Received:
21 March 2016

Revised:
6 July 2016

Accepted:
21 July 2016

<http://dx.doi.org/10.1259/bjr.20160264>

Cite this article as:

De Santis MC, Nardone L, Diletto B, Canna R, Dispinzieri M, Marino L, et al. Comparison of two radiation techniques for the breast boost in patients undergoing neoadjuvant treatment for breast cancer. *Br J Radiol* 2016; **89**: 20160264.

FULL PAPER

Comparison of two radiation techniques for the breast boost in patients undergoing neoadjuvant treatment for breast cancer

¹MARIA C DE SANTIS, MD, ²LUIGIA NARDONE, MD, ¹BARBARA DILETTO, MD, ²ROBERTA CANNA, MD, ¹MICHELA DISPINZIERI, MD, ³LORENZA MARINO, MD, ¹LAURA LOZZA, MD and ²VINCENZO VALENTINI, PhD

¹Radiotherapy Unit 1, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

²Department of Radiation Oncology, Catholic University of the Sacred Heart, Rome, Italy

³Division of Radiotherapy, REM-Istituto Oncologico del Mediterraneo, Catania, Italy

Address correspondence to: Dr Maria Carmen De Santis

E-mail: mariacarmen.desantis@istitutotumori.mi.it

Objective: After breast conservative surgery (BCS) and whole-breast radiotherapy (WBRT), the use of boost irradiation is recommended especially in patients at high risk. However, the standard technique and the definition of the boost volume have not been well defined.

Methods: We retrospectively compared an anticipated pre-operative photon boost on the tumour, administered with low-dose fractionated radiotherapy, and neoadjuvant chemotherapy with two different sequential boost techniques, administered after BCS and standard adjuvant WBRT: (1) a standard photon beam (2) and an electron beam technique on the tumour bed of the same patients. The plans were analyzed for the dosimetric coverage of the CT-delineated irradiated volume. The minimal dose received by 95% of the target volume (D_{95}), the minimal dose received by 90% of the target volume (D_{90}) and geographic misses were evaluated.

Results: 15 patients were evaluated. The sequential photon and electron boost techniques resulted in inferior target volume coverage compared with the anticipated boost technique, with a median D_{95} of 96.3% (range

94.7–99.6%) and 0.8% (range 0–30%) and a median D_{90} of 99.1% (range 90.2–100%) and 54.7% (range 0–84.8%), respectively. We observed a geographic miss in 26.6% of sequential electron plans. The results of the anticipated boost technique were better: 99.4% (range 96.5–100%) and 97.1% (range 86.2–99%) for median D_{90} and median D_{95} , respectively, and no geographic miss was observed. We observed a dose reduction to the heart, with left-sided breast irradiation, using the anticipated pre-operative boost technique, when analyzed for all dose–volume parameters. When compared with the sequential electron plans, the pre-operative photon technique showed a higher median ipsilateral lung D_{max} .

Conclusion: Our data show that an anticipated pre-operative photon boost results in a better coverage with respect to the standard sequential boost while also saving the organs at risk and consequently fewer side effects.

Advances in knowledge: This is the first dosimetric study that evaluated the association between an anticipated boost and neoadjuvant chemotherapy treatment.

INTRODUCTION

The standard dose of whole-breast radiotherapy (WBRT) is 50 Gy in 25 fractions of 2.0 Gy over 5 weeks.¹ Usually, patients receive a boost on the tumour bed between 10 and 16 Gy, according to the status of the surgical margins. For females undergoing breast-conserving therapy, boost radiotherapy (RT) to the tumour bed has been shown in two randomized trials to significantly reduce the risk of local recurrence.^{1–3} Although the use of boost irradiation is recommended, the standard technique and definition of the tumour bed volume have not been clearly established.^{4–6} The importance of the use of surgical clips and CT scan for the definition of the tumour bed was already reported

more than 15 years ago.^{7,8} CT-based RT planning is now widely adopted, and its use has become more common for boost volume definition.^{9–11} Recently, it was shown that the use of CT-based volume delineation and treatment planning involves a larger irradiated boost volume, which could increase the risk of side effects.^{12–17} One method to define the boost volume is the use of surgical clips,^{9,11} although post-operative breast tissue changes and remodelling can interfere with tumour bed localization.⁹ Moreover, a recent study demonstrated, especially in patients with seroma, a frequent volumetric change of the tumour bed during breast irradiation. In this case, resimulation is necessary.¹⁸

Concomitant radiochemotherapy, while having proven very effective for many tumours,^{19–21} with better local control and improved survival, has been hardly assessed for breast cancer,^{22–24} and very rarely in a pre-operative setting.^{25–28} Moreover, several authors have recently demonstrated that low-dose fractionated radiotherapy (LD-FRT) is able to enhance the effectiveness of multiple chemotherapeutic agents.^{29–31} Preliminary results of clinical trials combining LD-FRT with chemotherapy suggest that this treatment could be both feasible and effective.³² In our institution, we performed a Phase I trial demonstrating the feasibility of neoadjuvant radiochemotherapy treatment for patients with Stage IIA–IIIA breast cancer with LD-FRT associated with two different schedules of chemotherapy, resulting in a good toxicity profile.³³ Recently, we published the results of the Phase II trial that demonstrated a better response rate with respect to chemotherapy alone, suggesting different interactions between low-dose radiotherapy and molecular subtypes.³⁴

In this study, we retrospectively analyzed two different planning techniques for the breast boost in a group of patients treated with neoadjuvant chemotherapy: (1) a pre-operative boost technique on the tumour, administered with LD-FRT, concomitant with neoadjuvant chemotherapy and (2) the standard sequential boost technique to the tumour bed, following neoadjuvant chemotherapy, surgery and standard radiotherapy to the whole breast. The primary end point of the study was to evaluate the differences between these two boost techniques in terms of accuracy and resulting dose distributions to the target and organs at risk (OAR).

METHODS AND MATERIALS

In our study, we retrospectively analyzed a group of patients who received a pre-operative boost on the tumour with LD-FRT (two fractions of 0.4 Gy per day for 2 days, every 21 days) for a total dose of 9.6 Gy by photon technique and concomitant standard neoadjuvant chemotherapy with non-pegylated liposomal anthracyclines and docetaxel.³⁵ The patients analyzed in this study derived from a clinical Phase I-II study, approved by an ethics committee.^{33,34} For comparison purposes, the boost was replanned using a standard photon beam technique and an electron beam technique to the tumour bed of the same patients, after surgery and standard adjuvant WBRT, for a total dose of 10 Gy over five daily fractions of 2 Gy each.

We enrolled patients with invasive breast carcinoma (T2–3, N0–N1; Stage IIA–IIIA)³⁶ aged ≥ 18 years; patients were excluded if a distant metastatic disease or contralateral breast disease was identified, if they were cErbB2 positive or if they underwent previous treatment for other tumours. All patients had locally advanced tumours and in most cases positive lymph nodes. Core biopsy or surgical biopsy was performed before chemotherapy for the histologic diagnosis and evaluation of the hormonal receptors, c-erbB2, Ki-67, p53 and bcl-2. All patients had a complete clinical examination, mammography, breast ultrasound, breast dynamic contrast-enhanced MRI, complete blood count and serum chemistry, total body CT, bone scan, electrocardiogram and cardiac ultrasonography for the evaluation of the left ventricular ejection fraction at baseline. Dynamic

contrast-enhanced MRI was performed at the baseline, after three cycles of treatment and before surgery. The largest tumour diameter, as well as the largest diameter orthogonal to it, was measured.³⁷ Tumours were classified according to the International Union Cancer TNM 2010.³⁶

Patients received standard neoadjuvant chemotherapy with six cycles of liposomal doxorubicin (50mg/mq) and docetaxel (75mg/mq) every 21 days with concurrent LD-FRT (two fractions of 0.4 Gy per day for 2 days, every 21 days, for six cycles and for a total dose of 9.6 Gy). The concurrent LD-FRT, as anticipated boost, was administered in order to enhance the effect of chemotherapy.

The clinical target volume (CTV) of the pre-operative boost was represented by the gross tumour volume (GTV) with a margin of 1 cm. The GTV was based on pre-chemotherapy imaging studies and clinical examination during the simulation, when the radiation oncologist drew the area of the tumour on the patient skin. The planning target volume was CTV + 0.5 cm. Axillary lymph nodes were not included in the treatment, even if clinically or radiologically positive. Tangential fields were commonly used to cover the area of the tumour. The CTV of the two simulated boosts was defined as a rim of tissue around the original tumour excision area (tumour bed). The tumour bed was delineated according to the visualized seroma cavity and to surgical clips, when available, aided by clinical information from history, pre-operative imaging findings and operative report. The field margins of the boost fields were set with a safety margin of 1.5 cm around the tumour bed³⁸ to take into account the setup errors or movement of the internal margin (planning target volume). CT simulation was performed with the patient in the supine position on a breast board. We used two tangential fields for the photon technique and a single electron beam for the electron technique to cover the area of the tumour. Three separate plans were generated for each patient, respectively, for the pre-operative boost technique and for the standard sequential one, using Triple AAA Planning Software®.

The plans were analyzed for the dosimetric coverage of the CT-delineated irradiated volume. The pre-operative boost plans were evaluated and compared with the photons and electron plans using the following criteria: the minimal dose received by 95% of the target volume (D_{95}), the minimal dose received by 90% of the target volume (D_{90}), OAR dose constraints for the heart and lungs and geographic miss. A geographic miss was defined as any portion of the tumour bed receiving $<50\%$ of the prescribed dose. Dosimetric outcomes were measured by use of dose–volume histogram analysis. Moreover, the influence of breast volume and density on dosimetric outcomes on pre-operative and standard post-operative treatment plans was evaluated. To assess the effect of breast volume, the breast size was classified as small ($<750\text{ cm}^3$), medium ($750\text{--}1499\text{ cm}^3$) and large ($>1500\text{ cm}^3$). Breast density was evaluated by mammography and categorized into four types according to breast imaging-reporting and data system scoring: Type 1, fatty breast ($<10\%$ of dense tissue); Type 2, fibroglandular ($10\text{--}49\%$ of dense tissue); Type 3, heterogeneously dense ($49\text{--}90\%$ of

dense tissue); and Type 4, dense and homogeneous (>90% of dense tissue).³⁹

Acute toxicity (during treatment) and subacute toxicity (at 1 month of follow-up) were recorded by the treating physicians and graded according to the Radiation Therapy Oncology Group criteria.

Dosimetric parameters for the three planning techniques were summarized by the use of descriptive statistics including medians and ranges; distributions of these parameters in the two planning groups were compared by the use of Wilcoxon non-parametric tests. The influence of breast volume and density on dosimetric outcomes was evaluated using a linear regression model. MedCalc software (www.medcalc.be) was used for all statistical analysis.

RESULTS

15 females aged ≥ 18 years with invasive carcinoma (T2–3, N0–1) were recruited for this study. Patient and tumour bed characteristics are listed in Table 1. The median patient age was 55 years (range 37–70 years). All patients had a good performance status (Eastern Cooperative Oncology Group 0–1). Eight

right-sided and seven left-sided tumours were treated. Tumour stage was IIA in 5 (33%) patients, IIB in 8 (53%) patients and IIIA in 2 (13%) patients. 2 patients had lobular invasive cancer and 13 patients had invasive ductal cancer. The grading was Grade 3 in 8 patients and Grade 2 in 7 patients. The oestrogen receptor status was positive in 11 patients, while 10 patients had positive progesteron receptor; 11 patients received hormonal therapy.

A comparison of the dose–volume parameters between the three techniques is summarized in Table 2. The sequential photon technique resulted in a median irradiated volume of 189 cm³ (range 36–680 cm³); the median D_{95} and the median D_{90} were 96.3% (range 94.7–99.6%) and 99.1% (range 90.2–100%), respectively. The sequential electron technique showed a median irradiated volume of 189 cm³ (range 36–680 cm³); the median D_{95} was 0.8% (range 0–30%) and the median D_{90} and minimal dose received by 80% of the target volume was 54.7% (range 0–84.8%) and 83.2% (range 50–99.6%), respectively. We observed a geographic miss in 26.6% of patients. For the pre-operative boost technique, we obtained a median irradiated volume of 128.8 cm³ (range 55–372.6 cm³), a median D_{90} of 99.4% (range 96.5–100%) and a median D_{95} of 97.1% (range 86.2–99%). Neither sequential photon plans nor pre-operative boost plans showed geographic misses.

With the photon boost technique, we obtained a median lung $D_{\max}$ of 95.5% (range 86.6–102.1%) and a median heart D_{mean} of 2.8 Gy (1.1–8.9 Gy) for patients with tumour in the left-side breast. The electron boost technique demonstrated a median lung $D_{\max}$ of 76.1% (range 60.8–83%) and a median heart D_{mean} of 2 Gy (range 0.3–11 Gy). The pre-operative photon boost technique resulted in a lung $D_{\max}$ of 89.7% (24.9–108%) and a median heart D_{mean} of 2 Gy (1.4–8.2 Gy). Breast volume and density did not correlate with changes in the tumour bed volume. When we compared the anticipated pre-operative photon boost technique with the sequential electron boost technique, we found that coverage was significantly better as reported in Table 3 ($p < 0.0001$). This is probably due to the different physical characteristics of the electron boost. There are no statistically significant differences between pre- and post-surgery photon boost techniques. However, the volume irradiated with the sequential boost is lower, although not statistically significant ($p = 0.229$), probably because of the small sample size.

Concomitant neoadjuvant radiochemotherapy treatment with LD-FRT was well tolerated in the acute and subacute settings; there was one case of Grade 2 acute skin toxicity, while we did not observe Grade 3 acute toxicities or dermatitis with wet desquamation. After 1 month from the end of treatment, no patient showed skin toxicity. There were no Grade 3 or 4 haematologic and non-haematological events. Grade 1 hematologic toxicity was observed in 4 (26.6%) patients, mainly represented by anaemia and neutropenia without severity. All patients had nausea, diarrhoea and alopecia.

DISCUSSION

The standard dose of WBRT is 50 Gy in 25 fractions of 2.0 Gy over 5 weeks.¹ Hypofractionated schedule is a widespread option

Table 1. Patient characteristics and tumour parameters

Variable	N = 15 (%)
Median age (years) (range)	55 (37–70)
Laterality	
Right	8 (53.3)
Left	7 (46.6)
TNM stage	
IIA	5 (33.3)
IIB	8 (53.3)
IIIA	2 (13.3)
Grading	
Grade 2	7 (46.6)
Grade 3	8 (53.3)
Receptor status	
ER+	11 (73.3)
PR+	10 (66.6)
Breast volume (cm ³)	
<750	2 (13.3)
750–1499	11 (73.4)
≥ 1500	2 (13.3)
Breast density	
Type 1	2 (13.4)
Type 2	4 (26.6)
Type 3	6 (40)
Type 4	3 (20)

Table 2. Dosimetric analysis by treatment-planning technique

Variable	Sequential photon boost	Sequential electron boost	Pre-operative anticipated boost
Irradiated volume Median (range) (cm ³)	189 (36–680)	189 (36–680)	128.8 (55–372.6)
D_{95} Median (range) (%)	96.3 (94.7–99.6)	0.8 (0–30)	97.1 (86.2–99)
D_{90} Median (range) (%)	99.1 (90.2–100)	54.7 (0–84.8)	99.4 (96.5–100)
$D_{\max}$ lung Median (range) (%)	95.5 (86.6–102.1)	76.1 (60.8–83)	89.7 (24.9–108)
D_{mean} heart Median (range) (Gy)	2.8 (1.1–8.9)	2 (0.3–11)	2 (1.4–8.2)

D_{90} , minimal dose received by 90% of the target volume; D_{95} , minimal dose received by 95% of the target volume.

for performing whole-breast irradiation after breast-conserving surgery. There are three randomized trials performed in the past years that have compared hypofractionation with conventional radiotherapy for whole-breast irradiation.^{40–42} In the Canadian study, no patient received boost irradiation.⁴⁰ In the START A and B, although its use was not standardized, most patients received a radiotherapy boost.^{41,42} The American Society of Therapeutic Radiology and Oncology (ASTRO) guidelines reported that hypofractionated WBRT was appropriate in patients aged 50 years or older at diagnosis, with pathological stage T1–T2 N0 disease treated with breast-conserving surgery, without chemotherapy and with a dose inhomogeneity of <7% on radiation plan. The benefit of boost irradiation to significantly reduce the risk of local recurrence has been shown in two randomized trials.^{1,2} A European Organisation for Research and Treatment of Cancer (EORTC) trial demonstrated that the 20-year cumulative incidence of ipsilateral breast tumour recurrence was 16.4% (99% confidence interval: 14.1–18.8) in the no boost group *vs* 12.0% (9.8–14.4%) in the boost group.² Romestaing *et al*⁴ showed a significant reduction in local

recurrence from 4.5 to 3.6% ($p = 0.044$) with the addition of a 10-Gy boost to the tumour bed *vs* no further therapy.³ Although the use of boost irradiation is recommended, the standard technique and definition of the tumour bed volume have not been clearly established.^{4–6} Some use the surgical scar and clinical findings to estimate the tumour bed; a 2–3-cm margin is given around the surgical scar and radiation is delivered to this volume. Nevertheless, the modern oncoplastic and reconstructive breast surgery techniques could often move the tumour bed from the surgical scar. A study by Oh *et al*⁵ showed that geographic misses (defined as any portion of the lumpectomy cavity receiving <50% of the prescribed dose) occur frequently when the target volume is determined with a scar-based plan (SBP). However, when CT-based planning was used, there was no significant difference in coverage when the target volume was based on pre-WBRT CT *vs* post-WBRT CT.^{4,5} A significant limitation of CT-based treatment planning is the inability to consistently and accurately delineate the tumour bed. One method proposed by some investigators to overcome this shortcoming is the placement of surgical clips at lumpectomy to outline the tumour bed.^{8,12–14,17}

Table 3. Dosimetric analysis by treatment-planning technique

Variable	Sequential electron boost	Pre-operative photon boost	<i>p</i> -value
Irradiated volume Median (range) (cm ³)	189 (36–428.8)	128.8 (55–372.6)	0.229
D_{95} Median (range) (%)	69.2 (33.7–86)	96 (92.6–96.8)	<0.0001
D_{90} Median (range) (%)	75.8 (46.7–88.5)	96.8 (94.1–97.8)	<0.0001
D_{80} Median (range) (%)	81.9 (65.6–91)	98 (96–99)	<0.0001
$D_{\max}$ lung median (range) (%)	74 (31–80.7)	89.7 (25–108)	0.003
D_{mean} heart median (range) (Gy)	0.43 (0.04–1.1)	0.23 (0.14–1.1)	0.312

D_{80} , minimal dose received by 80% of the target volume; D_{90} , minimal dose received by 90% of the target volume; D_{95} , minimal dose received by 95% of the target volume.

The proposed definition of tumour bed boost volume appears to be very accurate as long as it is based on the use of three or more clips, because there is an increase in overlap between the pre-operative GTV and the clip area when this number of clips is used.⁹ Several reviews have shown that approximately 10–67% of SBP boosts were inaccurate in defining the boost volume when compared with surgical clip-based plans, resulting in geographical misses and unnecessary irradiation of the breast tissue beyond the tumour bed.^{7,8,43–45} However, surgical clips are not always placed at the time of surgery and hence may not be available to assist in target volume delineation.

Two reviews have shown that SBP results in geographical misses or modifications required in 70–80% of the cases when compared with CT-based plans.^{8,46} Benda et al⁴⁷ reported that only 51% of the SBP received 90% or more of the prescribed dose when compared with CT-generated boost plans. Moreover, SBP can not only miss the location of the tumour bed, but also underestimate the size. CT-based RT planning is now being widely adopted, and its use has become more common for boost volume definition.^{9–11} Al Uwin et al confirmed that the use of CT-based data for treatment volume delineation and treatment planning results in significantly larger irradiated boost volumes for external beam therapy with either a direct electron beam or a setup with several photon beams. These results agree with some monoinstitutional published planning data: Hanbeukers et al¹² showed in a planning study that the application of CT planning resulted in 1.6 times larger boost volumes than that of the conventional simulator-based treatment plans and Van der Laan et al¹³ showed that the use of CT-based treatment planning resulted in an increase of the irradiated boost volume by 29%. This larger boost volume may, however, unnecessarily increase the risk of side effects in normal tissues and adversely affect the cosmetic outcome.^{14–17} A recently published review evaluates the literature evidence for the relationship between the volume of the breast tissue irradiated and the late normal tissue complications including overall cosmesis, breast fibrosis, breast induration and teleangectasia. Breast volume, post-surgical cosmesis, boost radiation, chemotherapy, smoking and finally volumetric parameters influence normal tissue complications after breast RT. The EORTC “boost vs no boost” trial showed that there is a relationship between dose and boost volume irradiated. Collette et al¹⁶ highlighted that the boost volume irradiated, in univariate analysis, was associated with an increased risk of moderate/severe fibrosis. Vrieling et al¹⁷ demonstrated, in univariate analysis and 3 years of follow-up, a worse cosmetic outcome in patients with boost volume $>200\text{ cm}^3$ with respect to that in those with boost volume $\leq 200\text{ cm}^3$.^{4,17} In addition, the EORTC “boost vs no boost” trial showed a significant 15% decrease in excellent/good cosmesis in the boost arm.¹⁵

Perioperative boost has been widely investigated, especially in the field of intraoperative radiotherapy (IORT).^{48,49} IORT, an “anticipated boost”, demonstrated excellent long-term results.^{50–54}

A pooled analysis performed by six institutions of the International Society of the Intraoperative Radiation Therapy (ISIRT) Europe tested linear accelerator-based IORT with

electrons (IOERT), with 10 Gy as the anticipated boost modality in addition to whole-breast treatment, showing that an anticipated IOERT boost results in an accurate dose delivery with a consequent better local tumour control. With three-dimensional (3D) conformal plans, the photon boost technique seems to be superior to the electron one.^{55,56} This is the reason why in the Young Boost trial,² compared with the EORTC trial, photon boost was used more.

Recently, several studies have evaluated the administration of the boost with most modern techniques [intensity-modulated radiotherapy (IMRT) and volumetric modulated arc RT] in order to reduce the acute and late toxicity related to dishomogeneity of the 3D technique. Fiorentino et al⁵⁷ analyzed 112 females with a diagnosis of early breast cancer (T1–2, N0–1, M0) treated with IMRT and simultaneous integrated boost after breast-conserving surgery. The acute skin grade toxicity during the treatment was Grade 0 in 8 (7%) patients, Grade 1 in 80 (72%) patients and Grade 2 in 24 (21%) cases. No Grade 3 or higher acute skin toxicity was observed. At 24 months, skin toxicity was Grade 0 in 79 (71%) patients and Grade 1 in 33 (29%) patients. No case of Grade 2 or higher toxicity was registered. Jöst et al⁵⁸ compared 3D conformal RT with a hybrid technique consisting of IMRT and volumetric modulated arc RT during normally fractionated radiation of mammary carcinomas with simultaneous integrated boost, resulting in a reduction of the mean heart and lung dose with the hybrid technique ($p < 0.01$).

The use of concurrent chemoradiotherapy regimens in breast cancer is uncommon and is not a standard treatment. Sequential treatments have been found to be equally effective.²⁴ Many studies have shown an increase of toxicity with concomitant treatment.²² Formenti et al²⁸ performed a Phase I/II trial in which they demonstrated a high pathologic response rate (34%) after neoadjuvant treatment with paclitaxel (30 mg m^{-2} twice weekly for a total of 8–10 weeks) and concurrent RT (45 Gy at 1.8 Gy/fraction) in patients with locally advanced breast cancer; furthermore, they observed that pathologic response was associated with significantly better 5-year DFS and overall survival. A Grade 3 skin toxicity from paclitaxel RT was recorded in 7% of patients and they showed a high rate of surgical complications (14%), suggesting persistent normal tissue morbidity from paclitaxel-based chemoradiation.^{28,59}

In order to prevent the high skin toxicity rate and post-surgery complications, we preferred LD-FRT for the pre-operative boost. Mammalian cells exhibit hyper-radiosensitivity (HRS) to radiation doses of $<0.3\text{--}0.6\text{ Gy}$.⁶⁰ The transition towards the associated radiation resistance is generically described by the term “increased radioresistance” (IRR). The exact molecular mechanism that regulates the HRS/IRR phenomenon is still unknown; it is probably due to checkpoint controls in the Grade 2 phase of the cell cycle. Doses of approximately $<0.3\text{ Gy}$ lead to death of Grade 2-phase cells *via* apoptosis, producing HRS. Combined chemoradiotherapy strategies to enrich the Grade 2-phase fraction before radiotherapy showed promising results in the experimental setting. Dey and Spring combined low-dose fractionated irradiation with cell synchronization using taxanes to radiosensitize SCCHN tumour xenografts in nude mice.³⁰ Low

doses of radiation (10–60 cGy) were found to induce HRS phenomenon and doses >1 Gy demonstrated IRR. Several studies demonstrated that LD-FRT increases the effectiveness of chemotherapy.^{29–31,61–69} Valentini et al³² examined the response rate in 22 patients who underwent palliative treatment with LD-FRT (range 320–1280 cGy) and concurrent chemotherapy, mostly for the management of relapse or progressive disease after radical therapy. The overall response rate was 45% (42% in patients previously treated).

We recently performed a Phase I trial to demonstrate the feasibility of neoadjuvant treatment for Stage IIA–IIIA breast cancer with LD-FRT concomitant with myocet and docetaxel: we observed haematological toxicity in 2/10 patients (anaemia Grade 1 and leucopenia Grade 1), while neither acute skin toxicity nor post-surgery complications were observed.³³

The results of our retrospective analysis showed that the use of an anticipated pre-operative photon boost with LD-FRT, concomitant with chemotherapy, could reduce the irradiated volume and increase the accuracy. The pre-operative boost-planning technique achieved better dosimetric distribution than the sequential electron boost technique, resulting in a higher median D_{95} (97.1%) and a lesser irradiated volume (128.8 cm³). When analyzed for all dose–volume parameters, the anticipated pre-operative boost technique, when compared with the

sequential photon technique, resulted in a dose reduction to the heart, with left-sided breast irradiation, and to the ipsilateral lung; when it was compared with the sequential electron technique, it showed a greater median D_{max} to the ipsilateral lung. Moreover, the neoadjuvant LD-FRT regimen, concurrent with liposomal doxorubicin and docetaxel, was feasible and well tolerated in the acute and subacute settings, with a low haematological toxicity and skin toxicity profiles. Notwithstanding, this retrospective study has potential limits which could restrict the generalization of the results: the small size of the sample and the association with chemotherapy in a select subgroup of patients with breast cancer Stage IIA–B/IIIA.

CONCLUSION

Our results show the feasibility and accuracy of a neoadjuvant concomitant radiochemotherapy treatment with LD-FRT for Stage IIA–B/IIIA breast cancer. However, the efficacy of LD-FRT as anticipated boost and concomitant primary systemic treatment with liposomal anthracycline and docetaxel in terms of pathological response rate needs to be tested further. Additional investigations, from an evidence-based medicine point of view, are warranted. An anticipated pre-operative photon boost results in a better coverage with respect to the standard sequential boost while also saving the OAR and consequently fewer side effects, although the sample size does not allow definitive conclusions.

REFERENCES

- Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). 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 randomised trials. *Lancet* 2005; **366**: 2087–106.
- Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol* 2015; **16**: 47–56. doi: [http://dx.doi.org/10.1016/S1470-2045\(14\)71156-8](http://dx.doi.org/10.1016/S1470-2045(14)71156-8)
- Poortmans PM, Collette L, Bartelink H, Struikmans H, Van den Bogaert WF, Fourquet A, et al; EORTC Radiation Oncology and Breast Cancer Groups. The addition of a boost dose on the primary tumour bed after lumpectomy in breast conserving treatment for breast cancer. A summary of the results of EORTC 22881-10882 “boost versus no boost” trial. *Cancer Radiother* 2008; **12**: 565–70. doi: <http://dx.doi.org/10.1016/j.canrad.2008.07.014>
- Romestaing P, Lehingue Y, Carrie C, Coquard R, Montbarbon X, Ardiet JM, et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *J Clin Oncol* 1997; **15**: 963–8.
- Oh KS, Kong FM, Griffith KA, Yanke B, Pierce LJ. Planning the breast tumor bed boost: changes in the excision cavity volume and surgical scar location after breast-conserving surgery and whole-breast irradiation. *Int J Radiat Oncol Biol Phys* 2006; **66**: 680–6. doi: <http://dx.doi.org/10.1016/j.ijrobp.2006.04.042>
- Denham JW, Sillar RW, Clarke D. Boost dosage to the excision site following conservative surgery for breast cancer: it's easy to miss! *Clin Oncol (r Coll Radiol)* 1991; **3**: 257–61. doi: [http://dx.doi.org/10.1016/S0936-6555\(05\)80873-8](http://dx.doi.org/10.1016/S0936-6555(05)80873-8)
- Bedwinek J. Breast conserving surgery and irradiation: the importance of demarcating the excision cavity with surgical clips. *Int J Radiat Oncol Biol Phys* 1993; **26**: 675–9. doi: [http://dx.doi.org/10.1016/0360-3016\(93\)90287-6](http://dx.doi.org/10.1016/0360-3016(93)90287-6)
- Regine WF, Ayyangar KM, Komarnicky LT, Bhandare N, Mansfield CM. Computer-CT planning of the electron boost in definitive breast irradiation. *Int J Radiat Oncol Biol Phys* 1991; **20**: 121–5. doi: [http://dx.doi.org/10.1016/0360-3016\(91\)90147-V](http://dx.doi.org/10.1016/0360-3016(91)90147-V)
- Kirova YM, Fournier-Bidoz N, Servois V, Laki F, Pollet GA, Salmon R, et al. How to boost the breast tumor bed? A multidisciplinary approach in eight steps. *Int J Radiat Oncol Biol Phys* 2008; **72**: 494–500. doi: <http://dx.doi.org/10.1016/j.ijrobp.2007.12.059>
- Hepel JT, Evans SB, Hiatt JR, Price LL, DiPetrillo T, Wazer DE, et al. Planning the breast boost: comparison of three techniques and evolution of tumor bed during treatment. *Int J Radiat Oncol Biol Phys* 2009; **74**: 458–63. doi: <http://dx.doi.org/10.1016/j.ijrobp.2008.08.051>
- Fournier-Bidoz N, Kirova Y, Laki F. The contribution of the imaging registration in the localization of the tumor bed after breast conservative surgery. No.13. Presented at the 45èmes Journées Scientifiques de la Société Française de Physique Médicale: Lyon, France: June 2006.
- Hanbeukers B, Borger J, van den Ende P, van der Ent F, Houben R, Jager J, et al. Customized computed tomography-based boost volumes in breast-conserving therapy: use of three-dimensional histologic information for clinical target volume margins. *Int J Radiat Oncol Biol Phys* 2009; **75**: 757–63. doi:

- <http://dx.doi.org/10.1016/j.jrobp.2008.11.048>
13. Van der Laan HP, Dolsma WV, Maduro JH, Korevaar EW, Hollander M, Langendijk JA. Three-dimensional conformal simultaneously integrated boost technique for breast-conserving radiotherapy. *Int J Radiat Oncol Biol Phys* 2007; **68**: 1018–23. doi: <http://dx.doi.org/10.1016/j.jrobp.2007.01.037>
 14. Poortmans P, Bartelink H, Horiot JC, Struikmans H, Van den Bogaert W, Fourquet A, et al. EORTC Radiotherapy and Breast Cancer Groups. The influence of the boost technique on local control in breast conserving treatment in the EORTC “boost versus no boost” randomised trial. *Radiation Oncol* 2004; **72**: 25–33. doi: <http://dx.doi.org/10.1016/j.radonc.2004.03.007>
 15. Vrieling C, Collette L, Fourquet A, Hoogenraad WJ, Horiot JC, Jager JJ, et al. The influence of the boost in breast-conserving therapy on cosmetic outcome in the EORTC “boost versus no boost” trial. EORTC Radiotherapy and Breast Cancer Cooperative Groups. European Organization for Research and Treatment of Cancer. *Int J Radiat Oncol Biol Phys* 1999; **45**: 677–85. doi: [http://dx.doi.org/10.1016/S0360-3016\(99\)00211-4](http://dx.doi.org/10.1016/S0360-3016(99)00211-4)
 16. Al Uwini S, Antonini N, Poortmans PM, Boersma L, Hurkmans C, Leer JW, Horiot JC, Struikmans H, Bartelink H. The influence of the use of CT-planning on the irradiated boost volume in breast conserving treatment. *Radiation Oncol*. 2009 Oct; **93**(1): 87–93. doi: [10.1016/j.radonc.2009.05.002](http://dx.doi.org/10.1016/j.radonc.2009.05.002). Epub 2009 Jun 8.
 17. Vrieling C, Collette L, Fourquet A, Hoogenraad WJ, Horiot JH, Jager JJ, et al. The influence of patient, tumor and treatment factors on the cosmetic results after breast-conserving therapy in the EORTC “boost vs. no boost” trial. EORTC Radiotherapy and Breast Cancer Cooperative Groups. *Radiation Oncol* 2000; **55**: 219–32. doi: [http://dx.doi.org/10.1016/S0167-8140\(00\)00210-3](http://dx.doi.org/10.1016/S0167-8140(00)00210-3)
 18. Chung MJ, Suh YJ, Lee HC, Kang DG, Kim EJ, Kim SH, et al. Tumor bed volumetric changes during breast irradiation for the patients with breast cancer. *Radiat Oncol J* 2013; **31**: 228–33. doi: <http://dx.doi.org/10.3857/roj.2013.31.4.228>
 19. Langendijk JA, Leemans CR, Buter J, Berkhof J, Slotman BJ. The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: a meta-analysis of the published literature. *J Clin Oncol* 2004; **22**: 4604–12. doi: <http://dx.doi.org/10.1200/JCO.2004.10.074>
 20. Green JA, Kirwan JM, Tierney JF, Symonds P, Fresco L, Collingwood M, et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. *Lancet* 2001; **358**: 781–6. doi: [http://dx.doi.org/10.1016/S0140-6736\(01\)05965-7](http://dx.doi.org/10.1016/S0140-6736(01)05965-7)
 21. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA Jr, Al-Sarraf M, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA* 1999; **281**: 1623–7.
 22. Toledano A, Azria D, Garaud P, Fourquet A, Serin D, Bosset JF, et al. Phase III trial of concurrent or sequential adjuvant chemoradiotherapy after conservative surgery for early-stage breast cancer: final results of the ARCOSEIN trial. *J Clin Oncol* 2007; **25**: 405–10. doi: <http://dx.doi.org/10.1200/JCO.2006.07.8576>
 23. Rouëssé J, de la Lande B, Bertheault-Cvitkovic F, Serin D, Graïc Y, Combe M, et al. A phase III randomized trial comparing adjuvant concomitant chemoradiotherapy versus standard adjuvant chemotherapy followed by radiotherapy in operable node-positive breast cancer: final results. *Int J Radiat Oncol Biol Phys* 2006; **64**: 1072–80. doi: <http://dx.doi.org/10.1016/j.jrobp.2005.10.011>
 24. Arcangeli G, Pinnarò P, Rambone R, Giannarelli D, Benassi M. A phase III randomized study on the sequencing of radiotherapy and chemotherapy in the conservative management of early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 2006; **64**: 161–7. doi: <http://dx.doi.org/10.1016/j.jrobp.2005.06.040>
 25. Semiglazov VF, Topuzov EE, Bavli JL, Moiseyenko VM, Ivanova OA, Seleznev IK, et al. Primary (neoadjuvant) chemotherapy and radiotherapy compared with primary radiotherapy alone in stage IIb–IIIA breast cancer. *Ann Oncol* 1994; **5**: 591–5.
 26. Formenti SC, Dunnington G, Uziel B, Lenz H, Keren-Rosenberg S, Silberman H, et al. Original p53 status predicts for pathological response in locally advanced breast cancer patients treated preoperatively with continuous infusion 5-fluorouracil and radiation therapy. *Int J Radiat Oncol Biol Phys* 1997; **39**: 1059–68. doi: [http://dx.doi.org/10.1016/S0360-3016\(97\)00506-3](http://dx.doi.org/10.1016/S0360-3016(97)00506-3)
 27. Formenti SC, Symmans WF, Volm M, Skinner K, Cohen D, Spicer D, et al. Concurrent paclitaxel and radiation therapy for breast cancer. *Semin Radiat Oncol* 1999; **9** (2 Suppl. 1): 34–42.
 28. Formenti SC, Volm M, Skinner KA, Spicer D, Cohen D, Perez E, et al. Preoperative twice-weekly paclitaxel with concurrent radiation therapy followed by surgery and postoperative doxorubicin-based chemotherapy in locally advanced breast cancer: a phase I/II trial. *J Clin Oncol* 2003; **21**: 864–70. doi: <http://dx.doi.org/10.1200/JCO.2003.06.132>
 29. Short SC, Kelly J, Mayes CR, Woodcock M, Joiner MC. Low-dose hypersensitivity after fractionated low-dose irradiation *in vitro*. *Int J Radiat Biol* 2001; **77**: 655–64. doi: <http://dx.doi.org/10.1080/09553000110041326>
 30. Dey S, Spring PM, Arnold S, Valentino J, Chendil D, Regine WF, et al. Low-dose fractionated radiation potentiates the effects of Paclitaxel in wild-type and mutant p53 head and neck tumor cell lines. *Clin Cancer Res* 2003; **9**: 1557–65.
 31. Spring PM, Arnold SM, Shajahan S, Brown B, Dey S, Lele SM, et al. Low dose fractionated radiation potentiates the effects of taxotere in nude mice xenografts of squamous cell carcinoma of head and neck. *Cell Cycle* 2004; **3**: 479–85. doi: <http://dx.doi.org/10.4161/cc.3.4.786>
 32. Valentini V, Massacesi M, Balducci M, Mantini G, Micciché F, Mattiucci GC, et al. Low-dose hyperradiosensitivity: is there a place for future investigation in clinical settings? *Int J Radiat Oncol Biol Phys* 2010; **76**: 535–9. doi: <http://dx.doi.org/10.1016/j.jrobp.2009.02.075>
 33. Nardone L, Valentini V, Marino L, De Santis MC, Terribile D, Franceschini G, et al. A feasibility study of neo-adjuvant low-dose fractionated radiotherapy with two different concurrent anthracycline-docetaxel schedules in stage IIA/B–IIIA breast cancer. *Tumori* 2012; **98**: 79–85. doi: <http://dx.doi.org/10.1700/1053.11503>
 34. Nardone L, Diletto B, De Santis MC, D’Agostino GR, Belli P, Bufi E, et al. Primary systemic treatment and concomitant low dose radiotherapy for breast cancer: final results of a prospective phase II study. *Breast* 2014; **23**: 597–602. doi: <http://dx.doi.org/10.1016/j.breast.2014.06.005>
 35. Chan S, Davidson N, Juozaityte E, Erdkamp F, Pluzanska A, Azarnia N, et al. Phase III trial of liposomal doxorubicin and cyclophosphamide compared with epirubicin and cyclophosphamide as first-line therapy for metastatic breast cancer. *Ann Oncol* 2004; **15**: 1527–34.

36. Sobin LH, Gospodarowicz MK, Wittekind C, ed. *TNM Classification of Malignant Tumours*. 7th edn. Hoboken, NJ: Wiley-Blackwell, International Union Against Cancer (UICC); 2010.
37. Belli P, Costantini M, Ierardi C, Bufi E, Amato D, Mule' A, et al. Diffusion-weighted imaging in evaluating the response to neoadjuvant breast cancer treatment. *Breast J* 2011; **17**: 610–9. doi: <http://dx.doi.org/10.1111/j.1524-4741.2011.01160.x>
38. Holland R, Veling SH, Mravunac M, Hendriks JH. Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. *Cancer* 1985; **56**: 979–90. doi: [http://dx.doi.org/10.1002/1097-0142\(19850901\)56:5<979::AID-CNCR2820560502>3.0.CO;2-N](http://dx.doi.org/10.1002/1097-0142(19850901)56:5<979::AID-CNCR2820560502>3.0.CO;2-N)
39. Balleyguier C, Ayadi S, Van Nguyen K, Vanel D, Dromain C, Sigal R. BIRADS classification in mammography. *Eur J Radiol* 2007; **61**: 192–4. doi: <http://dx.doi.org/10.1016/j.ejrad.2006.08.033>
40. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010; **362**: 513–20. doi: <http://dx.doi.org/10.1056/NEJMoa0906260>
41. The START Trialists' Group; Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol* 2008; **9**: 331–41. doi: [http://dx.doi.org/10.1016/S1470-2045\(08\)70077-9](http://dx.doi.org/10.1016/S1470-2045(08)70077-9)
42. The START Trialists' Group; Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bentzen SM, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* 2008; **371**: 1098–107. doi: [http://dx.doi.org/10.1016/S0140-6736\(08\)60348-7](http://dx.doi.org/10.1016/S0140-6736(08)60348-7)
43. Harrington KJ, Harrison M, Bayle P, Evans K, Dunn PA, Lambert HE, et al. Surgical clips in planning the electron boost in breast cancer: a qualitative and quantitative evaluation. *Int J Radiat Oncol Biol Phys* 1996; **34**: 579–84. doi: [http://dx.doi.org/10.1016/0360-3016\(95\)02090-X](http://dx.doi.org/10.1016/0360-3016(95)02090-X)
44. Machtay M, Lanciano R, Hoffman J, Hanks GE. Inaccuracies in using the lumpectomy scar for planning electron boosts in primary breast carcinoma. *Int J Radiat Oncol Biol Phys* 1994; **30**: 43–8.
45. Kovner F, Agay R, Merimsky O, Stadler J, Klausner J, Inbar M. Clips and scar as the guidelines for breast radiation boost after lumpectomy. *Eur J Surg Oncol* 1999; **25**: 483–6. doi: <http://dx.doi.org/10.1053/ejso.1999.0683>
46. Messer PM, Kirikuta IC, Bratengeier K, Flentje M. CT planning of boost irradiation in radiotherapy of breast cancer after conservative surgery. *Radiother Oncol* 1997; **42**: 239–43. doi: [http://dx.doi.org/10.1016/S0167-8140\(96\)01891-9](http://dx.doi.org/10.1016/S0167-8140(96)01891-9)
47. Benda RK, Yasuda G, Sethi A, Gabram SG, Hinerman RW, Mendenhall NP. Breast boost: are we missing the target? *Cancer* 2003; **97**: 905–9. doi: <http://dx.doi.org/10.1002/cncr.11142>
48. Lemanski C, Azria D, Thezenas S, Gutowski M, Saint-Aubert B, Rouanet P, et al. Intraoperative radiotherapy given as a boost for early breast cancer: long-term clinical and cosmetic results. *Int J Radiat Oncol Biol Phys* 2006; **64**: 1410–5. doi: <http://dx.doi.org/10.1016/j.ijrobp.2005.10.025>
49. Merrick HW 3rd, Battle JA, Padgett BJ, Dobelbower RR Jr. IORT for early breast cancer: a report on long-term results. *Front Radiat Ther Oncol* 1997; **31**: 126–30.
50. Sautter-Bihl ML, Sedlmayer F, Budach W, Dunst J, Engenhart-Cabillic R, Fietkau R, et al. Intraoperative radiotherapy as accelerated partial breast irradiation for early breast cancer: beware of one-stop shops? *Strahlenther Onkol* 2010; **186**: 651–7. doi: <http://dx.doi.org/10.1007/s00066-010-8001-2>
51. Sedlmayer F, Fastner G, Merz F, Deutschmann H, Reitsamer R, Menzel C, et al. IORT with electrons as boost strategy during breast conserving therapy in limited stage breast cancer: results of an ISORT pooled analysis. *Strahlenther Onkol* 2007; **183**(Spec No 2): 32–4.
52. Wenz F, Budach W, Dunst J, Feyer P, Haase W, Harms W, et al. Accelerated partial-breast irradiation (APBI)—ready for prime time? *Strahlenther Onkol* 2009; **185**: 653–5. doi: <http://dx.doi.org/10.1007/s00066-009-8002-1>
53. Veronesi U, Orecchia R, Luini A, Galimberti V, Zurrada S, Intra M, et al. Intraoperative radiotherapy during breast conserving surgery: a study on 1,822 cases treated with electrons. *Breast Cancer Res Treat* 2010; **124**: 141–51. doi: <http://dx.doi.org/10.1007/s10549-010-1115-5>
54. Reitsamer R, Peintinger F, Kopp M, Menzel C, Kogelnik HD, Sedlmayer F. Local recurrence rates in breast cancer patients treated with intraoperative electron-boost radiotherapy versus postoperative external-beam electron-boost irradiation. A sequential intervention study. *Strahlenther Onkol* 2004; **180**: 38–44. doi: <http://dx.doi.org/10.1007/s00066-004-1190-9>
55. Kovacs A, Hadjiev J, Lakosi F, Glavak C, Antal G, Bogner P, et al. Comparison of photon with electron boost in treatment of early stage breast cancer. *Pathol Oncol Res* 2008; **14**: 193–7. doi: <http://dx.doi.org/10.1007/s12253-008-9015-2>
56. Park SH, Kim JC. Comparison of electron and x-ray beams for tumor bed boost irradiation in breast-conserving treatment. *J Breast Cancer* 2013; **16**: 300–7. doi: <http://dx.doi.org/10.4048/jbc.2013.16.3.300>
57. Fiorentino A, Mazzola R, Ricchetti F, Giaj Levra N, Fersino S, Naccarato S, et al. Intensity modulated radiation therapy with simultaneous integrated boost in early breast cancer irradiation. Report of feasibility and preliminary toxicity. *Cancer Radiother* 2015; **19**: 289–94. doi: <http://dx.doi.org/10.1016/j.canrad.2015.02.013>
58. Jöst V, Kretschmer M, Sabatino M, Würschmidt F, Dahle J, Ueberle F, et al. Heart dose reduction in breast cancer treatment with simultaneous integrated boost: comparison of treatment planning and dosimetry for a novel hybrid technique and 3D-CRT. *Strahlenther Onkol* 2015; **191**: 734–41. doi: <http://dx.doi.org/10.1007/s00066-015-0874-7>
59. Adams S, Chakravarthy AB, Donach M, Spicer D, Lymberis S, Singh B, et al. Pre-operative concurrent paclitaxel-radiation in locally advanced breast cancer: pathologic response correlates with five-year overall survival. *Breast Cancer Res Treat* 2010; **124**: 723–32. doi: <http://dx.doi.org/10.1007/s10549-010-1181-8>
60. Marples B, Collis SJ. Low-dose hyper-radiosensitivity: past, present, and future. *Int J Radiat Oncol Biol Phys* 2008; **70**: 1310–18. doi: <http://dx.doi.org/10.1016/j.ijrobp.2007.11.071>
61. Chendil D, Oakes R, Alcock RA, Patel N, Mayhew C, Mohiuddin M, et al. Low dose fractionated radiation enhances the radiosensitization effect of paclitaxel in colorectal tumor cells with mutant p53. *Cancer* 2000; **89**: 1893–900. doi: [http://dx.doi.org/10.1002/1097-0142\(20001101\)89:9<1893::AID-CNCR4>3.3.CO;2-2](http://dx.doi.org/10.1002/1097-0142(20001101)89:9<1893::AID-CNCR4>3.3.CO;2-2)
62. Short S, Mayes C, Woodcock M, Johns H, Joiner MC. Low dose hypersensitivity in the

- T98G human glioblastoma cell line. *Int J Radiat Biol* 1999; **75**: 847–55.
63. Arnold SM, Regine WF, Ahmed MM, Valentino J, Spring P, Kudrimoti M, et al. Low-dose fractionated radiation as a chemopotentiation of neoadjuvant paclitaxel and carboplatin for locally advanced squamous cell carcinoma of the head and neck: results of a new treatment paradigm. *Int J Radiat Oncol Biol Phys* 2004; **58**: 1411–17. doi: <http://dx.doi.org/10.1016/j.ijrobp.2003.09.019>
 64. Lambin P, Fertil B, Malaise EP, Joiner MC. Multiphasic survival curves for cells of human tumor cell lines: induced repair or hypersensitive subpopulation? *Radiat Res* 1994; **138**(1 Suppl): S32–6.
 65. Lambin P, Malaise EP, Joiner MC. The effect of very low radiation doses on the human bladder carcinoma cell line RT112. *Radiother Oncol* 1994; **32**: 63–72. doi: [http://dx.doi.org/10.1016/0167-8140\(94\)90450-2](http://dx.doi.org/10.1016/0167-8140(94)90450-2)
 66. Lambin P, Marples B, Fertil B, Malaise EP, Joiner MC. Hypersensitivity of a human tumour cell line to very low radiation doses. *Int J Radiat Biol* 1993; **63**: 639–50. doi: <http://dx.doi.org/10.1080/09553009314450831>
 67. Short SC, Mitchell SA, Boulton P, Woodcock M, Joiner MC. The response of human glioma cell lines to low-dose radiation exposure. *Int J Radiat Biol* 1999; **75**: 1341–8.
 68. Wouters BG, Sy AM, Skarsgard LD. Low-dose hypersensitivity and increased radioresistance in a panel of human tumor cell lines with different radiosensitivity. *Radiat Res* 1996; **146**: 399–413. doi: <http://dx.doi.org/10.2307/3579302>
 69. Marples B, Lambin P, Skov KA, Joiner MC. Low dose hyper-radiosensitivity and increased radioresistance in mammalian cells. *Int J Radiat Biol* 1997; **71**: 721–35.