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Accelerated partial breast irradiation

Accelerated partial breast irradiation with interstitial brachytherapy as second conservative treatment for ipsilateral breast tumour recurrence: Multicentric study of the GEC-ESTRO Breast Cancer Working Group

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ABSTRACT

Purpose: To analyse the clinical outcome after salvage lumpectomy and multi-catheter brachytherapy (MCB) for ipsilateral breast tumour recurrence (IBTR).

Material and methods: Between 09/00 and 09/10, 217 patients presenting an IBTR underwent lumpectomy and MCB (low, pulsed, or high-dose rate). Survival rates without second local recurrence (2nd LR), distant metastasis (DM), and overall survival (OS) were analysed as well as late effects and cosmetic results. Univariate and multivariate analyses (MVA) based on IBTR data were performed to find prognostic factors for 2nd LR, DM, and OS.

Results: Median follow-up after the IBTR was 3.9 years [range: 1.1–10.3]. Five and 10-year actuarial 2nd LR rates were 5.6% [range: 1.5–9.5] and 7.2% [range: 2.1–12.1], respectively. Five and 10-year actuarial DM rates were 9.6% [range: 5.7–15.2] and 19.1% [range: 7.8–28.3], respectively. Five and 10-year actuarial OS rates were 88.7% [range: 83.1–94.8] and 76.4% [range: 66.9–87.3], respectively. In MVA, histological grade was prognostic factor for 2nd LR ($p = 0.008$) and OS ($p = 0.02$); while tumour size was prognostic factor for DM ($p = 0.03$). G3-4 complication rate was 11%. Excellent/good cosmetic result was achieved in 85%.

Conclusion: This study suggests that in case of IBTR, lumpectomy plus MCB is feasible and effective in preventing 2nd LR with an OS rate at least equivalent to those achieved with salvage mastectomy.

Breast cancer is the most common cancer in women worldwide after skin cancer with an estimated 1.38 million new cancer cases diagnosed in 2008 (23% of all cancers) [1]. The risk of ipsilateral breast tumour recurrence (IBTR) for a given subject depends on a variety of factors, including age, inherited susceptibility, tumour characteristics, type of primary tumour treatment and other lifestyle factors such as obesity and alcohol consumption. In the early 21st century, the IBTR rates after completion of adjuvant therapy are still about 10% and 20% at 10 and 15 years, respectively [2].

In case of IBTR after breast conserving therapy (BCT) performed for the primary, salvage radical mastectomy is currently considered as the gold-standard. While in the early eighties, the concept of BCT combining quadrantectomy, sectorial resection, or lumpectomy plus post-operative radiation therapy (RT) was gaining respectability [3], a 2nd BCT based on salvage lumpectomy as sole therapy was proposed for IBTR [4]. The rate of second local recurrence (2nd LR) after salvage lumpectomy alone was reported as high as 20%, [5–10]. Therefore, post-operative re-irradiation (mainly based on a multi-catheter interstitial brachytherapy) was proposed in order to decrease the rate of 2nd LR [11–19]. The results of these small series showed encouraging results. Due to the lack of studies involving a significant number of patients, the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) Breast Cancer Working Group (BCWG) conducted a European multicentric, retrospective study and analysed the outcome of women who presented an IBTR after a previous radio-surgical conservative treatment and who underwent a 2nd BCT combining salvage lumpectomy and post-operative re-irradiation using interstitial implants.

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Material and methods

Patient, tumour and treatment characteristics

From September 2000 to September 2010, 217 patients presenting an IBTR were treated in eight European radiation therapy departments: Nice/France ($n = 76$); Vienna/Austria ($n = 71$); Erlangen/Germany ($n = 24$); Koeln/Germany ($n = 17$); Budapest/Hungary ($n = 15$); Bern/Switzerland ($n = 7$); Lubeck/Germany ($n = 5$) and Leuven/Belgium ($n = 2$). All the patients were treated for the primary tumour through a conservative approach consisting of breast-conserving surgery with sentinel lymph node biopsy or axillary lymph node dissection followed by whole breast irradiation (WBI) with or without regional nodal irradiation according to the pathological axillary status. Systemic adjuvant treatments (i.e. chemo-, hormonal or targeted therapies) were proposed according to the guidelines used in each center. Patients were followed up according to the rules applied by each investigators based on a physical exam and yearly mammograms.

IBTR was considered as a local recurrence occurring within the pre-treated breast, excluding in-breast skin and/or sub-cutaneous metastatic diseases. Once the diagnosis of IBTR without metastatic disease was established, the patient gets an offer for salvage radical mastectomy or 2nd BCT consisting of a reexcision (with or without axillary lymph node dissection according to the primary surgical procedure) with re-irradiation of the tumour bed using low (LDR), pulsed (PDR) or high-dose rate (HDR) multi-catheter interstitial brachytherapy (BT). Vector implantation was performed intra or post-operatively. Plannification was made based on post-implant CT-scan for PDR and HDR brachytherapy and X-ray orthogonal films for LDR brachytherapy. Those patients who chose 2nd BCT represented the study population for this retrospective analysis.

All the 217 patients analysed in this study met the inclusion criteria regarding primary and IBTR treatment modalities. The median age was 50.3 years [range: 19–83] and 60.6 [range: 28–85] at the time of primary breast tumour and IBTR, respectively (Table 1). The median time interval between primary and IBTR was 9.4 years [range: 1.1–35.4]. Breast recurrence site was in or close to the primary site in 67.3%, while this information remained unknown for 12%. Median tumour size was 15 mm [range: 1–60] for primary and 11.5 mm [range: 1–55] for IBTR. While the pathologic axillary lymph node status was well documented for the primary tumours (pN0 = 65%; unknown = 18.9%), surgical axillary staging was missing for 69.1% of the IBTR. Histological grade was mostly well to moderately differentiated (44.2% and 53% for primary and IBTR, respectively), whereas hormonal receptor status was negative (ER−/PR−) for 15.7% and 19.8% of the primary and IBTR, respectively. Her2 status (over-expression of the Human Epidermal Growth Factor Receptor 2) was poorly documented for the primary (69.6% of unknown data) while 28 patients (12.9%) over-expressed Her2 (+++). Furthermore, for the 13 patients (6%) who presented with a moderate over-expression of Her2 (++), the data related to the detection of Her2 gene amplification by FISH were not available. The median dose of post-operative RT delivered for the primary was 56 Gy [range: 30–69.6].

Regarding brachytherapy re-irradiation, postoperative multicatheter brachytherapy was delivered with HDR, PDR, and LDR implants for 102 (47%), 88 (40.6%), and 27 (12.4%) cases, respectively.

Table 1
Patient, tumour and treatment characteristics.

Characteristic		Primary		IBTR	
		#	Median % [range]	#	Median % [range]
#Patients				217	
Age (years)			50.3 [19–83]		60.6 [28–85]
Time to IBTR (years)					10.1 [1.1–35.3]
IBTR site	ITB			111	51.2
	Close to ITB			35	16.1
	Other quadrant			45	20.7
	Unknown			26	12.0
pT size (mm)			15.4 [1–60]		12.4 [1–55]
pLN status	Negative	141	65.0	59	27.2
	Positive	35	16.1	8	3.7
	Unknown	41	18.9	150	69.1
HG	1	36	16.6	34	15.7
	2	60	27.6	81	37.3
	3	40	18.4	58	26.7
	Unknown	81	37.3	44	20.3
HR status	Positive	93	42.9	158	72.8
	Negative	34	15.6	43	19.8
	Unknown	90	41.5	16	7.4
Her2 status	Negative	39	18.0	122	56.2
	+	7	3.2	28	12.9
	++	9	4.1	13	6.0
	+++	11	5.1	28	12.9
	Unknown	151	69.6	26	12.0
Hormonal therapy	Yes	84	38.7	141	65.0
	No	103	47.5	71	32.7
	Unknown	30	13.8	5	2.3
Chemotherapy	Yes	76	35.1	43	19.8
	No	137	63.1	171	78.8
	Unknown	4	1.8	3	1.4
Trastuzumab	Yes	3	1.4	4	1.8
	No	214	98.6	213	98.2
WBI dose (Gy)			56.0 [30–69.6]		

#Patients: number of patients; IBTR: ipsilateral breast tumour recurrence; ITB: initial tumour bed; pT size (mm): pathological tumour size; pLN status: pathological axillary lymph node status; HG: histological grade; HR status: hormonal receptor status (negative = both oestrogen AND progesterone receptor negative); Her2: Human Epidermal Growth Factor Receptor 2; WBI: whole breast irradiation.

The median clinical target volumes (CTV) were 52 cc [range: 23–86], 68 cc [range: 18–165] and 62 cc [range: 23–157] for LDR, PDR and HDR, respectively, while these data were not available for LDR technique (Supplementary Table 2). The median total dose delivered through LDR and PDR BT was 46 Gy [range: 30–55] and 50.4 Gy [range: 49–50], respectively and 32 Gy [range: 22–36] (EQD2 43 Gy_4) in 5–10 (median: 8) fractions (twice daily) for HDR BT. The median number of planes ranged between 2 and 3. Median V100 (volume of breast tissue encompassed by the 100% isodose), V150 and V200 were 80% [range: 37–123], 23% [range: 8–73], and 8% [range: 3–27], respectively. Median D90 (dose delivered to 90% of the CTV) was 96% of the prescribed dose [range: 63–143].

End point analysis

The GEC-ESTRO BCWG aimed to analyse the clinical outcome of the 217 patients who underwent a 2nd BCT after an IBTR. Efficacy was analysed based on 2nd LR and distant metastasis rates; cancer specific survival (CSS) which was defined as the time interval between the date of 2nd surgery and death due to breast cancer; and overall survival (OS) which was defined as the time interval between the date of 2nd surgery and death due to any cause or death due to the disease.

Long-term side effects of breast tissues were graded by the radiation oncologist and/or the surgeon according to the NCI Common Terminology Criteria for Adverse Events CTCAEV3.0. Objective breast toxicities were considered such as cutaneous and sub-cutaneous fibrosis, hyperpigmentation and telangiectasia. Cosmetic results were reported by the radiation oncologist and/or the surgeon using a cosmetic score derived from the scoring system described by Harris et al. [20]: excellent, good, fair and poor.

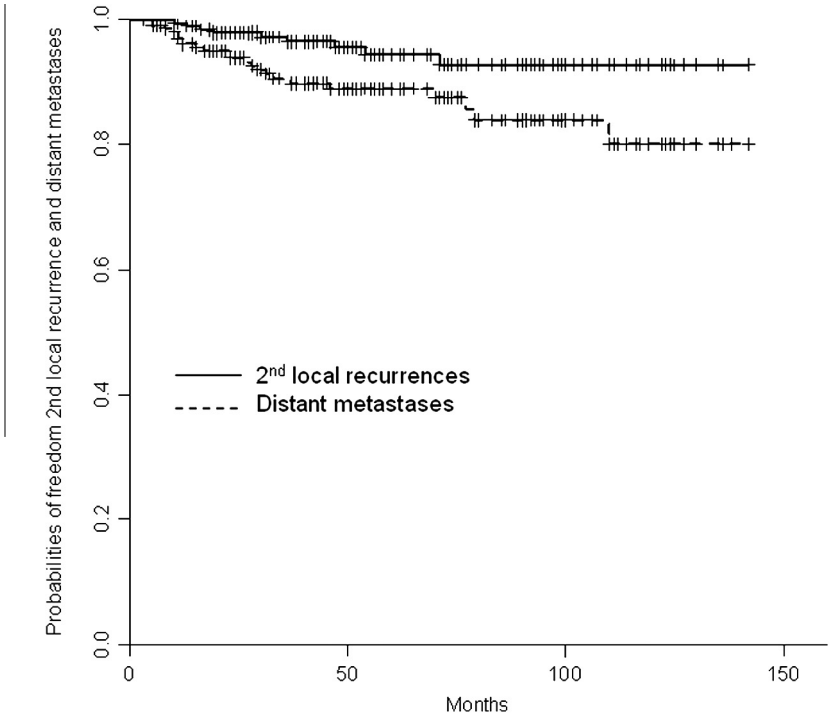
Statistical analysis

Tests of significance were two-sided and considered significant when the p value was 0.05 or less. Specific and overall survivals were estimated and presented graphically using the Kaplan Meier method. Patients were censored at the time of death or last follow-up. The survival curves were compared by the log-rank test. The chi-square statistic or Fisher's exact tests were used to establish differences in the distribution of discontinuous variables and student's test or Mann–Whitney's test to compare continuous variable. IBTR variables which were significant in univariate analysis were introduced in the model for multivariate analysis. The log rank test was used to compare time related parameter in univariate analyses. Multivariate analyses were performed using Cox models.

Results

Local control and survival rates

The median follow-up was 14.5 years [range: 3.5–38.2] and 3.9 years [range: 1.1–10.3] from the primary and the IBTR, respectively. Regarding the clinical outcome, at the time of analysis 9 patients (4.1%) presented a 2nd LR, leading to a 5- and 10-year actuarial rates of freedom from 2nd LR of 94.4% [95% CI: 90.5–98.5] and 92.8% [95% CI: 87.9–97.9], respectively (Fig. 1). The sites of 2nd LR are presented in the Fig. 2. One patient (0.5%) presented an isolated axillary recurrence. Twenty-three patients (10.6%) developed distant metastasis with 5- and 10-year actuarial rates of freedom from distant metastases of 88.9% [95% CI: 84.3–93.9] and 80.2% [95% CI: 70.8–90.8], respectively (Fig. 1). Among the 23 patients who developed distant metastases, isolated metastatic



	Time	0	12	24	36	48	60	120
2nd LR	# pts @ risk	217	200	165	129	97	69	11
	# events	0	1	3	2	1	1	1
Dist. met.	# pts @ risk	217	195	159	122	93	70	12
	# events	0	8	4	5	2	0	4

Fig. 1. Probabilities of freedom from 2nd local recurrence (blue line) and distant metastases (red line).

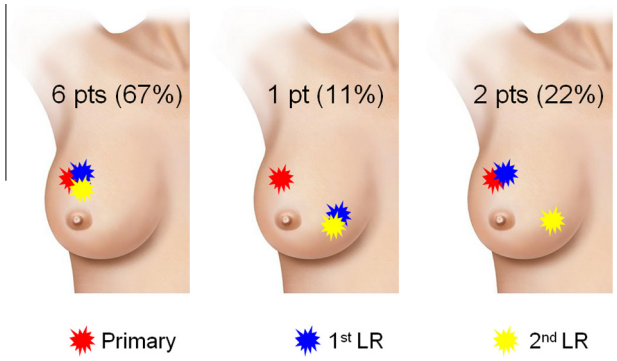


Fig. 2. Sites of 2nd local recurrence with primary tumour in red, 1st local recurrence (i.e. IBTR) in blue and 2nd local recurrence in yellow.

disease was observed in 19 (82.6%) (4 women presented a 2nd LR and distant metastases – simultaneously for 1 patient). Twenty-seven patients died from breast cancer giving 5- and 10-year actuarial rates of CSS of 90.5% [95% CI: 85.1–96.3] and 79.3% [95% CI: 69.9–90.0], respectively, whereas actuarial 5- and 10-year OS rates were 88.7% [95% CI: 83.1–94.8] and 76.4% [95% CI: 66.9–87.3], respectively (Fig. 3).

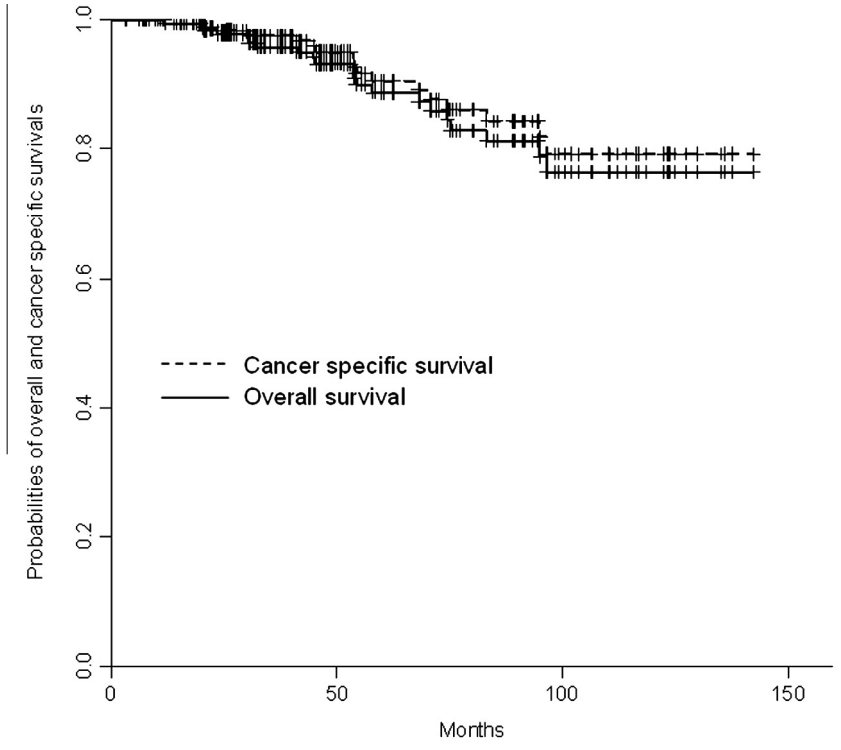
In univariate analysis, age at the time of IBTR (⩽55 vs >55 years; $p = 0.035$), histological grade (I–II vs III; $p = 0.0003$) and hormonal receptor status (positive vs negative i.e. ER−/PR−; $p = 0.001$) were prognostic factors for 2nd LR, while pathological size of IBTR (⩽20 vs >20 mm; $p = 0.03$) was prognostic factor for distant metastases (Table 3). For OS, pathological size ($p = 0.007$), histological grade ($p = 0.009$), and hormonal receptor status ($p = 0.01$) were considered as significant prognostic factors in univariate analysis. In multivariate analysis the following factors remained significant: histological grade for 2nd LR ($p = 0.008$) and for OS ($p = 0.02$); and pathological size for distant metastases ($p = 0.03$).

Morbidity and cosmetic results

Regarding toxicity assessment, 141 patients (65%) developed 193 late side effects. Types of long-term side effects of breast tissues were cutaneous and sub-cutaneous fibrosis (67%), telangiectasia (16%), hyperpigmentation (9%) and ulceration (1%). Consequently the majority of the patient (50%) presented in general Grade 1 late side effects while Grades 2, 3 and 4 represented 39%, 10% and 1% of the patients, respectively. Ninety-eight patients (45%) presented only one event as late effect while 34 (15.6%) and 9 (4.1%) patients presented simultaneous two or three different complications, respectively. Among the 109 women (50.2%) available for cosmetic assessment, the result was scored as excellent for 52 (48%), good for 40 (37%), fair for 14 (13%), and poor for 2 (2%).

Discussion

Actually, salvage mastectomy represents the standard local treatment strategy in case of IBTR. After salvage mastectomy, the rate of 2nd LR has been reported around 10% [range: 3–32%] [5,6,9,21,22] while it is about 20% [range: 7–32%] after a 2nd BCT based on salvage lumpectomy alone [5–10]. In case of 2nd BCT with post-operative irradiation, the rate of 2nd LR is around 10% [range: 3–32%] [11,12,14–18]. In terms of OS, the data available in the



	Time	0	12	24	36	48	60	120
CSS	# pts @ risk	217	196	167	131	98	71	12
	# events	0	1	2	1	3	4	6
OS	# pts @ risk	217	196	167	131	98	71	12
	# events	0	1	3	3	3	4	7

Fig. 3. Probabilities of cancer specific (red line) and overall (blue line) survivals.

Table 2
Univariate and multivariate analyses for prognostic factors of 2nd local recurrence, distant metastases and overall survival.

	UVA			MVA		
	IBTR data		*p* Value	IBTR data		*p* Value
2nd LR	Age (years)	>55	0.035			
	HG	III	0.0003	HG	III	0.008
	HR	HR−	0.001			
DM	pT (mm)	>20	0.03	pT	>20	0.03
OS	pT (mm)	>20	0.007			
	HG	III	0.009	HG	III	0.02
	HR	HR−	0.01			

UVA: univariate analysis; MVA: multivariate analysis; 2nd LR: second local recurrence; DM: distant metastases; OS: overall survival; pT: pathological tumour size (mm); HG: histological grade; HR: hormonal receptor status (HR− = ER−/PR−).

literature show 5-year OS rates around 72% [range: 61–84%] and 74% [range: 50–92%] after salvage mastecomy [5,6,9,21,22] and 2nd BCT with post-operative re-irradiation [11–15,18], respectively. According to our knowledge, to date this report represents the largest series focusing on a 2nd BCT for IBTR combining salvage lumpectomy plus re-irradiation. The presented results are comparable to those previously reported in the literature using the same treatment approach in terms of 2nd LR (7.2% at 10 years) and OS (76.4% at 10 years) and appear at least equivalent to the results described after salvage mastectomy. Furthermore, we reported a 5-year actuarial rate of freedom from 2nd LR of 94.4% which is in the range of the 5-year actuarial rate of LR (median follow-up: 3.5 years) recently reported by Leonardi et al. [23] for primary breast cancer, after accelerated partial breast irradiation (APBI) with intraoperative electrons: 1.9%, 7.4% and 7.7% for "good", "possible" and "contraindicated" candidates for APBI, respectively (GEC-ESTRO recommendations [24]).

One of the most important issues of IBTR remains the risk of systemic disease. This risk is correlated with the pathologic features of IBTR but also with the notion that, the new in-breast event is a true recurrence or a new primary tumour. The difference between the two entities is generally based on the pathologic characteristics and location of IBTR in contrast to the primary tumour [25]. Furthermore, the time interval between primary and recurrent tumour is of prognostic significance. Indeed, this interval was reported as an independent prognostic factor for OS with a cut-off ranging from 24 to 36 months [26]. We could not reinforce the prognostic effect of the delay, as the median time interval between primary and IBTR was long (median 9.4 years) in our series. Very few data focusing on the impact of systemic therapy on clinical outcome are available; however, in the study of Borner et al. [27] hormonal therapy (Tamoxifen) after IBTR significantly increased 5-year disease free survival rates from 36% to 59% compared with observation alone. A randomised phase III trial CALOR was conducted to determine the effectiveness of adjuvant chemotherapy in case of IBTR, but it has been prematurely closed for slow accrual [28]. The results presented by Wapnir et al. [28] show that adjuvant chemotherapy improves the results for ER negative patients and that a second isolated local recurrence following multimodality therapy including also the radiation therapy is a strong prognostic factor.

The toxicity and cosmetic analysis after a 2nd BCT should be performed cautiously taking into account (as far as possible) the impact of the first radio-surgical treatment for primary tumour, which was not evaluable in our cohort. Nevertheless, 90% of the long-term side effects of breast tissues were Grades 1–2 and the cosmetic result was scored as excellent/good in 85% of the cases. However, we did not extensively analyse the incidence on fat necrosis which is observed in about 20% in case of APBI using interstitial brachytherapy for primary breast cancer [29]. We reported smaller median V150 and V200 (25 cc and 15 cc, respectively) compared to the results provided by Wazer et al. [30] who stated that V150 (43 vs 59 cc; $p = 0.03$) and V200 (13 vs 19 cc; $p = 0.04$) were significantly correlated to excellent vs good cosmetic results in case of interstitial HDR BT applied for primary tumour as adjuvant accelerated partial breast irradiation.

Although our study is a retrospective non-randomised analysis, it provided substantial data regarding the feasibility, efficacy and safety of a 2nd BCT for IBTR combining lumpectomy and re-irradiation by multi-catheter BT avoiding the mutilation caused by a salvage mastectomy. Currently, in terms of evidence based medicine, there is no consistent proof for presenting salvage mastectomy as the treatment of reference for IBTR and to refuse 2nd BCT with adjuvant multicatheter interstitial BT. The appropriate approach how to validate and compare these two treatment strategies for IBRT could be a randomised trial comparing salvage mastectomy versus 2nd BCT with re-irradiation of the tumour bed [31]. Unfortunately, it is practically impossible to conduct such a trial due to the patients' reluctance for accepting randomisation between 2nd BCT and mutilating radical mastectomy. Actually, the GEC-ESTRO BCWG proposed a European multicentric phase II clinical trial evaluating the safety and efficacy of multi-catheter HDR/PDR BT in the treatment of IBTR after previous BCT. These studies will hopefully give further evidence and guidance for clinicians for selecting the best local treatment strategy for the management of IBTR.

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Conflict of interest statement

All authors must disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2013.03.026.

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