique on colonic lesions between 10-19 mm in size before progressing to larger lesions and piecemeal resection. At this point trainees would be encouraged to bring cases to dedicated training lists. LNPCP location and accessibility also confers increased lesion complexity in addition to size and rectal lesions where the bowel wall is thicker and access is easier may be an ideal starting point for obtaining hands-on experience. Trainers and mentors would be required to ensure that their performance data (KPIs) met minimum standards before supervising fellows.

- **Certification**

Dividing certification into provisional and full certification was strongly supported. Achieving provisional certification would be based on outcomes data and mentor opinion and would be the start of independent practice (i.e. trainer not in the room). Full certification would be obtained based on achieving satisfactory KPIs whilst provisionally certified in addition to mentor opinion and maintenance of full certification status would be dependent on achieving satisfactory KPIs.

- **Other potential training modalities**

Training workshops were suggested as a modality for reinforcing technical and decision making skills obtained during a fellowship programme whilst simulator and tissue simulator models allow hands-on exposure in a safe setting. There is also growing support for the use of live animal training models. In the UK, the British Society of Gastroenterology have indicated their support for this modality.

7.5) Reflections from undertaking thesis

- **Logistical Issues**

The development of an LNPCP management framework was a major undertaking requiring the coordination and cooperation of clinicians, both regionally and nationally, and large bodies such as the BSG and ACPGBI. The logistics required, in addition to the limited evidence base in certain areas, may explain why no previous attempts at the creation of a framework have been made.

- **Variation in Practice**

Whilst international surveys demonstrated clear variation in LNPCP practice such as assessment and management, and this may not be unexpected for clinicians practicing in relative isolation, it was surprising to see such a marked variation in practice within a region between a group of closely aligned BCSP endoscopists who meet and discuss cases regularly. This not only included the decision making process but endoscopic technique and equipment use such as snare choice, diathermy settings, submucosal lifting practice and the use of APC. Whilst greater coordination is sought, especially in light of a resultant variation in outcomes, this has allowed for analysis of important research questions such as the efficacy of APC use in pEMR that might not otherwise have been possible.

- **BCSP Database**

The use of the central BCSP database proved invaluable as a comprehensive information source for both retrospective and prospective data collection and reduced the logistical demands of data collection over a large regional area. However, the database appeared to lack information about follow-up procedures and findings for patients undergoing LNPCP therapy within the BCSP and subsequently discharged from the programme due to age (>75). Whilst this information was available via individual case review on relevant hospital sites, the inclusion of all follow-up information for LNPCPs managed within the BCSP on the central BCSP database may make further audit of practice easier.

- **Resistance to change in practice**

Although the result of work undertaken as part of this thesis was undertaken successfully with valuable contributions from many people, the level of resistance to service development proposals from some quarters was surprising. This appeared to be the case with regards to the implementation of the complex polyp MDM, especially the mandatory referral criteria. There were concerns voiced that the MDM was unnecessary, would make practice too prescriptive and serve as a means to centralise LNPCP management and

marginalise some clinicians. In addition, there was a concern that MDM recommendations could be mandated as management despite assurances to the contrary. These concerns may be a result of defensiveness, due to a perceived potential for increased personal scrutiny of practice and concerns about possible sanctions such as limiting autonomy of practice. It may also be the case that many experienced clinicians are simply uncomfortable with being told how to undertake a procedure they feel they have been performing well long beforehand.

- **Decision making**

The process of reaching consensus and collective decision-making were major components of the work undertaken. They formed the basis of the methodology used for the development of guidelines, KPIs and the complex polyp MDM. Although evidence-based decisions were sought wherever possible, opinion-based decision making was required in numerous cases, a situation commonplace in healthcare. The processes of collective decision-making in healthcare may be seen as inferior to other industries such as business which have used technology for a long time to optimise decision making. An example of this is the widespread use of organisation decision support systems (ODSS), databases consisting of various sources of information to predict the possibilities of outcomes using statistical decision theory (SDT) (294). ODSS supported decision making has been discussed as suitable in certain healthcare areas for some time due to the many factors and decision-makers often required in deciding management therapy, but this has not yet become commonplace (295, 296). Until recently, healthcare decision making regarding healthcare policy such as guidelines and management appears to have been based on individuals, with collective decision making a relatively new phenomenon(295). An example of this is management guideline development, in which the use of consensus methodology only recently appears to have been adopted internationally. However, the method commonly used, a derivative of the Delphi technique, was initially developed for use in the business setting by the RAND corporation in the 1950s (258). The decision making processes in LNCP management may be an area amenable to enhancement with the development of an ODSS (see later).

- **High malignancy incidence in North East dataset**

Another observation was the high incidence of malignancy in the North East region compared with nationally within the BCSP for polyps initially diagnosed as benign (28% vs

9.7%, $p < 0.0001$). Whilst this finding may be multifactorial it raises a query about whether lesion assessment skills in the North East are inferior to those nationally or whether management skills are inferior with endoscopists incorrectly believing that they can endoscopically manage malignant lesions.

7.6) Further Work

- **Management Guidelines**

Further potential work following on from these guidelines includes undertaking prospective studies in relation to the important research questions identified. In addition, in view of national and international questionnaires specifying the lack of guidelines and limited training as a major limiting factor in delivering optimal LNPCP management, an international questionnaire following widespread dissemination of guidelines may confirm if these guidelines have been effective in improving management and training.

- **KPIs**

The most important next step with regards to KPI development appears to be optimisation of the decision making domain/KPI, especially with regards to auditing the most complex lesions. With clear definitions of complex LNPCPS now available from internationally peer reviewed guidelines, the decision making 'surgery' KPI may be expanded further. For example the KPI may be expanded to sub-classify LNPCPS managed with primary surgery according to visual characteristics that suggest a 'high' or 'low' risk of malignancy or a 'high' or 'low' risk of failed endoscopic resection. This may help to better identify surgically managed LNPCPs that would have been better suited to endotherapy such as those with a low risk of malignancy and a high chance of successful endoscopic resection. Further work with regards to KPIs has commenced with the retrospective application of KPIs to existing regional BCSP data to determine applicability and feasibility. In addition, continuous annual prospective analysis and audit of LNPCP outcomes using KPIs in a programme with established high quality data collection such as the BCSP would help to establish whether the KPIs have led to improved standards and a large database to identify robust standards.

- **Retrospective analysis**

Further work arising from the BCSP case series includes ongoing audit of outcomes with the application of KPIs and recently agreed guidelines to assess for improvement in management. Furthermore, certain findings, such as the higher level of polyp recurrence following endotherapy in the caecum, improved outcomes in higher volume endoscopists and the potential benefit of argon plasma coagulation (APC) use as an adjunct to endotherapy indicate the need for larger studies. For example, in the case of APC use, a large randomised controlled trial (RCT) with a standardised proforma for APC application may unequivocally establish whether its use is associated with reduced lesion recurrence.

- **Pertinent future research questions**

The following research questions and potential studies were suggested by the GDG as the most feasible to expand the LNPCP management evidence base:

- How common are LNPCPs and what is the optimal number of LNPCP endoscopists per 100,000 population?
- What is an appropriate timeframe for the management of LNPCPs?
- What is the pre-resection accuracy of prediction of malignancy within an LNPCP and how can the endoscopic identification of malignant features be improved?
- What is the length of time to malignant transformation for LNPCPs and when is conservative management the most appropriate management strategy?
- Does continuation of aspirin prior to the endoscopic resection of LNPCPs result in increased post-polypectomy bleeding?
- What is the optimal type of submucosal injection solution for use in advanced polypectomy?
- Does the use of dye in submucosal injection fluid improve completeness of endoscopic resection?
- Does the use of adrenaline in submucosal injection fluid improve peri-procedural visibility and reduce immediate and delayed bleeding and post endoscopic resection?
- What are optimal diathermy settings for advanced polypectomy?

- Does the use of argon plasma coagulation on post resection margins reduce the risk of lesion recurrence
- When is the optimal time to restart anticoagulation/antiplatelet medication post-polypectomy?
- What are the appropriate KPI standards, where none currently exist?
- Does the implementation of a complex polyp MDT improve outcomes?
- What is the minimum number of procedures per year that is required to reach/maintain competency in the endoscopic management of LNPCPs?
- What is the role of laparoscopic-assisted endoscopic polypectomy?

- **Complex Polyp MDM**

Further work arising from the development of the complex polyp MDM includes the collection of longer term outcomes from the existing MDM case series, in addition to the ongoing collection of prospective cases. Long term outcomes from a larger case series over a sustained time period may strengthen the evidence supporting the use of a complex polyp MDM. In addition, an RCT comparing the outcomes from cases discussed in the MDM compared with outcomes from cases not discussed the MDM may also demonstrate a significant association with improved outcomes.

7.6.1) Alternative options in the development of LNPCP decision-making processes

Whilst logistical issues may limit the ability to implement an MDM, the development of the minimum dataset proforma and guidance regarding adequate imaging may still provide a means to improve decision making for those working in greater isolation, allowing for structured and comprehensive LNPCP discussion. This may be achieved by the use of an online centralised secure NHS or BSG national database where clinicians may post lesion information and imaging onto a shared website using the secure NHSmail email system for review by other relevant multidisciplinary clinicians and experts. This may enable clinicians to establish a national network, rather than working in isolation, potentially resulting in more robust management decisions and resulting in improved treatment options for patients. Furthermore, the popularity of current online endoscopy forums indicates the

potential for a scheme such as this, with an online forum used to directly improve patient care in addition to being an educational tool.

Another possibility is the harnessing of technology applied in the business world, through collaboration with a software technology company to create an ODSS software package to guide the decision making process. The piloting of the evidence based minimum dataset proforma during the MDM process suggests that all relevant patient and lesion information required can be obtained and entered into a database. In addition, a growing collection of images (photographic and video) and outcomes from the MDM could be used for comparison with referred lesion details and imaging to provide suggested management options and probability of their success. Although undoubtedly more difficult to achieve, this measure may provide an example of more scientifically sound decision making in the healthcare field than before and comparable with those used in business models.

7.7) Conclusions

It is hoped that the work undertaken as part of this thesis will lead to greater clinician support and more coordinated and improved LNPCP management both nationally and internationally, as well as enabling audit, monitoring and comparison of standards to benchmark LNPCP practice. Additionally, the identification of pertinent future research questions provides guidance on how to best improve the LNPCP evidence database.

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