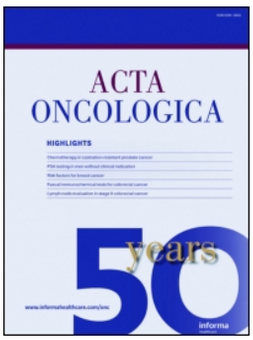

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Extending hypofractionated stereotactic body radiotherapy to tumours larger than 70cc – effects and side effects

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ABSTRACT

Background and purpose: Stereotactic body radiotherapy (SBRT) for tumours ≥5 cm is poorly studied and its utility and feasibility is uncertain. We here report the Karolinska experience of SBRT in this setting.

Material and methods: All patients had a gross tumour volume (GTV) ≥70 cc, a prescribed physical dose of at least 40 Gy and received treatment between 1995–2012.

Results: We included 164 patients with 175 tumours located in the thorax ($n = 86$), the liver ($n = 27$) and the abdomen ($n = 62$) and treated with a median prescribed dose ($BED_{\alpha/\beta\,10Gy}$) of 80 Gy (71.4–113). One- and 2- year local control rates were 82% and 61%. In multivariate analyses, minimum dose to the GTV and histological subtype were associated with local control. Renal cell carcinoma (RCC) histology showed the most favourable local control − 94% at 2 years for all histologies. Thirty-seven patients experienced grade 3–5 toxicity most likely related to SBRT. Seven of the ten patients with grade 5 toxicity, had a centrally located tumour in the thorax.

Conclusion: SBRT of tumours >5 cm in diameter may be an option for peripherally located lung and abdominal tumours. Histological origin and tumour location should be considered before treatment.

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Stereotactic; SBRT; hypofractionation

Introduction

Hypofractionated stereotactic body radiotherapy (SBRT) has mainly been used for tumours less than 5 cm in diameter, with reported local control exceeding 90% and acceptable side effects [1,2]. However, as noted in early clinical trials of SBRT of stage I–II, primary non-small cell lung cancer (NSCLC), local failure and ≥ grade 3 toxicity were observed more often in patients with T2-tumours as compared to patients with smaller sized tumours [1,3–5]. Subsequent analyses specifically focussing on tumour size in relation to local control have been conflicting [6] with both reports of increased rates of local failure with increasing tumour size [7–9] as well as reports where this difference could not be confirmed [10], which might be attributed to a higher prescribed dose [11]. These findings are consistent with results from pre-clinical *in vitro* experiments and probably reflects the greater number of clonogenic cells in a large tumour, requiring a higher absorbed dose to achieve local tumour control [12].

From a toxicity point of view, large tumours are also likely located close to radiation sensitive organs at risk (OAR) such as the proximal bronchial tree (PBT) for lung targets and the gut for abdominal targets, which may increase the risk for serious toxicity [2,13–18]. Hence, there is a delicate balance between keeping the dose to normal tissues within tolerance level and at the same time maintaining a required dose and dose coverage of the target to avoid local failure for these large-volume tumours.

We conducted this study based on the hypothesis that SBRT may be a treatment option for a subset of tumours larger than 5 cm. To define this subset of potentially treatable tumours, risk factors for local recurrence and high-grade toxic effects, such as radiation dose, target location and histological origin of the tumour, need to be defined.

In this retrospective study, we present local control- and toxicity rates in patients treated with SBRT for tumour lesions

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of ≥70 cc (corresponding to a tumour lesion of ≥5.1 cm in diameter), located in the thorax or the abdomen.

Material and methods

Study design

This is a retrospective, single institutional study of the patients treated with SBRT at Karolinska University Hospital between 1995 and 2012. The patients were identified in the local radiation oncology database. Criteria for inclusion in this retrospective study cohort were a gross tumour volume (GTV) of at least 70 cc and a prescribed physical dose of at least 8 Gy x 5 = 40 Gy corresponding to 72 Gy BED_{10Gy} (details on the technical aspects of the SBRT-treatment are described below). The cut off at 70 cc corresponds to a diameter of the tumour of approximately 5.1 cm assuming a spherical shape of the tumour. The cut off at 40 Gy in prescribed physical dose was chosen as a minimum dose level indicative for curative intention during the early era of SBRT at our institution. Details on patient selection are presented on the flowchart in electronic Supplement 1. Patients without available treatment plans or clinical records were excluded. Ethical approval was obtained from the regional ethical committee of Stockholm County Council, Dnr 2012/2143-31/2.

Radiation technique and dosimetry data

The technique used for SBRT immobilisation and treatment planning has been described in previous reports from our institution [1,19,20]. During the 17-year-long period during which patients in this study were included, the SBRT-technique changed somewhat with the major technical changes occurring in 2008/2009 with the introduction of on-line CBCT matching and the transition from the pencil beam (PB) to the AAA-dose calculation algorithm, and in 2011 with the introduction of volumetric modulated arc-therapy (VMAT) and tumour movement assessment with 4 D-CT. Generally, the patients were immobilised in the stereotactic body frame (SBF, Electa AB, Stockholm, Sweden) with or without abdominal compression depending on the amplitude of the tumour movements. The GTV comprised the visible tumour mass on CT, and the clinical target volume (CTV) encompassed the GTV and the diffuse tumour growth at the borders. The CTV-PTV margin was ≥5 mm in transversal plane and ≥10 mm in longitudinal plane, depending on the amplitude of the tumour movements. SBRT was delivered using a linear accelerator from Varian Medical systems with 6 MV energy by 4–12 static fields or using VMAT technology. Tumour movements were assessed by fluoroscopy or 4 D-CT. Geometrical verification of the target position was performed using a second CT immediately before treatment or on-line CBCT before each fraction. In general, doses were prescribed to the ~ 67% isodose line, encompassing the PTV. However, for these very large tumours prescription to other isodose lines encompassing the PTV were occasionally also used on an individual basis to tailor the treatment.

Maximum, mean and minimum dose to the GTV were retrieved and recalculated to $BED_{\alpha/\beta\,10Gy}$ using the Linear Quadratic model [21].

Clinical data

Clinical information on tumour- and patient characteristics at baseline and during follow-up until death were retrieved from medical records. The maximum grade of toxicity was scored for each patient using CTCAE 4.0. Local control was assessed using RECIST 1.0 with the last day of SBRT as starting point. In cases of no local recurrence, local control was estimated to prevail until the last clinical follow-up or death (maximum time-lapse of three months between a follow-up CT/MRI-scan showing local control and the last clinical follow-up/date of death). Following SBRT, patients treated curatively for primary NSCLC typically underwent a CT scan and physical examination every three months until two years post SBRT and thereafter every 6 months. Patients treated for metastases were followed on an individual basis at their outpatient clinic with regular CT-/MRI scans and physical examinations.

The tumours were classified based on location in four groups: peripheral-, central thoracic, abdominal and liver localisation. Central location of thoracic tumours was defined as tumours ≤1 cm from the main bronchi.

Statistical methods and data management

Multiple comparisons of continuous data were performed by analysis of variance, ANOVA. In the case of a statistically significant result in the ANOVA, statistical comparisons were made by use of the post-hoc test proposed by Fisher controlling for multiplicity. Statistical comparison testing for differences between two independent groups were made by use of the Student's t-test for uncorrelated means. In order to evaluate hypotheses of variables in contingency tables, the chi-square test was used or, in the case of small expected frequencies, Fisher's Exact Test. Regression analysis was used when evaluating the dependency between variables, and the Pearson correlation coefficient was used in order to test for independence between variables. Local-control rates were estimated by the Kaplan–Meier method and compared by the log-rank test. Cox regression analyses were performed for time-dependent variables, calculating hazard ratios (HR) with 95% confidence intervals (CI). All analyses were carried out by use of SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA). A p-value of $<.05$ was considered as significant.

Results

We included 164 patients with 175 tumours in the study. Eighty-six tumours were located in the thorax and of these, 40 tumours in 38 patients, in a central thoracic location. The median follow-up, as well as median overall survival for the entire cohort was 16.6 months. Table 1 summarises patient and treatment characteristics. Ninety-eight percent of the

Table 1. Baseline patient and treatment characteristics.

	N	(Range)/%
Patients	**164**	**100%**
Men/women	83/81	51%/49%
Age at SBRT *(median, years)*	70	(24–92)
Dead	160	98%
Follow-up *(median, months)*	16.6	(0.3–140.4)
No of treated tumours	**175**	**100%**
Tumour location		
Peripheral lung	46	26%
Central lung[a]	40	23%
Liver	27	16%
Abdomen[b]	62	35%
Tumours evaluable for local control	**165**	**100%**
Histology		
NSCLC	48	29%
CRC	32	19%
RCC	29	18%
Other[c]	56	34%
GTV *(median, cc)*	137	(70–1193)
Dose GTV *(median, Gy)*		
Prescribed physical dose	40	40–50
Prescribed dose BED (α/β10Gy)	80	71.4–112.5
Minimum	73	18–142.9
Mean	105.6	73.4–159.8
Maximum	113.6	81.4–202

[a]81 patients had at least one thoracic tumour with central or peripheral location.
[b]Lymph nodes, pelvic bones, adrenal glands and abdominal sarcomas.
[c]Malignant melanoma, sarcoma, breast cancer, HCC and others.

Table 2. KM-estimated local control rates.

Time point *(months)*	Total *% (95% CI)*	NSCLC *% (95% CI)*	CRC *% (95% CI)*	RCC *% (95% CI)*
6	92 (86–95)	96 (83–99)	87 (68–95)	100 (100–100)
12	82 (74–87)	73 (54–85)	68 (46–83)	100 (100–100)
18	71 (61–78)	54 (33–71)	44 (21–64)	94 (65–99)
24	61 (50–70)	48 (27–67)	18 (3–42)	94 (65–99)
36	57 (45–67)	48 (27–67)	-	94 (65–99)

KM-estimated local control rates for the total cohorts and per the three major tumour histologies. The numbers within brackets show 95% confidence interval.

patients were dead at the time of last follow up (details on overall survival is presented in electronic Supplement 2).

A wide range of fractionation schemes were used, which is partly explained by the individualised treatment planning approach to some of the targets close to an OAR. The two most frequently used fractionation schedules were 8 Gy × 5 and 10 Gy × 4, corresponding to 72 Gy and 80 Gy BED_{10Gy}, respectively. Several tumours close to an OAR had to be partly 'underdosed', which is reflected by the gap between median values for mean and minimum GTV doses, as well as by the wide range of minimum GTV doses (18–143 Gy (BED_{10Gy})).

Local control

Local control was evaluable for 165 tumours (in 154 patients); the histological distribution is presented in Table 1. Forty-nine percent of the targets were located in the thorax. The most common histological subgroup in the entire cohort comprised NSCLC (29%) followed by CRC (19%) and RCC (18%). The one-, two- and three-year-local control rates for the entire cohort were 82%, 61% and 57% respectively. As compared to tumours with NSCLC and CRC-histology, RCC-histology showed superior results with a three-year-local control rate of 94% (Table 2 and Figure 1). Tumour histology was also significantly associated with local control in both uni- and multivariate analyses ($p < .001$).

The median GTV of 137 cc (Table 1) corresponds to a tumour diameter of 6.4 cm assuming a spherical shape of the tumour. Minimum, median and maximum doses to the GTV were all significantly correlated with local control in the univariate analyses (*p*-value below .05) but in multivariate analyses the minimum dose to the GTV ($p = .0009$) remained the only statistically significant dose-volume factor. No other parameters showed a significant correlation with local control with either ANOVA or Cox regression analyses.

Toxicity

Toxic effects were evaluable for 164 patients. Twenty-four patients experienced maximum grade 3 toxicity consisting of pneumonia/radiation pneumonitis ($n = 9$), fatigue ($n = 4$), dyspnoea ($n = 3$), thoracic pain ($n = 3$), abdominal pain ($n = 2$), diarrhoea ($n = 2$), the appearance of a liver abscess and radiation induced brachial plexopathy ($n = 1$). Maximum recorded grade 4 toxicity was scored in four patients and included radiation pneumonitis/pneumonia ($n = 2$), esophago-tracheal fistula ($n = 1$) and gastric perforation ($n = 1$).

There were ten cases of possible grade 5 toxicities, presented in detail in Table 3. For these lethally affected patients seven had been treated for a centrally located thoracic tumour, one patient for a peripherally located lung tumour and two patients had received treatment for abdominal targets. Eighteen percent of the patients with centrally located thoracic tumours experienced grade 5 toxicity, compared with only 2% of the peripherally located. All lung-related grade 5 toxicities occurred within 6 months post SBRT (Table 3) Given the small number of events, the diversity of the type of events and the different locations of the treated targets with proximity to different organs at risk, no formal statistical analyses of risk factors for high grade toxicity have been made. However, except for tumour location, all other tumour- and clinical characteristics appeared to be equally distributed between the patients experiencing grade 5 toxicity and the rest of the cohort.

Discussion

We here report local control and toxicity post SBRT of very large tumours (>5cm) in the thorax and the abdomen. We have shown that tumour histology (RCC showing the highest rate of local control and CRC the lowest) and minimum doses to the GTV were significantly associated with local control. Seventy percent of all grade 5 toxicities occurred in patients with centrally located thoracic tumours (Table 3).

In this study, we found that local control was strongly affected by the histology of the treated tumour lesion as shown in Figure 1 and Table 2. For NSCLC, the estimated local control in our analysis (58% at 18 months and 48% at 24 and 36 months) was inferior compared with other SBRT-series of NSCLC with tumours larger than 5 cm (local control

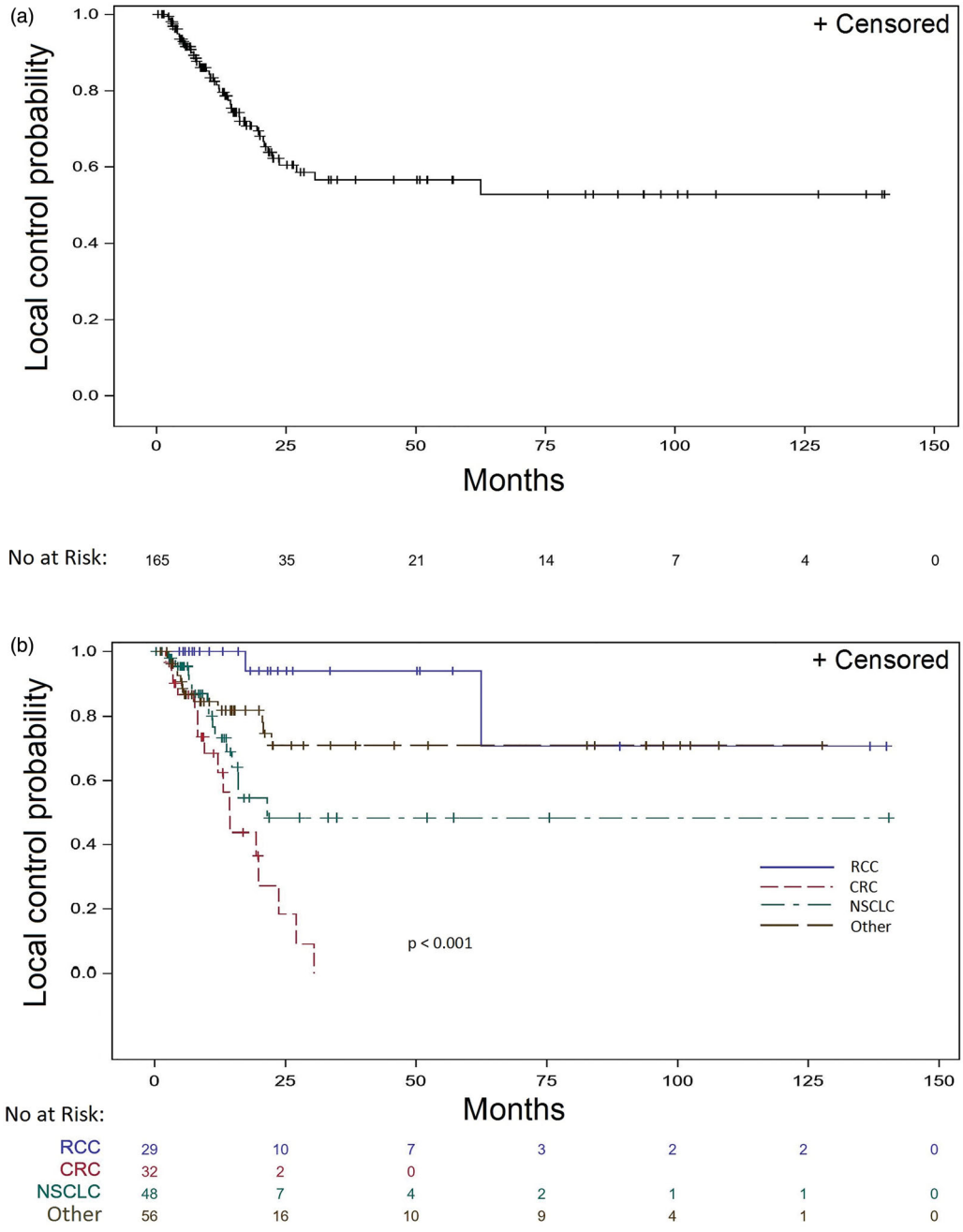

Figure 1. (a) KM-estimated local control for the total cohort. (b) KM-estimated local control per histology.

of 73–96%) [22–25]. The difference is likely due to the higher prescribed target doses with >90% of the patients in the referred studes receiving at least 100 Gy BED_{10Gy}, which is an accepted dose-threshold for SBRT of primary NSCLC [26] as compared to only 33% of the NSCLC patients in our study. [27]. However, a direct comparison of the absorbed doses is not possible since the dose prescription and dose delivery methods differ and full dosimetric data rarely is presented. Also, large tumours typically contain both a higher amount of clonogenic cells [12] as well as a higher ratio of hypoxic cells [28], as compared to smaller sized tumours, so that an even higher absorbed dose may be required to achieve tumour ablation for these large tumours.

We found that CRC histology had the lowest local control rate. From an SBRT-point of view, metastases from CRC are known to have increased radioresistance [29–31], which may be compensated for by dose escalation [30–33], although an optimal dose has not yet been established. One possible explanation for the mechanism behind this increased radioresistance is related to tumour hypoxia [28,31,34,35]. Other reports have shown dependence between tumour size and local control specifically for this histological subgroup [35–38]. In our cohort, the tumours were larger than in previous SBRT-series with CRC-metastases, and prescribed doses were generally lower (median BED_{10Gy} = 80 Gy, current study), two factors that may explain the poor local tumour control. Thus, increasing the dose to the target might be one option to increase local tumour control, which, however, has to be balanced against too high doses to OAR. This may be clinically challenging and one may question whether

Table 3. Target and treatment characteristics in patients with possible grade 5 toxicity.

	Tumour location	GTV (cc)	Fractionation schedule	Time to G5 tox (months)	Local control (Y/N)
Thoracic targets					
Hemoptysis	Central[a]	142	8 Gy x 5	5	Y
	Central	70	7 Gy x 6	6	Y
	Central[b]	391	12 Gy x 4	2	Y
	Central[c]	210	8 Gy x 5, 8 Gy x 4	1	Y
Radiation pneumonitis / Pneumonia	Central	149	10 Gy x 5	1	Y
	Central	88	10 Gy x 5	1	Y
	Central	291	10 Gy x 4	2	Y
	Peripheral	111	8 Gy x 5	1	Y
Abdominal targets					
Gastro-intestinal bleeding	Liver	270	7 Gy x 6	34	Y
Duodenal perforation	Liver	147	10 Gy x 4, twice[d]	11	N

Grade five toxicity divided per target location and symptom. Each row represents one patient.
[a]This patient previously received conventionally fractionated radiotherapy 60 Gy.
[b]This patients received simultaneous SBRT 10 Gy x 4 to a peripheral lung lesion (34 cc).
[c]8Gy x 4 was delivered to a part of the tumour mass but due to local progression, 8 Gy x 5 was prescribed to the total tumour mass.
[d]The patient was treated with a 9-month-interval twice with 10 Gy x 4.

tumours >5 cm with CRC histology are possible to treat successfully with SBRT.

At the other end of the spectrum, patients treated for large lesions with RCC-histology showed the most responsive histology as compared to the two other main sub-groups (NSCLC and CRC) (Table 2, Figure 1). These results are truly promising and in line with previous reports on SBRT for large RCC. Siva *et al* [39] reported 4-year-local control of 97.8% of primary RCC treated with SBRT. Only 3 cases of local failure were noted and 110 of the 223 analysed patients had tumours exceeding 4 cm in size. Three other studies, however, with small patient materials, report local control of 86–100% of the treated lesions [40,41]. The cited studies on SBRT of renal cell carcinoma are summarised in detail in electronic Supplement 3. Thus, based on our own results and the current literature, RCC appears to be highly responsive to SBRT despite large tumour volumes and varying fractionation schedules [39]. Our study suggests that SBRT may be a valuable treatment option for large tumour lesions from RCC.

Interestingly when analysing the entire study cohort, tumour size could not be defined as a separate risk factor for local recurrence neither in the current analysis nor in previous studies evaluating tumours > 5 cm [22–25]. In the other studies examining SBRT of >5cm NSCLC, no dosimetry data or tumour characteristics prognostic for local failure were defined [22–24]. Our results, however, imply that the minimum dose to the GTV might be an important dose parameter. This may mirror the fact that the tumour might have been located close to an OAR, resulting in suboptimal coverage of the target, to prevent toxic effects. However, a threshold dose for local control cannot be estimated from the current data due to limitations in the accuracy of the minimum target dose. All patients treated before 2008 (80%) were planned using a pencil-beam dose calculation algorithm. When comparing the minimum dose (subanalysis, data not shown) calculated with the pencil-beam algorithm to the values resulting from the more accurate AAA algorithm for 18 patients, differences of up to 30 Gy BED_{10Gy} were found, overestimating the minimum dose near lung tissue and sometimes underestimating the dose in the mediastinum and abdomen. Moreover, as a point dose parameter, the planned minimum dose is likely to differ greatly from the delivered minimum dose. The fact that the minimum dose was found to be a significant predictor of local control, despite the uncertainties in this parameter, is probably explained by the great range of doses in our cohort (Table 1).

In total, 23% of all patients in the cohort had grade 3-5 toxic effects. Toxicity resulting in death were noted predominately in centrally located thoracic tumours (7 of 10 cases) which is a high-risk tumour location at SBRT [13,14,42,43]. Tekatli and colleagues reported 19% of the patients experiencing possible or likely grade 5 toxicity for large volume tumours [25], which is somewhat higher than in the present study, and probably due to the higher radiation doses delivered in the Amsterdam study. Two other reports present a single case each of grade 5 toxicity [23] – one with mediastinal involvement [27], while no other SBRT series on large tumours of the thorax or abdomen report any grade 5 events [22,24,39,40,44]. Interestingly, in our cohort, the treatment was generally well tolerated for targets in the abdomen and in the periphery of the lungs.

This study suffers several limitations. Firstly, its retrospective nature compromises the interpretation of toxicity, and the full DVHs from the treatment plans have not been possible to retrieve. Secondly, despite the large number of treated tumours, the cohort is highly heterogeneous in terms of tumour histology, treatment doses, tumour location as well as other previous and subsequent treatments. The limited follow-up and rapid decline in patients at risk for an event also limits the interpretation of both toxic effects and local tumour control (e.g. only 37 tumours were 'at risk' for local failure at 25 months post SBRT). Thirdly, the study spanned over many years in which the radiotherapy technique changed, resulting in a variation in the accuracy of the estimated planned dose as the dose calculation algorithm and image guidance at treatment improved over time.

Conclusion

SBRT of tumours larger than 5 cm in diameter may be a treatment option for peripherally located lung tumours and abdominal tumours, whereas centrally located thoracic

tumours (i.e. < 1cm from the main bronchi) should be avoided due to risk for high-grade toxicity. Prior treatment, the histologic subtype, given the prescription dose and the necessity to compromise on target coverage due to any organs at risk, should be considered.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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