10-19-2009

Tubular carcinoma of the breast versus invasive ductal carcinoma treated with breast conservation therapy

Gene-Fu Liu

TUBULAR CARCINOMA OF THE BREAST

VERSUS INVASIVE DUCTAL CARCINOMA

TREATED WITH BREAST CONSERVATION THERAPY

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Gene-Fu F. Liu

2009

ABSTRACT

TUBULAR CARCINOMA OF THE BREAST VERSUS INVASIVE DUCTAL CARCINOMA TREATED WITH BREAST CONSERVATION THERAPY

Gene-Fu F. Liu, Qifeng Yang, Bruce G. Haffty,, Meena S. Moran.

Department of Therapeutic Radiology, Yale University, School of Medicine, New Haven, CT.

Purpose: The purpose of our study is to evaluate our institutional experience of treating Tubular Carcinoma of the Breast (TC) and Invasive Ductal Carcinoma (IDC) with Breast Conservation Therapy (BCT), consisting of conservative surgery (CS) and radiation therapy (RT), and to compare clinical-pathologic features and long-term outcomes.

Materials and Methods: A review of our institution's tumor registry from 1975-2007 was performed, followed by a central pathology review of available slides, yielding 71 cases of Stage I/II TC and 2238 cases of Stage I/II IDC treated with BCT.

Results: Clinical-pathologic features and outcomes were then analyzed by subtype to detect significant differences. The median follow-up was 7 years. The TC cohort presented more frequently with pT1 disease (97% vs. 80%, p=0.0007), pN0 disease (95% vs. 74%, p=0.0004), hormone-receptor positivity (ER+: 89% vs. 62%, p=0.0001; PR+: 81% vs. 52%, p=0.0001), and HER-2 negativity (89% vs. 71%, p= 0.04). Clinical outcomes also favored the TC cohort, with lower rates of breast cancer-related death (1% vs. 10%; p = 0.0109) and distant metastasis (1% vs. 13%; p = 0.0028), and higher rates of 10-year overall (90% vs. 80%; p=0.033), cause-specific (99% vs. 86%; p=0.011), and disease-free (99% vs. 82%; p=0.003) survival. There was a non-significant trend towards improved breast relapse-free survival for the TC cohort (95% vs. 87%; p=0.062) but no difference in nodal relapse-free survival or contralateral breast relapse-free survival (all p-values > 0.05) between the cohorts.

Conclusion: Our institutional experience suggests that TC, when compared to IDC, is associated with more favorable clinical-pathologic features and comparable, if not superior, outcomes following BCT, suggesting the appropriateness of a conservative approach to this rare subtype.

ACKNOWLEDGEMENTS

I would like to thank:

Dr. Meena Moran, my mentor and thesis advisor, for her guidance, patience, and commitment to my success, providing me a level of attentiveness that I can never repay.

Dr. Bruce Haffty for his sage advice and allowing me to utilize the database he masterfully constructed at Yale, laying a foundation for breast cancer research for years to come.

Dr. Qifeng Yang for his patience, dedication to research, and expertise in biostatistics and breast cancer pathology.

Dr. Lynn Wilson for welcoming me into the world of radiation oncology and recommending that I work with Dr. Moran.

Teresita Vega and the tireless staff at the Yale Tumor Registry for all that they do.

The Yale Office of Student Research for providing me with funding and guidance to complete my first research project!

The International Journal of Radiation Oncology, Biology, Physics for accepting my manuscript for publication.

The American Radium Society for inviting me to give an oral presentation at its national meeting and awarding me with a grant to facilitate my travel.

TABLE OF CONTENTS

INTRODUCTION

Breast conservation therapy (BCT), consisting of a wide excision of the primary breast lesion and loco-regional radiotherapy (RT), has been demonstrated in multiple randomized trials to be equivalent to mastectomy with regards to disease-free survival (DFS) and overall survival (OS) in the treatment of early stage breast cancer.[1,2] However, these reports have not stratified patients by subtype and were mostly comprised of patients with invasive ductal carcinoma (IDC), which constitute approximately 68-79%. of invasive breast cancer histologies.[3-5] Few studies have analyzed the outcomes of BCT on less prevalent histologies of the disease. Tubular carcinoma (TC) is one such subtype, comprising approximately only 1% of all invasive breast cancers.[3,4]

Table 1. Demographic characteristics of 139,310 women diagnosed with nine different histologic types of breast cancer

Histology	n	Percent
Invasive Ductal	102,463	73.6%
Invasive Lobular	11,275	8.1%
Ductal/Lobular	9,636	6.9%
Mucinous	3,248	2.3%
Comedo	2,222	1.6%
Inflammatory	2,095	1.5%
Tubular	1,983	1.4%
Medullary	1,617	1.2%
Papillary	618	0.4%

Table taken from Li CI, Uribe DJ, Daling JR. Clinical characteristics of different histologic types of breast cancer. British J Cancer. 2005 Oct 31;93(9):1046-52.

Histopathology

Once termed the "well-differentiated carcinoma of the breast" or "orderly carcinoma of the breast,"[6] TC can appear merely as benign tubules on microscopic examination. Though its histopathologic definition has evolved over time, it currently consists of three main characteristics: 1.) Well-differentiated tubules in a stellate infiltrating configuration, 2.) Bland epithelium with non-pleomorphic nuclei, and 3.) Myoepithelial cells absent on immunohistochemical staining.[7]

The first characteristic is the presence of well-differentiated tubules, with a stellate infiltrating configuration,[7] i.e., the tubules radiate outward through normal mammary tissue. In addition, TC characteristically incites a fibrous reaction and thus is typically surrounded by a reactive fibrous stroma on microscopic exam.[8] Though the tubules often contain secretory material and cellular debris, they remain widely patent, helping to differentiate TC from other lesions featuring obliterated tubules and ducts, e.g., sclerosing adenosis.[9] Finally, the tubules are often angular in conformation, and their pointed ends are referred to as "prows," as they resemble the front of a ship or boat.[10]

The minimal percentage of tumor cells forming tubules—also known as "tubularity"—required to diagnose a TC has evolved in the literature. Initially, pathologists established 90% as the minimal tubularity required. Such lesions merited the diagnosis of a "pure" TC. Correspondingly, lesions between 75-90% tubular histology were labeled "mixed TC."[11] The cutoff of 75% has been established to hold clinical significance in numerous studies, including one by Carstens et al., which reported that patients with lesions of 50-75% tubularity shared survival outcomes similar to IDC at 20 years ($p>0.998$). In contrast, there was a highly significant difference in Kaplan-Meier

survival curves between a cohort of IDC versus a cohort of mixed and pure TC cases ($p < 0.001$).[12]

Currently, however, the distinction between mixed and pure TC is considered unnecessary, as their prognostic equivalency has been established by several studies. In particular, a large review by Peters, et al. of 100 cases, demonstrated the association between percent tubular histology and tumor aggressiveness.[13] In the review, there was no difference in the incidences of local recurrence, distant metastasis, or death from breast cancer between cases of mixed and pure TC. In contrast, patients with lesions with less than 75 percent tubular histology suffered proportionally worse rates of the aforementioned clinical parameters, in addition to larger mean tumor size (Table 2).

Table 2. Comparative Features of Carcinomas of Varying Tubular Component

Percent Tubular Histology	n	Mean Size (cm)	Percent Local Recurrence	Percent Distant Metastasis	Percent Dead of Disease
100	16	1.79	0	0	0
76-99	20	2.15	0	0	0
51-75	16	2.01	6	31	0
31-50	23	2.50	4	48	17
5-30	22	2.54	4	25	4

Figure taken from *Peters GN, Wolff M, Haagensen CD. Tubular carcinoma of the breast. Clinical pathologic correlations based on 100 cases. Ann Surg 1981; 193: 138-149.*

Of note, the 75% cutoff does not apply to lesions of mixed tubular and cribriform

carcinoma histology. In these cases, the diagnosis is that of the dominant histology found in greater than 50% of the lesion because both cribriform and tubular lesions share excellent prognoses. However, the same classification criteria does not apply to mixed tubular and lobular lesions, as described in greater detail below.

In addition to the presence of well-defined tubules, the second diagnostic criteria of TC is a lack of nuclear pleomorphism,[14] and more than 90% of the cells must feature nuclear grade I, as codified by various nuclear grading systems, e.g., Bloom-Richardson or Nottingham, from grades 1 to 3.[7] Grade I nuclei are devoid of condensed chromatin, prominent nucleoli, and frequent mitotic figures, and the presence of such pleomorphism in a TC is highly unusual; its presence should prompt a search for an alternative histologic diagnosis. In addition to low-grade nuclei, the tumor cells themselves are also well-differentiated, being uniform in conformation, either normal or moderately enlarged in size, and arranged in a single epithelial layer.[7]

However, the presence of tubules and a single-layer of bland epithelium are not pathognomonic findings. Indeed, the aforementioned description also depicts the histology belonging to normal breast tissue or benign sclerosing lesions, such as sclerosing adenosis.[15] At this juncture in the differential diagnosis, the delimiting factor is the third characteristic of a TC: the presence or absence of a myoepithelial cell layer, the lack of which is a feature shared amongst all invasive breast cancers. Myoepthelial cells are detected via immunohistochemical staining against a variety of markers (Table 3) and their absence confirms the invasive nature of a lesion. Their presence supports an *in situ* process.[7]

Table 3. Immunohistologic Markers of Myoepithelial Cells

Marker	Sensitivity	Specificity
Calponin	Excellent	Very good
p63	Excellent	Excellent
Smooth muscle myosin heavy chain	Good	Excellent
CD10 (CALLA)	Good	Good
High molecular weight cytokeratin	Very good	Poor
Maspin	Good	Poor
S100	Good	Very poor
Actin	Good	Very poor

Table from *Kempson R. Stanford School of Medicine Surgical Pathology Criteria: Tubular carcinoma of the breast. <Available at: http://surgpathcriteria.stanford.edu/breast/tubularcabr>. Accessed, 2008.*

Associated Lesions

TC is frequently associated with foci of ductal carcinoma in situ (DCIS). Historically, the relationship between the lesions was cited so often in the literature (Table 4) that many postulated that TC was an intermediate histology between DCIS and IDC.

Table 4. Frequency of Associated Intraductal Disease Observed in Tubular Carcinoma

Study	No. of Patients	No. with DCIS (%)
Deos[6]	145	99 (68%)

Winchester[16]	50	16 (32%)
Cabral[17]	44	23 (52%)
Oberman[18]	25	21 (84%)
McBoyle[19]	22	14 (64%)
Total	286	173 (60%)
Abbreviations: DCIS = ductal carcinoma *in situ*		

Differential Diagnosis

The well-differentiated histopathology of TC dictates that lesions graded as II or III in *overall* histology (by various grading systems) are not tubular by definition.[7] As another consequence of its appearance, TC can be readily misclassified as benign lesions, e.g., sclerosing adenosis, microglandular adenosis, tubular adenosis, radial scar, and thus demands adequate tissue examination when its diagnosis is suspected. At a minimum, a core-needle biopsy is required, as examination with fine-needle aspiration cytology is associated with a high false negative rate.[20,21]

Even with adequate tissue, however, differentiating TC from other lesions can be difficult. One such challenge is the important distinction between TC, an invasive breast cancer, and sclerosing adenosis, a benign subtype of mammary hyperplasia, as both growths feature tubular formation and benign appearing epithelium. The comparative ultrastructure only has subtle, non-specific differences (Table 5). TCs feature tubules with a stellate, infiltrating pattern, patent ducts, minimal branching, and a single layer of cells. In contrast, sclerosing adenosis has tubules with a circumscribed and nodular pattern, obliterated lumens, frequent branching, and occasional regions of multi-layered

epithelium. As stated above, the crucial difference is the presence or absence of myoepithelium as detected by immunohistochemistry.

Table 5. Comparative Ultrastructure of Tubular Carcinoma Versus Sclerosing Adenosis	
Tubular Carcinoma	Sclerosing Adenosis
Stellate infiltrating pattern	Circumscribed, nodular
Patent ducts, gaping lumens	Occasional obliterated ducts
Minimal branching	Frequent branching
Single layer of cells	Occasional multi-layered epithelium

Table from *Kempson R. Stanford School of Medicine Surgical Pathology Criteria: Tubular carcinoma of the breast. <Available at: http://surgpathcriteria.stanford.edu/breast/tubularcabr>. Accessed, 2008.*

Another important distinction is differentiating TC versus tubulo-lobular carcinoma, with the latter carrying a worse prognosis between that of tubular and infiltrating lobular carcinoma.[22] In this differential, the percentage of tumor cells organized into tubules is the defining factor (Table 6). If greater than 90% of the lesion features tubules, then it is termed a TC. But if greater than 10% of the lesion has lobular carcinomatous feautures, then it is considered a tubulolobular carcinoma. Of note, molecular staining against E-cadherin typically yields positive findings for both lesions.[23]

Table 6. Comparative Ultrastructure of Tubular Carcinoma Versus Sclerosing Adenosis	
Tubular Carcinoma	Sclerosing Adenosis
90% pure tubular pattern	Mixed tubular and lobular patterns

Stellate infiltrating architecture	Linear infiltrative pattern, frequently concentric

Table from *Kempson R. Stanford School of Medicine Surgical Pathology Criteria: Tubular carcinoma of the breast. <Available at: http://surgpathcriteria.stanford.edu/breast/tubularcabr>. Accessed, 2008.*

Of less importance is the distinction between TC and a small, well-differentiated, low-grade IDC. Though there are differences in the ultrastructure of both (Table 7), a small, low-grade, well-differentiated infiltrating ductal carcinoma probably carries such an excellent prognosis that the prognostic information gained in such a distinction is minimal.[7]

Table 7. Comparative Ultrastructure of Tubular Carcinoma Versus Grade I Infiltrating Ductal Carcinoma

Tubular Carcinoma	Grade I Infiltrating Ductal Carcinoma, NOS
Stellate infiltration	Irregular infiltration
90% tubules	May have >10% ribbons or cords
Infrequent branching	Frequent budding and branching
Single layer of cells	May show stratification
Uniform chromatin	Slightly irregular chromatin
Nucleoli inconspicuous	Nucleoli may be prominent

Table from *Kempson R. Stanford School of Medicine Surgical Pathology Criteria: Tubular carcinoma of the breast. <Available at: http://surgpathcriteria.stanford.edu/breast/tubularcabr>. Accessed, 2008.*

Prognostic Features

Size

TC is associated with excellent prognostic features. First, TC is smaller at

presentation than most breast cancer histologies, averaging only 1 cm in largest diameter.[6,11,13] A recent review of the SEER (Surveilance, Epidemiology, and End Results) database reported that 95% of tubular carcinoma presented at a size of 2.0 cm or less, compared with 61% of IDC, 42% of medullary carcinoma, and 57% of papillary carcinoma.[4]

Its small size makes palpation exceedingly difficult and consequently the majority of tubular carcinomas, approximately 64-84%, are detected with the aid of mammographic screening.[16,19] Of note, TC does not have any unique mammographic or sonographic features which differentiate it from other lesions, malignant or benign, [24] and though certain features may suggest its diagnosis, the current literature recommends that diagnosis should be based solely on histologic examination.

Mammography is so important in the detection of TC that it may have introduced artifact to the existing literature. For instance, though the incidence of TC has steadily increased over the past decade (Table 8),[3] it has been postulated that the increase is merely a byproduct of increased mammographic screening.

Table 8. Number of cases of tubular carcinoma by year.

Year	Number of cases of tubular carcinoma
1992-1993	239
1994-1995	331
1996-1997	367
1998-1999	516
2000-2001	530

Table taken from Li CI, Uribe DJ, Daling JR. Clinical characteristics of different histologic types of breast cancer. British J Cancer. 2005 Oct 31;93(9):1046-52.

This theory is bolstered by the disproportionate percentage of TC in cohorts of patients with mammographically-detected breast cancer. One Australian study noted that TC comprised a disproportionate 3.4% of one such cohort.[25] Another possible artifact of mammographic detection is the high rate of positive family histories of breast cancer documented amongst patients with TC. Positive family histories were reported in 40% (6/15) in a study by Lagios et al.[26] and 33% (13 of 39) in a study by Holland et al.[27] Previous authors have hypothesized that this phenomenon is not truly reflective of the hereditability of TC.[26] Rather, it is argued that patients with TC often have positive family histories because those with a family history of breast cancer may be more motivated to comply with rigorous mammographic screening and are thus more apt to detect smaller lesions. Nevertheless, other studies have challenged the very notion of an increased hereditary component of TC. Specifically, Claus et al, in a study defining a family history to include only first-degree relatives, found TC to have the least association with positive family histories among six histologic breast cancer subtypes.[28] Furthermore, Burki et al. reported that there was no stastical difference in the relative risk of breast cancer between first-degree relatives of patients with tubular, invasive ductal, or medullary carcinoma.[29]

Regional Lymph Node Involvement

In early-stage disease, the regional lymph node status, as determined by axillary or sentinel node dissection, is the single most important prognostic factor,[30] and patients with TC often have negative nodes. The SEER review cited above reported that cases of

TC had positive lymph nodes only 7% of the time, compared with 33% of IDC, 29% of medullary carcinoma, and 22% of papillary carcinoma.[4]

Predictive Features

Predictive features predict response to treatment. In breast cancer, the predictive features which most influence management are estrogen receptor (ER), progesterone receptor (PR), and HER-2 status.

Hormone Receptor Status

Patients with cancers expressing ER or PR are candidates for endocrine modulating therapy to prevent estrogen-mediated growth stimulation of cancer cells. Such therapy can be accomplished via different strategies in premenopausal and postmenopausal women. In premenopausal patients, ovarian ablation, removal, or temporary pharmacologic suppression (with gonadotropin releasing hormone analogs, e.g., goserelin, leuprolide) are viable options. Postmenopausal patients have the option of inhibiting estrogen production via aromatase inhibitors, such as anastrazole, letrozole, or exemestane. Finally, adjuvant tamoxifen, a selective estrogen receptor modulator represents another standard option for women with hormone receptor positive tumors.

A recent review of the SEER database reported that 95% of TC are ER positive and 81% are PR positive, thus making endocrine regulating therapy a regularly prescribed component of TC management. In comparison, only 78% and 67% of IDC are ER- or PR-positive, respectively.[4]

HER-2 Status

The HER2 oncogene encodes for a member of the epidermal growth factor receptor family. As a prognostic feature, HER2 over-expression is associated with higher rates of disease recurrence and death and influences chemotherapy utilization in such patients.[31] As a predictive feature, HER2 status is predictive for resistance to systemic therapy but also predicts response to trastuzumab or lapatinib, humanized anti-HER2 monoclonal antibodies.[32] Almost all cases of TC are HER2 negative.{Oakley, 2006}

Significance of Prognostic Features

A large multi-institutional review of cases of tubular, mucinous, and IDC compared features of breast cancer between the three histologies and found that in addition to having a smaller size at presentation and decreased nodal positivity as compared to IDC, TC was also more frequently associated with estrogen receptor (ER)-positivity (91% vs. 82%; p = 0.001), progesterone receptor (PR)-positivity (75% vs. 61%; p = 0.001), low S-phase fraction (89% vs. 50%;p = 0.001), and diploid DNA ploidy (81% vs. 44%; p =0.05).

Interestingly, however, none of these traditional prognostic features influenced clinical outcomes for cases of TC in the study. Univariate and multivariate analyses of disease-free survival for TC (n=277, 14 events) demonstrated that neither tumor size, nodal status, ER status, PR status, nor S-phase fraction correlated with disease-free survival. In addition, previous small, single-institution studies of TC also suggest that nodal spread is not associated with worse prognosis,[16,33,34] making this cancer distinct from the majority of breast cancer histologies. One of the only features of TC

demonstrated to correlate with a clinical parameter is lymphovascular invasion; in a single-institution Italian study of 307 patients, lymphovascular invasion correlated with loco-regional recurrence (p=0.001).[35]

Treatment

Because of the rarity of TC, there is insufficient data to determine the extent of treatment necessary for this uncommon lesion. It is currently treated as a favorable, early-stage breast cancer.

Systemic Therapy

Due to the rarity of the disease, the role of systemic chemotherapy in the treatment of TC has not been firmly established. Though one study by Kitchen, et al. of 85 cases reported an 85% decrease in risk of death for patients receiving more than one course of chemotherapy,[33] another larger study by Diab et al. reported that of 277 patients, chemotherapy did not correlate with disease-free survival (p = 0.73).[36] Consequently, the current National Comprehensive Cancer Network (NCCN) only recommends the use of chemotherapy for ER- and PR-negative tubular lesions greater than three centimeters in size or with positive regional nodal metastasis, which is a higher threshold than that prescribed for invasive ductal lesions.[37]

Likewise, the role of endocrine therapy is equally uncertain. Despite the high percentage of ER-positivity in tubular lesions, most studies do not demonstrate a survival benefit or reduction in local failure. In particular, Diab et al., reported that of 277 patients, adjuvant endocrine therapy did not correlate with disease-free survival (p =

0.16), [36] and in 48 ER-positive patients, Sullivan, et al. reported no decrease in risk of local failure in 24 patients receiving tamoxifen.[38] Therefore, the NCCN also advocates for a higher threshold for the usage of tamoxifen than is prescribed for IDC. [37]

Breast Conservation Therapy

As an early stage breast cancer, cases of TC are typically eligible for breast conservation therapy (BCT), which is defined as a wide local excision of the tumor with negative margins—accomplished with either lumpectomy, segmental mastectomy, or excisional or incisional biopsy—combined with post-operative radiation therapy. But prior to discussing BCT as it pertains to TC, an introduction to this relatively modern approach is appropriate.

Though surgery remains integral to the management of patients with early-stage breast cancer, the efficacy of post-operative radiotherapy introduced the notion of providing select patients with a less aggressive alternative to mastectomy. Now after numerous randomized control trials worldwide, the clinical equivalency of mastectomy and BCT has been firmly established with regards to survival. In particular, two landmark trials by Fisher, et al. and Veronesi, et al., randomizing patients to either breast conserving surgery plus radiation versus mastectomy now have 20 years of follow up data and have demonstrated the long-term DFS and OS rates to be equivalent in both mastectomy and BCT cohorts. [1,2]

In the Veronesi trial, the rate of death from all causes was 41.7% in the breast conservation arm and 41.2% in the mastectomy arm ($p = 1.0$) at 20 years; the rates of breast-cancer related death was 26.1% in the BCT arm and 24.3% in the mastectomy arm

($p = 0.8$). However, 30 women in the BCT cohort had an ipsilateral breast recurrence, in contrast to 8 women in the mastectomy cohort ($p < 0.001$), which provides a crude local recurrence rate of 8.8% vs. 2.3%. However, there were no significant differences in rates of contralateral breast carcinomas, distant metastases, or second primary cancers.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) trial conducted by Fisher et al. reported similar results to the Veronesi trial at 20 years, with no significant differences observed with respect to disease-free survival, distant-disease-free survival, or overall survival among patients randomized to BCT or mastectomy. In addition, the hazard ratio for death among the BCT cohort, as compared with the mastectomy cohort, was 0.97 (95 percent confidence interval, 0.83 to 1.14; P=0.74). Therefore despite an increase in local failure rate, BCT has largely been established as the treatment of choice for early stage breast cancers in regards to survival and cosmesis.

Unfortunately, rare breast cancer subtypes lack sufficient patients to conduct large single-institution studies or randomized trials to determine the adequacy of BCT in their treatment. However, studies by Vo, et al.,[39] Weiss, et al.,[40] and Thurman, et al.[41] evaluated the outcomes of BCT for these uncommon subtypes in comparison to those of IDC. In the study by Vo, et al., 1,643 patients formed the study population and consisted of 61 cases of mucinous carcinomas, 37 cases of medullary carcinomas, 60 cases of TC, and 1,485 cases of IDC. Amongst the groups, no statistically significant differences were found in the local failure rate after a 10.6-year median follow-up, suggesting the adequacy of BCT in their treatment. Of note, patients with TC had better 5- and 10-year OS rates ($p = .013$) than the three other histologies. A study by Thurman, et al. of 20 cases of mucinous carcinoma, 27 cases of medullary, 28 cases of TC, and 1055 cases of

IDC found similar results. After a 10 year follow-up period, a lower long-term rate of DFS was observed in the IDC cohort, though this was not significantly different than that of the other subtypes. A third study by Weiss, et al. comparing the same subtypes reported similar results.[40]

Benefit of Radiation

The NSABP trial described above also featured a third cohort of women treated with lumpectomy alone, which demonstrated the utility of radiotherapy. These women suffered a cumulative incidence of ipsilateral breast recurrence of 39.2%, as compared with 14.3% in women undergoing lumpectomy and post-operative irradiation at 20 year follow-up ($p < 0.001$). The hazard ratio for death among the cohort receiving lumpectomy alone, as compared with the mastectomy cohort, was 1.05 (95 percent confidence interval, 0.90 to 1.23; P=0.51). Treatment by lumpectomy alone has been demonstrated in numerous randomized trials to be associated with a three-fold increase in local failure (Table 9).[42-45] Though individual trials did not report differences in survival, two recent metanalyses report a small, but statistically significant compromise in survival of 5.3% and 8.6% by omission of radiation.[42,46,47]

Table 9. Randomized Trials of Breast-Conserving Therapy With or Without Radiation

			Rates of Local Relapse	
Study	n	Follow-up	Radiotherapy	No Radiotherapy
Fisher et al.[43]	930	10 years	12.4%	40.9%
Liljegren et al.[44]	381	10 years	8.5%	24%

Veronesi et al.[2]	567	10 years	5.83%	23.5%
Clarke et al.[47]	837	3 years	5.5%	25.7%
Winzer et al.[45]	347	5.9 years	3.2%	27.8%

Table taken from Haffty B, Wilson, LD. Handbook of Radiation Oncology: Basic Principles and Clinical Protocols. First ed: Jones and Bartlett Publishers, 2008:797.

Just as the adequacy of BCT in the treatment of TC has not been established, few have addressed the precise role of radiation in the treatment of TC. A study by Leonard, et al. of 44 patients with pure TC treated only by wide local excision reported a crude local failure rate of 96% (2/44), 5- and 10-year local control rates of 100% and 87%, and actuarial 5- and 10-year OS and DFS rates of 80% and 52%, and 100% and 91%.[48] It should be noted, however, that the patients in this study had lesions of pure tubular histology and a median tumor size of only 6.5mm (range 2-30 mm). Further, the median age was 67 years (range 40-96 years). Therefore, this retrospective study suggests that breast irradiation might be omitted after conservative surgery in older patients with small TC.

However, a literature review by Sullivan, et al. suggests that radiation may still provide a benefit in local control to patients with TC.

Table 10. Literature Review of Conservatively Treated Cases of Tubular Carcinoma

	Conservative surgery Without Radiotherapy		Conservative surgery With Radiotherapy		Follow-up
	Cases with local failure	Total cases	Cases with local failure	Total cases	

Tobon et al.[49]	0	2	0	1	23-month mean
Carstens[12]	2	5	-	-	24-month mean
Oberman et al.[18]	2	2	-	-	67-month mean
Peters et al.[13]	0	1	0	2	74-month mean
Deos et al.[6]	3	8	-	-	144-month mean
McDivitt[8]	1	12	0	3	36-month mean
Weiss et al.[40]	-	-	2	18	61-month median
Winchester et al.[16]	0	5	0	16	58-month median
Schnitt et al.[50]	0	7	-	-	56-month median
Haffty et al.[51]	-	-	0	21	113-month median
Bradford et al.[52]	0	17	0	21	48-month median
Kitchen et al.[33]	0	5	0	22	144-month median
Holland et al.[27]	2	6	0	23	34.5-month median
Cabral et al.[17]	1	21	0	13	58-month mean
Thurman et al.[41]	-	-	2	28	120-month minimum
Livi et al.[35]	2	52	8	218	101-month median
Sullivan et	0	13	3	49	93-month median

al.[38]					
Total	13	156	15	435	
		8.3%		3.4%	

Table from Sullivan T, Raad RA, Goldberg S, Assaad SI, Gadd M, Smith BL, Powell SN, Taghian AG. Tubular carcinoma of the breast: a retrospective analysis and review of the literature. Breast Cancer Research and Treatment. 93: 199-205, 2005.

Future of Breast Conservation Therapy

Two recent randomized trials have questioned the need for radiation therapy in elderly women. A study by Hughes, et al. randomized patients over 70 years of age with early-stage, node-negative, ER-positive breast cancer to either radiotherapy and tamoxifen or tamoxifen alone.[53] At five years, radiotherapy significantly lowered local failure rates, when compared to the tamoxifen alone group (1% vs. 4%, $p < 0.001$), but there were no significant differences between the two groups with regard to the rates of mastectomy for local recurrence, distant metastases, or overall survival (87% vs. 86%, $p = 0.94$). In comparison, a study by Fyles, et al. of patients greater than 50 years of age also demonstrated no significant differences in the rates of distant metastasis or overall survival.[54] However, the five-year disease-free survival rates (84% vs. 91%; $p = 0.004$) and local relapse rates (7.7% vs. 0.6%, $p < 0.001$) favored the radiation cohort. Longer follow-up data for both studies is awaited.

Another potential development in BCT is the use of partial breast irradiation following lumpectomy. For patients with low-risk disease, this approach allows for less radiation to be delivered over a shorter course to a restricted breast volume. The radiation can be delivered utilizing a variety of techniques including multiplane interstitial catheters, Mammosite-brand balloon, or external beam conformal therapy.

The efficacy and safety of partial breast irradiation is currently being studied in an ongoing randomized trial, as compared to traditional BCT.

Breast Conservation Therapy in the Treatment of Tubular Carcinoma

Despite its benign histopathologic characteristics, however, TC has been observed to have features which are potentially incompatible with a conservative approach to local therapy. In particular, numerous studies have documented an increased frequency of multi-centricity and synchronous or metachronous contralateral disease.[16,26,27] These characteristics may indicate an increased risk of local recurrence or second primary and demand a more aggressive means of local therapy.

STATEMENT OF PURPOSE

The purpose of our investigation was to identify patients with TC treated with BCT at our institution. Like studies by Vo, et al.[39] Weiss, et al.,[40] and Thurman, et al.[41] discussed above, we aim to elucidate the role of BCT for the treatment of TC by comparing the clinical-pathologic features and long-term outcomes of patients with TC to those of our large cohort of patients with IDC. Our hypothesis is that patients with TC will have more favorable pre-treatment clinical-pathologic characteristics than those of the IDC cohort and that clinical outcomes will be comparable between the two subtypes following BCT.

MATERIALS AND METHODS

Prior to initiating this study, institutional review board (IRB) approval was obtained by Dr. Meena Moran to review hospital charts and pathology slides. From tumor registry data, a list of all tubular breast cancer cases treated at the facilities of Yale University School of Medicine was compiled by Gene-Fu Liu (GFL) with the aid of the Yale Tumor Registry and was referenced against a list compiled by Drs. Bruce G. Haffty (BGH) and Meena S. Moran (MSM). To identify which of these TC patients were treated with BCT, medical chart reviews were conducted by GFL.

Our study cohort was therefore comprised of Stage I/II TC patients who all received conservative surgery and radiation therapy. Patients with TC who had pathology slides available for review underwent central pathology review. Slides were read by a single breast pathologist, Dr. Qifeng Yang (QY), at the Pathology Department of Yale New Haven Hospital. Tubular histology was designated to any cases that had greater than 75% tubular histology as designated by the Stanford Surgical Pathology Criteria.[7] Patients with lesions comprised of less than 75% tubular histology were excluded from the TC cohort; as stated above, such lesions have been demonstrated to exhibit a natural history similar to that of IDC.[12,13] Our comparison cohort consisted of 2238 patients with Stage I or II invasive ductal histology treated with BCT, identified from our departmental breast cancer database, which was compiled by BGH and MSM. Chart reviews from the Departments of Therapeutic Radiology of Yale University were conducted by GFL to gather clinical, pathologic and outcomes data on the tubular cohort, and the relevant information was entered into our database for analysis. Data on the invasive ductal cohort was collected previously by BGH and MSM.

All patients analyzed in this study were treated with conservative surgery and radiation therapy. Conservative surgery consisted of excisional biopsy, lumpectomy, quadrantectomy or partial mastectomy, with or without re-excision, to attempt to achieve negative surgical margins. Whole breast RT was delivered to a median dose of 48 Gy using standard tangential techniques, and all patients received a conedown/boost field. The boost was delivered in the majority of patients using an en-face electron field which was designed to encompass the surgical scar plus a generous margin. The total median dose (including cone-down) for both cohorts was 64 Gy. Regional nodal radiation was delivered as previously described.[55] Systemic therapy was delivered at the discretion of the treating oncologist. Patients who received neoadjuvant chemotherapy were excluded from analysis. All clinical and pathologic variables of the 2 cohorts were statistically analyzed using SAS, Version 9.1 (SAS Institute, Cary, NC). All tests of statistical significance were 2-sided and significance was defined as a p value less than 0.05. Bivariate analysis for the association between co-variables and histology were performed using chi^2 analysis and the Fisher's exact test. Outcome parameters were defined as follows: breast recurrence free survival: time of diagnosis to time of local failure within breast; nodal recurrence free survival: time of diagnosis to time of relapse in the axilla, supraclavicular fossa or internal mammary nodes; distant metastasis free survival: time of diagnosis to disease failure outside of the local-regional area. All events were calculated using standard life table methods and the differences were compared using Cox regression models.

RESULTS

The median follow-up for the two cohorts was 7 years. Table 11 stratifies the pre-treatment characteristics of patients by subtype.

Table 11. Pre-Treatment Characteristics by Subtype

	Stage I/II Invasive Ductal Carcinoma	Tubular Carcinoma	P value
Age	55.8 yrs (range 20-90)	55.6 yrs (range 35-84)	NS
Detected by Mammography	954/1891 (50%)	51/64 (80%)	<0.0001
T1 Disease	1445/1798 (80.37%)	65/67% (97.01%)	0.0004
N0 Disease	938/1273 (73.68%)	40/42(95.24%)	0.0016
ER positivity	943/1530 (61.67%)	42/47 (89.36%)	0.0001
PR positivity	719/1391 (51.69%)	35/43 (81.40%)	0.0001
HER-2 positivity	123/422 (29.15%)	3/27 (11.11%)	0.043
Family history	665/1837 (36.20%)	29/64 (45.31%)	NS (0.1366)
Positive margins	127/1412 (8.99%)	1/49 (2.04%)	NS (0.1207)
Adjuvant Hormonal Therapy	669/2068 (32.35%)	27/66 (40.91%)	NS (0.1443)
Adjuvant Chemotherapy	571/2075 (27.52%)	6/70 (8.57%)	0.0004

Abbreviations: NS = not significant

Central Pathology Review

Forty-seven patients had pathology slides available for review. Of these, 77% (36/47) were confirmed as being of the TC subtype. 11 patients were deemed to have <75% tubular histology and were subsequently not included in the clinical-pathologic and outcomes analysis.

Patient characteristics

The average age at presentation was 55.6 years (range 35-84 years) for TC and 55.8 years (range 20-90) for IDC, respectively (p=NS). A significantly greater percentage of TC lesions were detected mammographically (80% vs. 50%; p<0.0001). Of the 64 TC patients with known family history, 29 (45%) have a family history of breast cancer compared with 36% of the IDC cohort (p=0.14).

Tumor characteristics

At presentation, the TC cohort was associated with a greater percentage of pathologic T1 disease (97% vs. 80%; p=0.0007). Furthermore, of the 43 TC patients with axillary staging (15 by sentinel node biopsy and 25 by axillary node dissection), nodal spread was detected in only 2 cases (5%), which is significantly less than the 26% (335/1272) of IDC patients with nodal metastases (p = 0.0016). TC cases also exhibited increased estrogen (ER) and progesterone receptor (PR) expression in comparison to IDC lesions, 89% vs. 62% (p=0.0001) and 81% vs. 52% (p=0.0001), respectively. HER-2 status was reported

as positive in 11% of the TC cases and 29% of IDC cases (p = 0.04)

Adjuvant systemic therapy

Following definitive local therapy, adjuvant hormonal therapy was administered in approximately equal proportions of TC and IDC cases (41% vs. 32%; p = 0.14). Significantly fewer TC patients received adjuvant chemotherapy, 9% versus 28% (p = 0.0004).

Clinical outcomes

Figure 1 shows survival curves by outcome. At ten years, overall survival (90% vs. 80%; p=0.033), cause-specific survival (98 vs. 86%; p=0.011), disease-free survival (99% vs. 82%; p=0.003) all favored the TC cohort. Though there was a trend towards improved breast relapse-free survival for the TC cohort than IDC (95% vs. 87%), this difference did not achieve statistical significance (p=0.062). There was no difference in nodal relapse-free survival (100% vs. 97%; p=0.216) and contralateral breast relapse-free survival (85% vs. 87%; p=0.868) between the 2 cohorts.

Table 12. Clinical Outcomes by Subtype

	Stage I/II Invasive Ductal Carcinoma	Tubular Carcinoma	P value
10-year Overall Survival	80%	90%	0.033
10-year Cause-Specific Survival	86%	98%	0.011

10-year Ipsilateral Breast Relapse-Free Survival	87%	95%	NS (0.062)
10-year Disease-Free Survival	82%	99%	0.003
10-year Nodal Relapse-Free Survival	97%	100%	NS (0.216)
10-year Contralateral Breast-Relapse Free Survival	87%	85%	NS (0.868)
Abbreviations: NS = not significant			

DISCUSSION

This study compares the clinical-pathologic features and long-term outcomes of a relatively large cohort of patients with TC treated with BCT with those of a similarly treated cohort of patients with IDC. Overall, prognostic features and clinical outcomes parameters favored the TC cohort. Specifically, pathologic T and N stages and rates of hormone receptor negativity or HER-2 over-expression were higher in the IDC cohort. In regards to outcomes, cause-specific, disease-free, and overall survival also favored patients with TC over those with IDC. The excellent outcomes of our TC cohort support the adequacy of a conservative approach to the treatment of TC.

Though these results may be expected from a subtype once termed the "well-differentiated carcinoma of the breast,"[26] there have been concerns over the use of BCT in regards to two observed features of TC. First, Lagios et al. reported a 56% rate of multicentricity in 17 cases of TC,[26] which may suggest a potential for increased risk of local recurrence with a conservative therapy. Second, numerous studies have noted an increased incidence of contralateral cancer before, during, or after the initial diagnosis of TC, with a review of the literature revealing a 14% incidence of metachronous/synchronous contralateral disease (Table 13).

Table 13. Incidence of Contralateral Invasive Disease in Patients with Tubular Carcinoma

Study	No. of Patients	No. with Contralateral Carcinoma (%)
Carstens et al.[11]	42	5 (12%)

Cooper et al.[34]	12	2 (17%)
Oberman et al.[18]	25	3 (12%)
Lagios et al.[26]	16	6 (38%)
Peters et al.[13]	36	3 (8%)
Deos et al.[6]	90	9 (10%)
Winchester et al.[16]	50	13 (26%)
Taylor et al.[56]	33	6 (18%)
Thurman et al.[41]	38	3 (8%)
Günhan-Bilgen et al. [57]	32	4 (13%)
Liu et al. (current study)	71	11 (15%)
TOTAL	445	65 (15%)

This figure is slightly higher than the 2-11% incidence reported for all subtypes[58] and may suggest a propensity towards developing a second primary lesion. The basis of increased contralateral disease in TC is unknown, though it had been once been postulated to arise from the subtype's high frequency of intraductal disease. However, this concept was not supported by a subset analysis by Winchester et al., which did not show a correlation between intraductal disease and contralateral disease in patients with TC.[16] Also of note, our study does not demonstrate that patients with TC are more likely than those with IDC to have had or develop metachronous contralateral breast cancer.

Our results are consistent with the existing literature addressing TC. The 5-year 99% DFS and 96% OS exhibited by our TC cohort agree with the clinical outcomes of a larger multi-institutional study comparing TC with IDC by Diab et al., which included

cases treated with mastectomy,[36] as well as with three smaller single-institution studies comparing TC to other histologies treated exclusively with BCT by Vo et al[39], Weiss, et al.,[40] and Thurman et al. (Table 14).[41] Of note, in our review of the literature, this is the largest known single-institution study comparing cases of TC to IDC treated exclusively with BCT.

Table 14. Subsets of Patients with Tubular Carcinoma Treated with BCT in Previous Studies

Study	Local Recurrence Rate	Follow-up
Winchester, et al. [16]	0/16 (0%)	58 months *median*
Sullivan, et al.[38]	3/49 (6%)	90.5 months *median*
Livi, et al.[35]	8/218 (4%)	100.8 months *median*
Cabral, et al.[17]	0/13 (0%)	55 months *mean*
Thurman, et al. [41]	2/28 (7%)	10 years, *minimum*
Vo, et al.[39]	*8/60 (13%)*	10.6 years, *median*
Liu, et al. (current study)	4/70 (6%)	84 months *median*
Total	*15/366 (4%)*	

Abbreviations: BCT = breast conservation therapy

However, this study has several weaknesses which merit discussion. Given the time span of nearly 3 decades in which these patients were treated, and the fact that a significant portion of the patients had surgery elsewhere and were subsequently referred to our institution for radiation treatment, the availability of slides for central pathology review was limited. Furthermore, of the slides available for review, nearly one-quarter

were re-classified by our pathologist as a different histologic subtype due to the stringent criteria applied. Of note, there was no stratification of pure versus mixed TC (defined in the literature as consisting of greater than 90% and 75% tubular histology, respectively) as previous studies have indicated similar outcomes for both histologies.[13,17,59]

Another weakness of our study was the inability to perform multivariate analysis due to the relatively small number of patients in the TC cohort, which may also have underpowered the study to detect statistically significant differences. Specifically, it is possible that the breast and nodal relapse free survival for the TC may indeed be better than for IDC, but our study may have been limited in numbers of patients to detect this difference as significant. Furthermore, this may have compromised our assessment of conventional prognostic and predictive features, e.g., nodal positivity or hormone receptor status. An important question that our study did not address was how cases of TC fare with BCT versus mastectomy, however, our breast database consists of patients treated with only breast conservation, and therefore we are unable to address this question. Finally, the retrospective nature of this study introduces significant bias, with respect to patient selection and intrinsic, retrospective data collection.

Though not directly compared between our two cohorts, an interesting phenomena described in the literature is the high percentage of patients with positive family histories in patients with tubular histology of breast cancer. In our study, of the 58 cases in which family history was documented, 28 (47%) reported a positive history, which is consistent with studies by Lagios et al.[26] and Holland et al.[27] Though the number of TC cases reporting positive histories was not significantly different than that of our IDC patients (36%), it is important to note that a large number of patients (22%) from the IDC cohort

did not have family history data available for analysis, which potentially confounds this analysis.

In conclusion, patients with TC of the breast treated with BCT have excellent long-term outcomes that are comparable to, if not more favorable than, those of similarly treated patients with IDC. These findings support the routine utilization of BCT for the management of this rare histologic subtype.

REFERENCES

1. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002 Oct;347(16):1233-41.
2. Veronesi U, Salvadori B, Luini A, et al. Breast conservation is a safe method in patients with small cancer of the breast. Long-term results of three randomised trials on 1,973 patients. Eur J Cancer. 1995 Sep;31A(10):1574-9.
3. Li C, Moe R, Daling J. Risk of mortality by histologic type of breast cancer among women aged 50 to 79 years. Arch Intern Med. 2003 Oct;163(18):2149-53.
4. Li C, Uribe D, Daling J. Clinical characteristics of different histologic types of breast cancer. Br J Cancer. 2005 Oct;93(9):1046-52.
5. Dixon J, Page D, Anderson T, et al. Long-term survivors after breast cancer. Br J Surg. 1985 Jun;72(6):445-8.
6. Deos P, Norris H. Well-differentiated (tubular) carcinoma of the breast. A clinicopathologic study of 145 pure and mixed cases. Am J Clin Pathol. 1982 Jul;78(1):1-7.
7. Kempson R. Stanford School of Medicine Surgical Pathology Criteria: Tubular carcinoma of the breast. <Available at: http://surgpathcriteria.stanford.edu/breast/tubularcabr>. Accessed, 2006.
8. McDivitt R, Boyce W, Gersell D. Tubular carcinoma of the breast. Clinical and pathological observations concerning 135 cases. Am J Surg Pathol. 1982 Jul;6(5):401-11.
9. Becker R, Mikel U, O'Leary T. Morphometric distinction of sclerosing adenosis from tubular carcinoma of the breast. Pathol Res Pract. 1992 Oct;188(7):847-51.
10. Carstens P. Tubular carcinoma of the breast. A study of frequency. Am J Clin Pathol. 1978 Aug;70(2):204-10.
11. Carstens P, Huvos A, Foote FJ, Ashikari R. Tubular carcinoma of the breast: a clinicopathologic study of 35 cases. Am J Clin Pathol. 1972 Sep;58(3):231-8.
12. Carstens P, Greenberg R, Francis D, Lyon H. Tubular carcinoma of the breast. A long term follow-up. Histopathology. 1985 Mar;9(3):271-80.
13. Peters G, Wolff M, Haagensen C. Tubular carcinoma of the breast. Clinical pathologic correlations based on 100 cases. Ann Surg. 1981 Feb;193(2):138-49.
14. Erlandson R, Carstens P. Ultrastructure of tubular carcinoma of the breast. Cancer. 1972 Apr;29(4):987-95.
15. Jao W, Recant W, Swerdlow M. Comparative ultrastructure of tubular carcinoma and sclerosing adenosis of the breast. Cancer. 1976 Jul;38(1):180-6.
16. Winchester D, Sahin A, Tucker S, Singletary S. Tubular carcinoma of the breast. Predicting axillary nodal metastases and recurrence. Ann Surg. 1996 Mar;223(3):342-7.
17. Cabral A, Recine M, Paramo J, McPhee M, Poppiti R, Mesko T. Tubular carcinoma of the breast: an institutional experience and review of the literature. Breast J.9(4):298-301.
18. Oberman H, Fidler WJ. Tubular carcinoma of the breast. Am J Surg Pathol. 1979 Oct;3(5):387-95.
19. McBoyle M, Razek H, Carter J, Helmer S. Tubular carcinoma of the breast: an institutional review. Am Surg. 1997 Jul;63(7):639-44; discussion 44-5.
20. Mitnick J, Gianutsos R, Pollack A, et al. Tubular carcinoma of the breast: sensitivity of diagnostic techniques and correlation with histopathology. AJR Am J Roentgenol. 1999 Feb;172(2):319-23.
21. Dawson A, Logan-Young W, Mulford D. Aspiration cytology of tubular carcinoma. Diagnostic features with mammographic correlation. Am J Clin Pathol. 1994 Apr;101(4):488-92.
22. Fisher E, Gregorio R, Redmond C, Fisher B. Tubulolobular invasive breast cancer: a variant of lobular invasive cancer. Hum Pathol. 1977 Nov;8(6):679-83.
23. Kuroda H, Tamaru J, Takeuchi I, et al. Expression of E-cadherin, alpha-catenin, and beta-catenin in tubulolobular carcinoma of the breast. Virchows Arch. 2006 Apr;448(4):500-5.
24. Elson B, Helvie M, Frank T, Wilson T, Adler D. Tubular carcinoma of the breast: mode of presentation, mammographic appearance, and frequency of nodal metastases. AJR Am J Roentgenol. 1993 Dec;161(6):1173-6.
25. Victoria B. 1997 Annual Statistical Report. Melbourne: BreastScreen Victoria Inc., 1998.
26. Lagios M, Rose M, Margolin F. Tubular carcinoma of the breast: association with multicentricity, bilaterality, and family history of mammary carcinoma. Am J Clin Pathol. 1980 Jan;73(1):25-30.
27. Holland D, Boucher L, Mortimer J. Tubular breast cancer experience at Washington University: a

review of the literature. Clin Breast Cancer. 2001 Oct;2(3):210-4.
28. Claus E, Risch N, Thompson W, Carter D. Relationship between breast histopathology and family history of breast cancer. Cancer. 1993 Jan;71(1):147-53.
29. Bürki N, Buser M, Emmons L, et al. Malignancies in families of women with medullary, tubular and invasive ductal breast cancer. Eur J Cancer. 1990 Mar;26(3):295-303.
30. Fitzgibbons P, Page D, Weaver D, et al. Prognostic factors in breast cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med. 2000 Jul;124(7):966-78.
31. Goldhirsch A, Wood W, Gelber R, Coates A, Thürlimann B, Senn H. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol. 2007 Jul;18(7):1133-44.
32. Hudis C. Trastuzumab--mechanism of action and use in clinical practice. N Engl J Med. 2007 Jul;357(1):39-51.
33. Kitchen P, Smith T, Henderson M, et al. Tubular carcinoma of the breast: prognosis and response to adjuvant systemic therapy. ANZ J Surg. 2001 Jan;71(1):27-31.
34. Cooper H, Patchefsky A, Krall R. Tubular carcinoma of the breast. Cancer. 1978 Nov;42(5):2334-42.
35. Livi L, Paiar F, Meldolesi E, et al. Tubular carcinoma of the breast: outcome and loco-regional recurrence in 307 patients. Eur J Surg Oncol. 2005 Feb;31(1):9-12.
36. Diab S, Clark G, Osborne C, Libby A, Allred D, Elledge R. Tumor characteristics and clinical outcome of tubular and mucinous breast carcinomas. J Clin Oncol. 1999 May;17(5):1442-8.
37. Network NCC. Cancer Guidelines for Patients and Physicians by Cancer Experts. 2008.
38. Sullivan T, Raad R, Goldberg S, et al. Tubular carcinoma of the breast: a retrospective analysis and review of the literature. Breast Cancer Res Treat. 2005 Oct;93(3):199-205.
39. Vo T, Xing Y, Meric-Bernstam F, et al. Long-term outcomes in patients with mucinous, medullary, tubular, and invasive ductal carcinomas after lumpectomy. Am J Surg. 2007 Oct;194(4):527-31.
40. Weiss M, Fowble B, Solin L, Yeh I, Schultz D. Outcome of conservative therapy for invasive breast cancer by histologic subtype. Int J Radiat Oncol Biol Phys. 1992;23(5):941-7.
41. Thurman S, Schnitt S, Connolly J, et al. Outcome after breast-conserving therapy for patients with stage I or II mucinous, medullary, or tubular breast carcinoma. Int J Radiat Oncol Biol Phys. 2004 May;59(1):152-9.
42. Clark R, Whelan T, Levine M, et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. Ontario Clinical Oncology Group. J Natl Cancer Inst. 1996 Nov;88(22):1659-64.
43. Fisher B, Bryant J, Dignam J, et al. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. J Clin Oncol. 2002 Oct;20(20):4141-9.
44. Liljegren G, Holmberg L, Adami H, Westman G, Graffman S, Bergh J. Sector resection with or without postoperative radiotherapy for stage I breast cancer: five-year results of a randomized trial. Uppsala-Orebro Breast Cancer Study Group. J Natl Cancer Inst. 1994 May;86(9):717-22.
45. Winzer K, Sauer R, Sauerbrei W, et al. Radiation therapy after breast-conserving surgery; first results of a randomised clinical trial in patients with low risk of recurrence. Eur J Cancer. 2004 May;40(7):998-1005.
46. Vinh-Hung V, Verschraegen C. Breast-conserving surgery with or without radiotherapy: pooled-analysis for risks of ipsilateral breast tumor recurrence and mortality. J Natl Cancer Inst. 2004 Jan;96(2):115-21.
47. Clarke M, Collins, R, Darby, S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. Lancet. 2005;366:2087-106.
48. Leonard C, Howell K, Shapiro H, Ponce J, Kercher J. Excision only for tubular carcinoma of the breast. Breast J.11(2):129-33.
49. Tobon H, Salazar H. Tubular carcinoma of the breast. Clinical, histological, and ultrastructural observations. Arch Pathol Lab Med. 1977 Jun;101(6):310-6.
50. Schnitt S, Hayman J, Gelman R, et al. A prospective study of conservative surgery alone in the treatment of selected patients with stage I breast cancer. Cancer. 1996 Mar;77(6):1094-100.
51. Haffty BG PP, Ward B, Moran M, Beinfeld M, McKhann c, Fischer D, Carter D. Conservatively

treated breast cancer: outcome by histologic subtype. Breast Journal. 1997;3:7-14.
52. Bradford WZ CW, Fraser H, Cloninger TE. Treatment of pure tubular carcinoma of the breast. Breast J. 1998;4:437-40.
53. Hughes K, Schnaper L, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med. 2004 Sep;351(10):971-7.
54. Fyles A, McCready D, Manchul L, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med. 2004 Sep;351(10):963-70.
55. Haffty B, Yang Q, Moran M, Tan A, Reiss M. Estrogen-dependent prognostic significance of cyclooxygenase-2 expression in early-stage invasive breast cancers treated with breast-conserving surgery and radiation. Int J Radiat Oncol Biol Phys. 2008 Jul;71(4):1006-13.
56. Taylor H, Norris H. Well-differentiated carcinoma of the breast. Cancer. 1970 Mar;25(3):687-92.
57. Günhan-Bilgen I, Oktay A. Tubular carcinoma of the breast: mammographic, sonographic, clinical and pathologic findings. Eur J Radiol. 2007 Jan;61(1):158-62.
58. Chen Y, Thompson W, Semenciw R, Mao Y. Epidemiology of contralateral breast cancer. Cancer Epidemiol Biomarkers Prev. 1999 Oct;8(10):855-61.
59. Fernández-Aguilar S, Simon P, Buxant F, Simonart T, Noël J. Tubular carcinoma of the breast and associated intra-epithelial lesions: a comparative study with invasive low-grade ductal carcinomas. Virchows Arch. 2005 Oct;447(4):683-7.

FIGURES

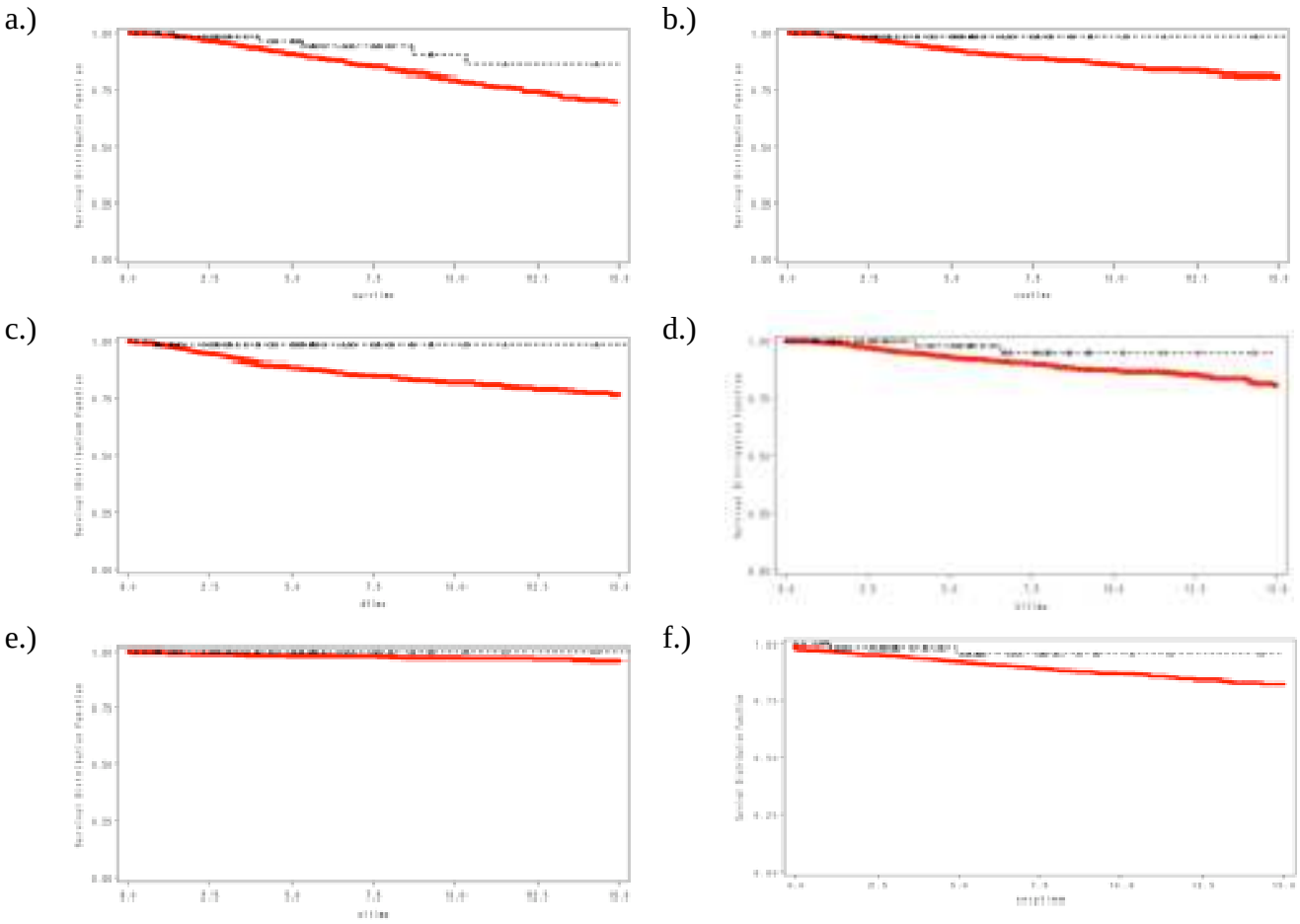

Figure 1. Survival curves for Tubular Carcinoma versus Invasive Ductal Carcinoma.

Solid Line: Invasive Ductal Carcinoma, Broken Line: Tubular Carcinoma

a.) Overall Survival b.) Cause-Specific Survival c.) Disease-Free Survival d.) Breast Relapse-Free Survival e.) Nodal Relapse-Free Survival f.) Contralateral Breast Relapse-Free Survival