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ORIGINAL RESEARCH ARTICLE

Hypofractionated whole-breast radiotherapy and concomitant boost after breast conservation in elderly patients

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ABSTRACT

Aims: To report the 5- and 10-year results of accelerated hypofractionated whole-breast radiotherapy (WBRT) with concomitant boost to the tumor bed in 83 consecutive patients with early breast cancer aged >70 years.
Methods: All patients were treated with breast conservation and hypofractionated WBRT. The prescription dose to the whole breast was 45 Gy (2.25 Gy/20 fractions) with an additional daily concomitant boost of 0.25 Gy to the surgical cavity (2.5 Gy/20 fractions up to 50 Gy). The maximum detected toxicity was scored according to the Common Terminology Criteria for Adverse Events, version 3.0. We considered as skin toxicity: erythema, edema, desquamation, ulceration, hemorrhage, necrosis, telangiectasia, fibrosis-induration, hyperpigmentation, retraction and atrophy. Cosmetic results were assessed as set by the Harvard criteria.
Results: With a median follow-up of 60 months (range 36-88), no local recurrence was observed. The maximum detected acute skin toxicity was G0 in 57% of patients, G1 in 40% and G2 in 3%. Late skin and subcutaneous toxicity was generally mild with no ≥G3 events. The cosmetic results were excellent in 69% of patients, good in 22%, fair in 5%, and poor in 4%.
Conclusions: The present results support the use of hypofractionation employing a concomitant boost to the lumpectomy cavity in women aged >70 years. This is a convenient treatment option for both this type of population and health-care providers.

Keywords: Breast cancer, Concomitant boost, Elderly, Hypofractionation, Simultaneous integrated boost

Introduction

Postoperative whole-breast radiotherapy (WBRT) subsequent to breast-conserving surgery (BCS) is regarded as a standard of care in the multimodality management of early breast cancer (EBC) (1). WBRT is able to halve the average annual rate of disease relapse and to reduce by about a sixth the annual breast cancer-related death rate (2). Nevertheless, WBRT is quite frequently omitted and a non-negligible percentage of patients are treated with BCS only, especially in the age group of 70 to 80 years (3). This generally leads to a potential increase in the local recurrence rate in this subset of patients (4). Theoretically, withholding WBRT after BCS should be an option only for selected elderly patients with favorable clinical and biological prognostic factors (node negative, hormone sensitive, low-grade disease) and relevant comorbid conditions potentially affecting the life expectancy (5). Historically, WBRT has been delivered using conventional fractionation (1.8-2 Gy daily), up to a total dose of 50 Gy over 5 weeks with a subsequent boost dose of 10-16 Gy to the tumor bed for a 6- to 7-week overall treatment time (1). The addition of a boost dose to the site of surgical excision was shown to further raise local control (6). Hypofractionation (HF) delivers a lower nominal total dose in larger and fewer fractions, generally over a shorter overall treatment time, which is an attractive option to both patients and health-care providers as it decreases treatment costs and increases logistic convenience (7, 8). We previously reported on the long-term results in EBC patients treated with WBRT after BCS with a hypofractionated schedule and a concomitant boost to the tumor bed (9-11). In the present paper we describe the clinical results in terms of oncological outcome and toxicity profile of an observational study involving a selected patient population aged >70 years treated with this treatment schedule.

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Materials and methods

Between 2005 and 2012, we submitted a consecutive series of 83 EBC patients to WBRT after BCS employing HF and a concomitant boost to the tumor bed. All patients had a minimum observation time of 36 months at last follow-up examination. Written informed consent was obtained from all patients.

Eligibility criteria

The patients to be analyzed underwent BCS for EBC and subsequent adjuvant WBRT and were aged >70 years at the time of radiation. Detailed inclusion and exclusion criteria can be found in Cante et al (9, 10).

Setup, simulation and target definition

Immobilization and setup were acquired with patients on a wing-board with their arms raised above their heads and radiopaque markers along the clinical borders of the breast. Afterwards, 5-mm slice thickness computed tomography (CT) was performed from the lower aspect of the mandible including the whole thorax; an isocenter was then found in virtual simulation. The whole-breast clinical target volume (WB-CTV) encompassed the palpable breast, with superior and inferior borders within the extent of the radiopaque catheters. A uniform limit of 5 mm divided WB-CTV from the skin surface and the thoracic wall. The whole-breast planning target volume (WB-PTV) was generated with the addition of a 5-mm isotropic margin around the WB-CTV. The lumpectomy cavity was defined using radiopaque clips placed at the time of surgery. The concomitant-boost clinical target volume (CB-CTV) was generated with the addition of a 5-mm isotropic margin around the lumpectomy cavity, while the concomitant-boost planning target volume (CB-PTV) required an adjunctive margin of 5 mm. The heart was outlined as an organ at risk up to the level of the pulmonary trunk superiorly, with the inclusion of the pericardium and the exclusion of the major vessels. Both lungs were also contoured.

Treatment schedule and delivery

The treatment schedule consisted of 45 Gy to the WB-PTV in 20 fractions (2.25 Gy each day) delivered with 2 opposing 6 MV tangential fields; an additional 0.25 Gy boost dose was concomitantly delivered daily to the CB-PTV for a total dose of 5 Gy, using a direct 6 MV photon field. The cumulative nominal dose to the tumor bed was 50 Gy. Radiation was delivered either immediately after BCS (<3 months) in patients at low risk of distant failure, or sequentially after adjuvant chemotherapy in case of high-risk features. Radiobiological considerations and beam arrangement have been discussed elsewhere (9). Setup verification was done by portal images taken weekly and compared with digitally reconstructed radiographs obtained from planning CT scans.

Follow-up, toxicity and cosmesis

During follow-up, patients underwent clinical examination 3 and 6 months after the end of WBRT and twice a year thereafter. Surveillance for disease included a clinical examination at every time point, plain chest x-ray and mammography once a year, complete blood cell count and serological markers twice a year; other radiological examinations were performed when needed. Acute skin toxicity was assessed at the completion of WBRT and after 3 months, while late skin toxicity was evaluated 6 months after radiotherapy. The maximum detected toxicity was scored according to the Common Terminology Criteria for Adverse Events, version 3.0 (12). We considered as skin toxicity events the following clinical cutaneous and subcutaneous conditions: erythema, edema, desquamation, ulceration, hemorrhage, necrosis, telangiectasia, fibrosis-induration, hyperpigmentation, retraction and atrophy. Cosmetic results were assessed at the end of WBRT and thereafter at every follow-up time point, using a physician-rated scale consisting of different categories (excellent, good, fair or poor) in the comparison between the treated and untreated breast, as set by the Harvard criteria (13). Basically, at each follow-up examination, physicians were asked to judge the cosmetic results as follows: an ''excellent'' score was assigned when the treated breast looked essentially the same as the contralateral breast; a ''good'' score was assigned for minimal but identifiable radiation effects; a ''fair'' score meant that significant radiation effects were readily observable; a ''poor'' score was used for radiation-induced severe late effects on the breast tissue (13).

Statistical analysis

Follow-up time was calculated as the interval between the end of WBRT and last follow-up examination. Disease recurrence was defined as local recurrence (LR) if occurring in the ipsilateral breast or overlying skin; as regional recurrence (RR) if involving the ipsilateral axillary, supraclavicular or internal mammary lymph nodes; and as systemic with distant metastasis (DM) if arising at other sites. All LR, RR and DM were evaluated to calculate the disease-free survival (DFS). Death from breast cancer was defined as death preceded by disease failure. Death from any cause was taken into account for overall survival (OS). Survival curves and actuarial rates of relapse were calculated using the Kaplan-Meier method. The significance of clinical prognostic factors with respect to both DFS and cancer-specific survival (CSS) was assessed by the log-rank test. A p value <0.05 between groups was considered significant. The StatView software (version 5.0) was employed for the analysis.

Results

Mean follow-up time was 60 months (range 36-88). The baseline patient characteristics are detailed in Table I. All patients were aged >70 with an invasive primary <2 cm in diameter (69%), node negative (63%), hormone sensitive (88%), moderately differentiated (67%) with ductal histology (64%), low proliferation index (64%) and no c-erbB2 amplification (88%). Most patients underwent quadrantectomy or lumpectomy and sentinel lymph node biopsy (82%). Only 17% also underwent axillary dissection. Almost 88% of patients received concomitant hormonal therapy, while 16% were given adjuvant chemotherapy. All patients completed the radiation program with no need for interruptions.

TABLE I - Patient characteristics

Characteristic	No. (%)
Age (years)	
70-80	77 (93%)
>80	6 (7%)
Pathological tumor stage	
pT1a	7 (8.5%)
pT1b	10 (12%)
pT1c	36 (43%)
pT2	26 (31%)
Pathological nodal stage	
pN0	52 (63%)
pN1	25 (30%)
pNx	5 (7%)
Grade	
G1	11 (13%)
G2	55 (67%)
G3	17 (20%)
Estrogen receptor status	
>80%	64 (77%)
<80%	9 (11%)
0%	10 (12%)
Progesterone receptor status	
>80%	32 (38%)
<80%	33 (40%)
0%	18 (22%)
c-erbB2	
Amplification	10 (12%)
No amplification	57 (88%)
Ki67	
<20%	52 (64%)
20-40%	21 (26%)
>40%	3 (5%)
Not available	3 (5%)
Vascular invasion	
Positive	12 (14%)
Negative	66 (79%)
Not available	5 (7%)
Perineural invasion	
Positive	4 (5%)
Negative	67 (81%)
Not available	12 (14%)

Pattern of failure, survival and prognostic factors

The median observation time was 60 months (range 12-88). Six patients died: 2 of breast cancer and the remaining 4 of other causes. Oncological events were observed in 4 patients: 2 patients developed DM (bone and liver: 1; lung and brain: 1)

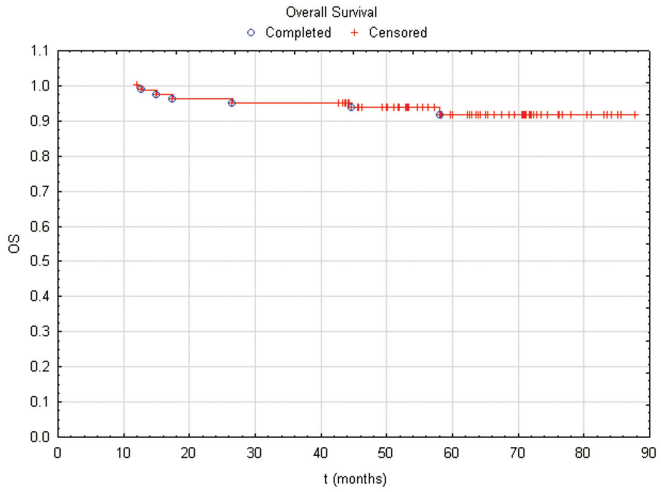

Fig. 1 - Overall survival.

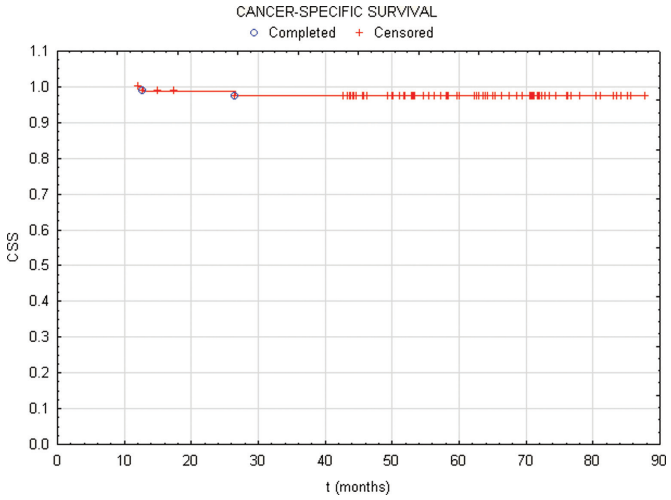

Fig. 2 - Cancer-specific survival.

and 2 patients had RR in the supraclavicular (1) and axillary (1) lymph nodes. No LR was observed by the time of last examination. Actuarial 5-year OS, CSS, DFS and local control rates were 92% (95% confidence interval [CI] 81.3%-96.4%), 97.5% (95% CI 87.6%-98.8%), 95% (95% CI 86.7%-97.3%) and 100% (95% CI 44.8%-100%), respectively (Figs. 1-3). The relationship between clinical variables and survival is outlined in Table II. Univariate analysis showed that Ki67 (≤20% vs. >20%; p<0.01) had statistically significant impact on DFS. Concerning CSS, no clinical variable showed any statistically significant difference.

Toxicity

The maximum acute skin toxicity was grade 0 in 57%, grade 1 in 40% and grade 2 in 3% (Tab. III). No grade 3-4 acute skin toxicities were seen. Late skin and subcutaneous toxicity was generally mild (Tab. IV): no grade >2 events were observed. A grade 1 score was given to fibrosis-induration in 9% of patients, atrophy in 3%, telangiectasia in 2%, hyperpigmentation in 5%,

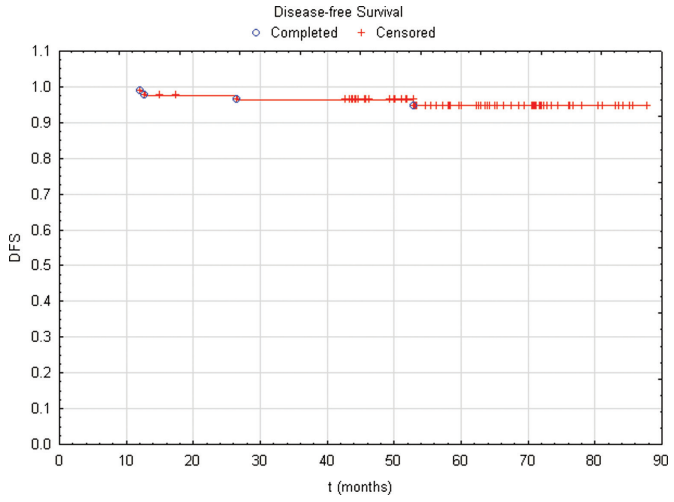

Fig. 3 - Disease-free survival.

and striae in 2%. A grade 2 score was observed only for fibrosis (3%), telangiectasia (1%) and hyperpigmentation (2%). Cosmetic results were excellent in 69% of patients, good in 22%, fair in 5%, and poor in 4% (Tab. IV).

Discussion

The option of delivering a daily dose higher than 1.8-2 Gy with HF is quite common nowadays in WBRT after BCS for EBC (14). Conventionally fractionated schedules have historically been the most common strategy in this context, but HF has been employed in several hospitals for decades and investigated in randomized controlled trials (8, 15). Recently, comprehensive guidelines drafted by the United Kingdom's National Institute of Clinical Excellence (NICE) on the management of EBC recommended 40 Gy given in 15 fractions as the standard of care (16). The advocated advantages of HF have spillover effects towards patients, radiotherapy departments and health-care providers in terms of both general convenience and treatment costs (7). Different hypofractionated schedules have been investigated so far, with results suggesting that the α/β ratio of breast cancer may range between 3 and 5 Gy, close to the values of surrounding normal tissues (17). Hence, a mild increase in the dose per fraction with a slight reduction of the total dose at the same time may provide the same local control rate as conventional fractionation with no increase in toxicity as in other oncological settings (18). Our retrospective data, even with a medium-term observation time, showed that HF with concomitant boost may be a viable treatment option for a subset of women aged >70 years with excellent oncological outcome, mild toxicity and promising cosmesis. The optimal management of EBC in elderly women remains controversial, given that most clinical trials exclude these patients from accrual. Hence, one option is to withhold WBRT for older patients after BCS, especially in the presence of low-risk features and hormone sensitivity. Nevertheless, some clinical data suggest that preventing local relapses and consequent breast-cancer-related deaths with WBRT may

TABLE II - Predictive factors for all-site relapse and cancer-specific survival

Factor	Pts.	Relapse	P value (log rank)	BC death	P value (log rank)
Age (years)					
70-80	77	3	NS	2	NS
>80	6	1		0	
Tumor stage					
Tis-T1	57	2	NS	2	NS
T2	26	2		0	
Axillary status					
pN0	52	3	NS	2	NS
pN1	31	1		0	
Grade					
G1-G2	66	1	NS	1	NS
G3	17	3		1	
Hormonal status					
Positive	65	1	NS	1	NS
Negative	18	3		1	
HER2					
Positive	73	1	NS	0	NS
Negative	10	3		2	
Vascular invasion					
Positive	12	1	NS	1	NS
Negative	71	3		1	
Perineural invasion					
Positive	4	0	NS	0	NS
Negative	67	4		2	
Hormonal therapy					
Yes	10	1	NS	0	NS
No	57	3		2	
Chemotherapy					
Yes	13	1	NS	1	NS
No	70	3		1	
Axillary dissection					
Yes	24	0	NS	0	NS
No	59	4		2	
Ki67					
≤20%	55	0	p<0.01	0	NS
>20%	28	4		2	

Pts. = number of patients; BC = breast cancer; NS = not significant.

TABLE III - Acute skin toxicity

Skin toxicity	Grade	Patients	%
No change over baseline	0	47	57
Follicular, faint or dull erythema/epilation/dry desquamation/decreased sweating	1	33	40
Tender or bright erythema, patchy moist desquamation/moderate edema	2	3	3
Confluent, moist desquamation other than skin folds, pitting edema	3	0	0
Ulceration, hemorrhage, necrosis	4	0	0

TABLE IV - Late toxicity and cosmesis

Parameter	Grade (%)			
	G1	***G2***	***G3***	***G4***
Fibrosis-induration	8 (9)	3 (3)	0	-
Atrophy	3 (3)	0	-	-
Telangiectasia	2 (2)	1 (1)	0	-
Hyperpigmentation	4 (5)	2 (2)	-	-
Striae	2 (2)	0	-	-
Ulceration	-	0	0	0
	Cosmesis			
Definition	*Poor*	*Fair*	*Good*	*Excellent*
	3 (4)	4 (5)	18 (22)	57 (69)

be a valid option also in older patients. In this respect, the Oxford overview of randomized trials of BCS with or without WBRT showed a 2-fold reduction of first relapse even in "low-risk" older patients, although the absolute reduction in 10-year risk of any locoregional or distant recurrence was lower in women ≥70 years than in younger women (8.8% vs. 17.7%) (2). However, several trials investigated the possibility to avoid WBRT after BCS in elderly patients with low-risk hormone-receptor-positive breast tumors. The CALGB 9343 trial randomized 636 women with EBC aged ≥70 years (of whom 55% >75 years) after BCS and adjuvant tamoxifen to WBRT or no WBRT. The results showed an absolute decrease in the ipsilateral breast tumor recurrence rate of 3% (1% vs. 4%) at a median follow-up of 5 years and 7% (2% vs. 9%) at a median follow-up of 10.5 years in the radiotherapy group. However, no difference in OS was found between treatment arms (19). The recent PRIME II trial confirms these data in patients with <3 cm breast cancer and age >65 years, with a modest benefit, when WBRT was added, in terms of local failure reduction (1.3% vs. 4.1%; p = 0.0002) but no influence on regional recurrence, metastasis rate, contralateral breast cancer or OS (20). So a potential option is to avoid adjuvant radiation in elderly patients, especially when low-risk features are present. The suitability of observation only, when the biology of the tumor is favorable, has been confirmed by a recent Italian multicenter randomized trial, which found no difference in terms of in-breast local failure with or without WBRT in breast cancer patients aged 55-75 years with ≤2.5 cm tumors after modified quadrantectomy and adjuvant hormonal therapy (80%). After a median follow-up of 108 months, the local failure rate was 3.4% with radiation vs. 4.4% without. OS was similar (81.4% vs. 83.7%), as were metastasis-free survival and breast cancer-specific death (21). These results confirm the viability of omitting WBRT for indolent breast cancer, strengthening the application of this approach in the subset of elderly patients with no detrimental effects even on local control. Another option for this subset of patients is accelerated partial breast irradiation (APBI), which combines the possibility of sparing part of the breast tissue from irradiation with a more convenient treatment schedule (22). This approach would provide the possibility to offer WBRT with a potential benefit in terms of local control also to an elderly population, with a more favorable logistic profile. Nevertheless, given that clinical data for this treatment approach still need long-term confirmation, APBI should not be considered a consolidated clinical standard. Thus, irradiation of the whole breast still remains the standard approach and HF is an attractive option for WBRT in a selected elderly population. It provides an efficient means to improve local control and lower the salvage mastectomy rate. It may represent a convenient treatment option for both patient and health-care providers, decreasing the overall treatment costs and logistic difficulties. Boosting the tumor bed may further increase local control (17). Tumor bed boost integration within the whole-breast phase shortens the overall treatment time, with increased clinical benefit and fewer hospital visits. However, the role of the boost dose in an elderly population is questionable. A recent update of the EORTC "boost versus no boost" trial showed that an extra dose of 16 Gy to the tumor bed had no impact on OS but could improve local control, especially in younger patients (age <60). For older patients this benefit seems negligible and on average outweighed by the risk of moderate to severe fibrosis in the lumpectomy cavity region (23). Our study protocol employing HF with concomitant boost was drafted before the publication of mature results of this approach and was driven by the will to provide patients with a potential benefit in local control, with very

low risk of late fibrosis due to boost integration within the whole breast phase, very good dose distribution, and good homogeneity and conformity. The toxicity associated with our treatment schedule was generally mild. Acute skin toxicity was acceptable, with a 3% rate of G2 events and no G3-G4 events. Late skin toxicity was generally manageable with a maximum 3% G1 rate for atrophy, 1% G2 rate for telangiectasia, 2% G2 rate for hyperpigmentation, and 2% G1 rate for striae. Subcutaneous tissue toxicity consisted of a 9% G1 and 3% G2 rate for fibrosis. These results are consistent with those of hypofractionated 3-week schedules: the Canadian trial reported a 5% G2-G3 toxicity rate for fibrosis and a 3% G2-G3 toxicity rate for skin toxicity at 5 years (24). The START B trial results at 5 years are not directly comparable because the normal-tissue end points were slightly different (25). However, WBRT can be further accelerated, as shorter treatment schedules than the one we used do exist. In fact, given the promising results of moderate HF (dose per fraction: 2.5-3 Gy), regimens employing highly hypofractionated schedules have been tested. Radiobiologically, 5 fractions of 5.7-6 Gy are thought to be equivalent to 50 Gy in 25 fractions in terms of tumor control according to the linear-quadratic model. The French group at the Curie Institute reported on 50 elderly patients (≥70 years) treated with 5 once-weekly fractions of 6.5 Gy delivered once a week as adjuvant radiation after breast conservation, with no boost to the lumpectomy cavity (26). At a median observation time of 93 months, G1-G2 induration was observed in 33% of patients, while no G3-G4 events were reported. The 5- and 7-year cause-specific survival, locoregional relapse-free survival and metastases-free survival were similar to those of patients treated with conventional fractionation (with or without a boost to the tumor bed). Cutuli et al (27) reported on women older than 70 treated with BCS followed by WBRT, including 133 patients submitted to HF with 32.5 Gy in 5 weekly fractions. The authors reported excellent locoregional control, with no difference compared to patients treated with conventional WBRT. Along these lines, the randomized British FAST trial is testing HF in more than 900 EBC patients after BCS, comparing 5 fractions of 5.7 Gy or 6 Gy delivered once weekly to 50 Gy in 25 fractions in terms of both late toxicity and local control (28). The first results suggest that 28.5 Gy given in 5 fractions may be as gentle to normal tissues as conventionally fractionated radiation (29). These data seem to be confirmed on a medium- to long-term basis in a recent retrospective study (30). Given all this evidence, in our radiotherapy department, WBRT employing HF was proposed in routine clinical practice and found to be an acceptable treatment option after BCS compared with conventionally fractionated WBRT, as it yielded favorable outcome results in terms of local control, toxicity and cosmesis. Our study provides a single-institution experience with mature follow-up time, representing further proof of principle that HF with concurrent administration of a boost dose to the surgical cavity represents a safe and effective postoperative treatment modality with excellent results in elderly patients. However, several other treatment strategies may be employed in this subset of patients, which are potentially more convenient both clinically and logistically. Shorter treatment schedules, no boost strategies, omission of WBRT after BCS, and APBI represent useful options also for elderly patients. The treatment choice should be based on tailored and personalized clinical decision-making.

Abbreviations

APBI	accelerated partial breast irradiation
BCS	breast-conserving surgery
CB	concomitant boost
CI	confidence interval
CSS	cancer-specific survival
CT	computed tomography
CTV	clinical target volume
DFS	disease-free survival
DM	distant metastasis
EBC	early breast cancer
HF	hypofractionation
LR	local recurrence
OS	overall survival
PTV	planning target volume
RR	regional recurrence
WB	whole breast
WBRT	whole-breast radiotherapy

Disclosures

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