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Breast radiotherapy

Boosting the tumor bed from deep-seated tumors in early-stage breast cancer: A planning study between electron, photon, and proton beams

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ABSTRACT

Purpose: To assess the potential dosimetric advantages and drawbacks of photon beams (modulated or not), electron beams (EB), and protons as a boost for the tumor bed in deep-seated early-stage breast cancer.

Material and methods: Planning CTs of 14 women with deep-seated tumors (i.e., $\geqslant$4 cm depth) were selected. The clinical target volume (CTV) was defined as the area of architectural distortion surrounded by surgical clips. The planning treatment volume (PTV) was the CTV plus 1 cm margin. A dose of 16 Gy in 2 Gy fractions was prescribed. Organs at risk (OARs) were heart, lungs, breasts, and a 5-mm thick skin segment on the breast surface. Dose–volume metrics were defined to quantify the quality of concurrent treatment plans assessing target coverage and sparing of OAR. The following treatment techniques were assessed: photon beams with either static 3D-conformal, dynamic arc (DCA), static gantry intensity-modulated beams (IMRT), or RapidArc (RA); a single conformal EB; and intensity-modulated proton beams (IMPT). The goal for this planning effort was to cover 100% of the CTV with $\geqslant$95% of the prescribed dose and to minimize the volume inside the CTV receiving >107% of the dose.

Results: All techniques but DCA and EB achieved the planning objective for the CTV with an inhomogeneity ranging from 2% to 11%. RA showed the best conformity, EB the worst. Contra-lateral breast and lung were spared by all techniques with mean doses <0.5 Gy (zero for protons). The ipsi-lateral lung received a mean dose <10% of that prescribed with photon beams and <2% with IMPT, increasing to 17% with EB. The heart, in left-sided breast tumors, received also the highest dose with EB. The skin was best protected with RA with a mean dose of 5.4 Gy and V_{15Gy} = 2.4%.

Conclusions: Boosting the tumor bed in early-stage breast cancer with optimized photon or proton beams may be preferred to EB especially for deep-seated targets. The marked OAR (i.e., ipsi-lateral breast, lung, heart, and skin surface) dose-sparing effect may allow for a potential long-term toxicity risk reduction and better cosmesis. DCA or RA may also be considered alternative treatment options for patients eligible for accelerated partial breast irradiation trials.

Breast-conserving surgery followed by whole breast radiation therapy (WBRT) and a boost to the tumor bed is the treatment of choice for most patients with stages I–II breast cancer. Not only are disease-free and overall survival rates after such treatment comparable with those of patients treated by mastectomy [1,2] but in addition breast-conserving therapy offers an obvious cosmetic advantage that may enhance quality of life and lead to less psychological and emotional treatment-related distress [3].

The rationale for boosting the tumor bed is based on the hypothesis that higher local control rates may be achieved if a higher dose of radiation is administered to the region of the breast bearing the greatest tumor burden [4]. Although the use of a tumor bed boost (10–20 Gy, depending on tumor size and surgical margins) is routine practice, there is no standard treatment delivery technique. Some authors recommend the use of interstitial implants but most studies report the use of electron beams (EBs) to boost the tumor bed [5,6]. Most frequently, single 9–12 MeV EB with 2–3 cm margin around the estimated tumor bed is used. Such energy range helps to adequately treat shallow targets inside the breast. Deep-seated tumors, however, may not adequately be treated with EB, though contemporary highly conformal photon beam techniques may be able to reduce the dose inhomogeneity within the target while optimally decreasing the dose to the surrounding non-target tissues.

The present study aimed to assess the potential dosimetric advantages and drawbacks of the following treatment techniques:

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photon beams (i.e., dynamic conformal arcs, DCA; fixed gantry intensity-modulated RT, IMRT; and RapidArc, RA) and protons (intensity-modulated beams with spot scanning, IMPT). More conventional approaches with conformal static fields with photons (3DC) or also single field EB techniques were considered in the study as "baseline" modalities, commonly available in any clinic.

Methods and materials

This study included fourteen patients (age range 34–75, median 54 years) who had received conservative surgery for early-stage unilateral breast cancer (six right-sided and eight left-sided tumors). Distal tumor margins were located $\geqslant$4 cm below the breast surface (i.e., deep-seated tumors) in all patients. Three patients presented with intra-ductal carcinoma, 7 patients with stage I, and 4 with stage II invasive carcinoma. All patients had negative surgical margins after lumpectomy. Tumor and target characteristics are summarized in Table 1.

The planning CT of the breast region in a free-breathing setting was performed postoperatively with the patient in treatment position (i.e., patient on a breast board, lying supine, and with the ipsi-lateral arm above the head), using a *Philips Tomoscan AV Helical CT scanner*. CT images were acquired in 5 mm slice intervals from the mandible through the lung bases. The anatomic information from the CT scan was used to define the target volume and normal structures at risk. The following organs at risk (OARs) were outlined: ipsi-lateral and contra-lateral breasts and lungs, heart, and the skin covering the ipsi-lateral breast (a 5-mm thick segment on the breast surface). In all cases surgical clips were placed by the surgeon (IR) surrounding the tumor cavity at the time of lumpectomy.

All patients were first treated with 6 MV photon beams (*Clinac 23-EX, Varian Medical Systems, Palo Alto, California, USA*) to the entire breast with two tangential fields. A total dose of 50 Gy in 25 daily fractions during 5 weeks was delivered. The boost clinical target volume (CTV) was defined as the area of architectural distortion inside the breast (i.e., tumor bed) surrounded by metallic seeds implanted around the resection cavity by the surgeon. All contouring was reviewed and approved by an experienced radiologist (AH). To account for treatment set-up uncertainties and breathing motion the boost planning treatment volume (PTV) was defined as a 1.0-cm expansion of the CTV. The prescribed dose was 16 Gy in eight daily fractions. The goal for this planning effort and for all techniques was to cover 100% of the CTV with $\geqslant$95% of the prescribed dose and to minimize the volume inside the CTV receiving >107% of the dose (ICRU definition).

Table 1
Tumor characteristics of the 14 patients included in this study.

Characteristics	*n*
Tumor site	
Left breast	8
Right breast	6
Proximal depth tumor (mm)	
Mean	7.0
Std dev.	5.7
Distal depth tumor (mm)	
Mean	53.9
Std dev	9.5
CTV (cc)	
Mean	30
Std dev	19
PTV (cc)	
Mean	101
Std dev	47

Std dev, standard deviation; CTV, clinical target volume; PTV, planning target volume.

Planning techniques

All treatment plans have been implemented on an Eclipse treatment-planning system (Varian Medical Systems, Palo Alto, USA) except for the dynamic conformal arc and the intensity-modulated techniques with photons that were planned on the iPlan4 treatment-planning system (*BrainLAB A.G., Heimstetten, Germany*).

Dynamic conformal arcs

Treatment is delivered with a micromultileaf collimator (mMLC) with 26 pairs of leaves, the central ones with a 3-mm width at the isocentre, allowing for dynamic field shaping around the PTV while the gantry rotates. The start and end of the arc were chosen according to optimization criteria and the need to spare the contra-lateral breast and OARs. DCA plans were computed using the pencil-beam algorithm implemented in iPlan4 [7–9]. All patients were planned with a single arc ranging from 210° to 250° (mean: 232.7°, standard deviation: 3°), except one patient with two arcs of 70° to avoid a high dose region.

Intensity-modulated radiotherapy with static gantry

Treatment plans were optimized with multiple fixed fields and fluence-based optimization with 4–5 fields per plan. For left-sided tumors, beam angles ranged from 300° to 160°, approximately evenly distributed over the range, whereas for right-sided tumors this range was 200° to 60°. Plans were calculated with the aforementioned pencil beam algorithm and optimized according to the method by Llacer [10].

RapidArc

Plans were calculated with the AAA algorithm [11] and optimized using the PROII algorithm, release 8.6 as described by Fogliata et al. [12]. A first set of plans was optimized with a single arc covering 360 degrees (RA-F) while a second set of plans (RA-P) was realized with single partial arcs, covering approximately 220 degrees of rotation around the target volume and avoiding direct entrance through the contra-lateral organs [13–15].

3D-conformal static fields

Multiple static fields (5 except 4 in one case) were used with a similar beam arrangement as in the IMRT plans with simple field conformation to the PTV. All static fields included an enhanced dynamic wedge (EDW) (except the central one in the cases with 5 fields). Plans were calculated with the pencil beam algorithm based on the work by Sturchi et al. [16,17].

Electron beams

The boost was planned with a single conformal portal. The beam energy was selected in order to comply with the dosimetric goal mentioned above. The entry angle was selected so that the entrance surface was approximately perpendicular to the beam central axis. Eight patients were planned with 20 MeV electron beam and six with 16 MeV, respectively. The dose distribution was computed with the Generalized Gaussian Pencil Beam model [18,19].

Proton beams

Intensity-modulated proton plans were obtained for a generic proton beam through a spot-scanning optimization [20,21]. The process consists of the simultaneous optimization of the weight of each individual spot (from any number of fields) inside a point cloud describing OAR and targets. Energy layers are determined in a pre-processing phase. The maximum energy available was 250 MeV with an energy spacing of the layers of 10 MeV. Spot spacing was set to 3 mm, circular lateral target margins were set to 5 mm, proximal margin to 5 mm and distal margin to 2 mm. In all cases a two-beam arrangement was adopted, both beams

having an incidence almost normal to the skin surface and being separated by about 100 degrees.

Two photon techniques used pencil beam algorithms (3D-conformal and IMRT) and two used the AAA algorithm (dynamic arcs and RapidArc). Admittedly, intrinsic differences between algorithms exist and might introduce some bias in the numerical analysis as discussed in a several papers [22–24]. This should therefore be borne in mind when interpreting the results has been mentioned above.

Tools for analysis

Quantitative evaluation of plans was performed by means of standard Dose–Volume Histogram (DVH). For PTV and CTV, the values of $D_{99\%}$ and $D_{1\%}$ (dose received by 99%, and 1% of the volume) were defined as metrics for minimum and maximum doses and consequently reported. To complement the appraisal of minimum and maximum dose, $V_{95\%}$ $V_{107\%}$ (the volume receiving at least 95% or at most 107% of the prescribed dose) were reported. The inhomogeneity of the treatment was expressed in terms of $D_{5\%}$–$D_{95\%}$. The conformity of the plans was measured with a conformity index, ($CI_{95\%}$: ratio between the volume receiving at least 95% of the prescribed dose and the volume of the PTV). For OARs, the analysis included the mean dose, the maximum dose expressed as $D_{1\%}$ and a set of appropriate V_X and D_Y values.

Average cumulative DVH for PTV, OARs and healthy tissue was built from the individual DVHs. These histograms were obtained by

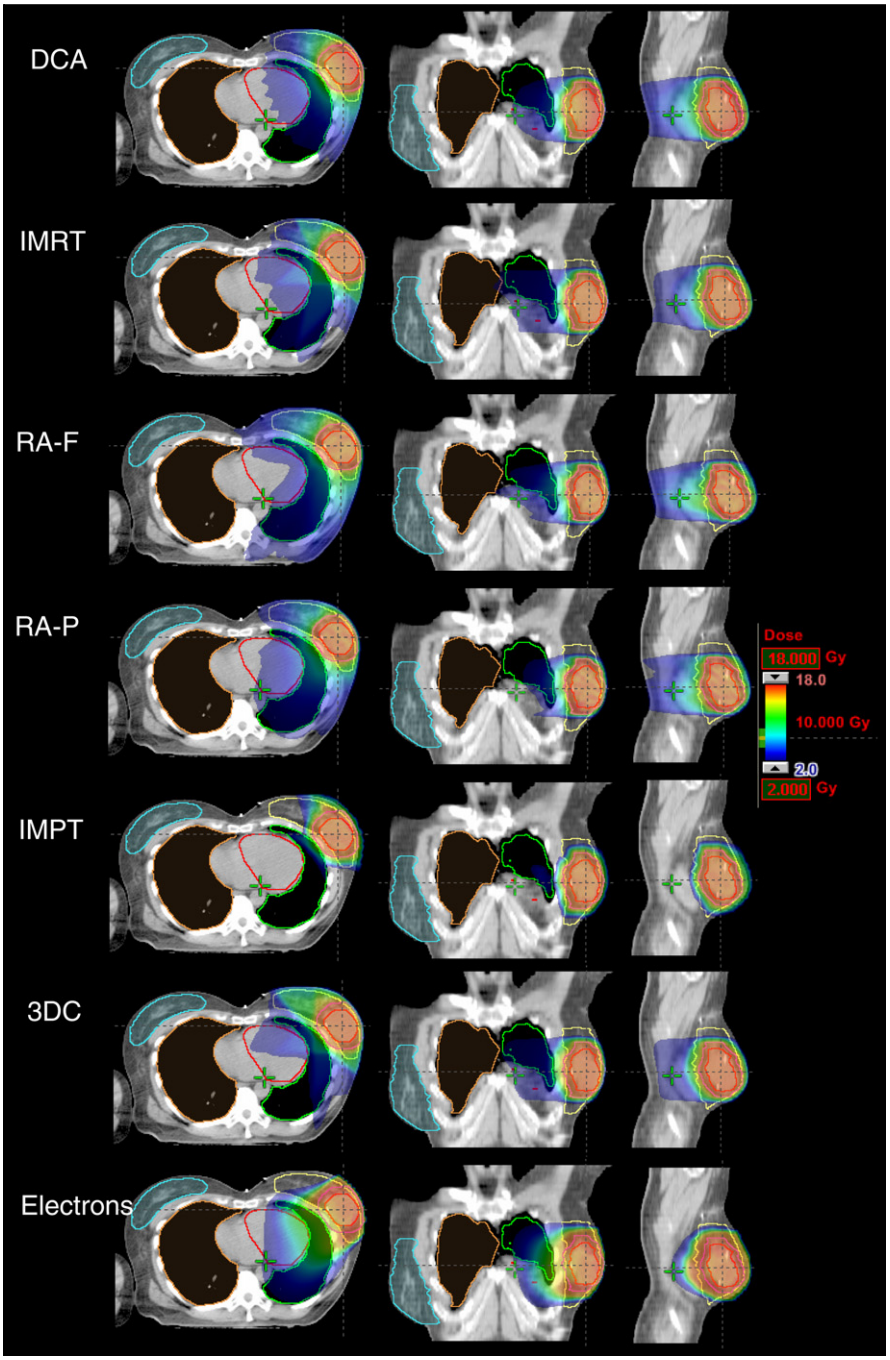

Fig. 1. Isodose distributions in axial, coronal and sagittal planes for one example case. Colour wash is cut between 2 Gy and 18 Gy. Also shown the overlay of CTV, PTV, breast and main organs at risk.

averaging the corresponding volumes over the whole patient's cohort for each dose bin of 0.05 Gy.

Results

Dose distributions are displayed for one patient in Fig. 1 with axial, coronal and sagittal views. Fig. 2 shows the average DVH plots for the CTV, PTV, OAR, and healthy tissue. Table 2 reports numerical findings from the DVH analyses on CTV, PTV and healthy tissue (integral dose), Table 3 on OARs. Data are presented as averages over the fourteen patients in the study and errors indicated inter-patient variability at 1 standard deviation level.

As presented in Table 2, all techniques, but DCA and EB, met the planning objectives for the CTV (within a fraction of a percent). EB plans, in addition, showed the lowest coverage and the largest inter-patient variability. Dose inhomogeneity ranged from 2% (IMRT) to 11% (DCA and electrons). $V_{107\%}$ was zero for all techniques except for DCA with a marginal over-irradiation. The conformity was relatively poor (ideal value of CI = 1) due to the relatively small target volume. The best conformity, however, was obtained with RA while the worst was achieved with 3DC (25% worse) or electron beams (50% worse).

No specific planning objectives were imposed to the PTV but IMRT and IMPT resulted in the best coverage with $V_{95\%} > 95\%$ followed by the group of RA and 3DC in the range of 93–95% and worst coverage was achieved with DCA and EB with $V_{95\%} < 90\%$.

Significant differences were observed for the ipsi-lateral breast according to the treatment technique (DCA, IMRT, RA, and IMPT versus 3DC and EB) regarding V_{15Gy}. All techniques produced an adequate sparing of the contra-lateral breast and lung with a maximum dose not exceeding 10% of the prescription and an average dose of <0.5 Gy. An even better sparing was obtained with RA-P in addition to EB and IMPT.

The mean dose to the ipsi-lateral lung ranged from 8% to 10% of the dose prescription for all photon techniques reached 17% for electrons and was <2% for IMPT. The same trend was observed for all other dose–volume parameters. When comparing the three-arc therapy techniques, the IMRT, and the static photon fields, RA-P succeeded to maximally decrease the dose to the lung. It should be noticed that known different levels of accuracy in the photon dose algorithms used for the study might weaken the quantitative relevance of the observed differences. Electrons on the contrary showed largely worse results while IMPT outperformed all other techniques.

All techniques enabled the delivery of similar mean and maximum doses to the heart (best with IMPT), with the exception of the EB plans for left breast-sided tumors with maximum doses exceeding 8 Gy and roughly 13% of the heart receiving doses >5 Gy. RA and IMPT plans provided the highest skin protection, DCA and IMRT provided intermediate skin sparing, while 3DC and EB were the worst techniques in protecting the skin.

Regarding the integral dose to healthy tissues, both RA plans showed the lowest volume irradiated to mean-low doses (e.g. V_{5Gy}) especially RA-P, while 3DC and EB resulted in the highest integral dose. IMPT plans succeeded to combine the best target coverage, the lowest dose to the OAR, and a 2–3× reduction in integral dose when compared to all other treatment techniques.

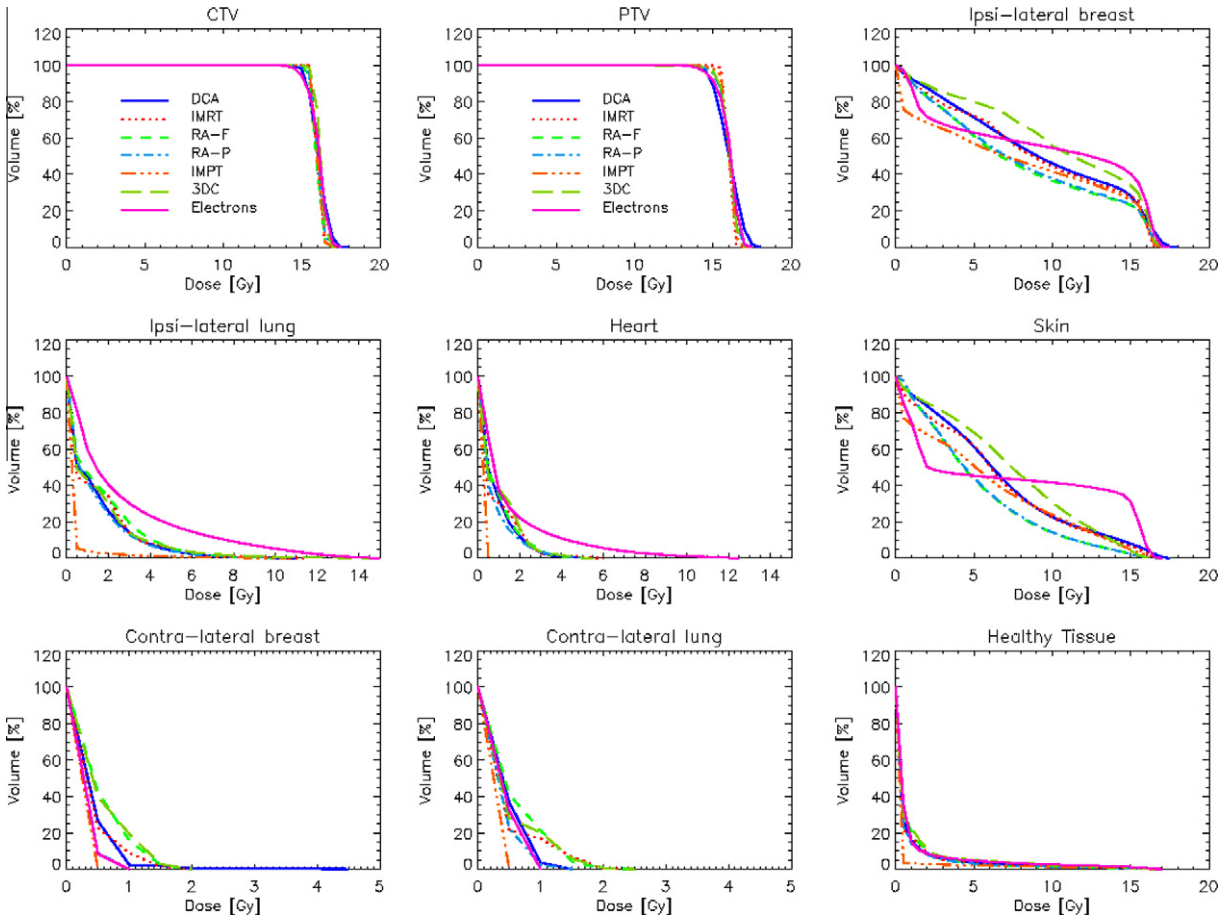

Fig. 2. Mean dose–volume histograms for CTV, PTV, organs at risk and healthy tissue (integral dose).

Table 2
Summary of DVH analysis for CTV, PTV.

	DCA	IMRT	RA-F	RA-P	IMPT	3DC	Electrons
CTV (30 ± 19 cm^3)							
Mean (Gy)	16.1 ± 0.1	16.0 ± 0.0	15.9 ± 0.1	16.0 ± 0.1	16.0 ± 0.1	16.2 ± 0.1	16.0 ± 0.1
$D_{1\%}$ (Gy)	17.1 ± 0.2	16.2 ± 0.1	16.5 ± 0.2	16.7 ± 0.2	16.6 ± 0.3	16.6 ± 0.1	17.0 ± 0.2
$D_{5\text{-}95\%}$ (Gy)	1.7 ± 0.2	0.3 ± 0.1	0.9 ± 0.1	1.0 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	1.7 ± 0.3
$D_{99\%}$ (Gy)	15.0 ± 0.3	15.8 ± 0.1	15.8 ± 0.1	15.8 ± 0.1	15.7 ± 0.1	15.3 ± 0.2	14.7 ± 0.6
$V_{95\%}$ [%]	94.5 ± 5.0	100.0 ± 0.0	99.6 ± 0.6	99.2 ± 1.4	100.0 ± 0.0	100.0 ± 0.1	91.7 ± 7.1
$V_{107\%}$ (%)	2.6 ± 3.8	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.1	0.3 ± 0.5	0.0 ± 0.1	0.8 ± 1.4
PTV (101 ± 47 cm^3)							
Mean (Gy)	16.0 ± 0.0	16.0 ± 0.0	16.0 ± 0.0	16.0 ± 0.0	16.0 ± 0.0	16.0 ± 0.0	16.0 ± 0.0
$D_{1\%}$ (Gy)	17.4 ± 0.3	16.4 ± 0.2	16.9 ± 0.2	16.9 ± 0.2	16.8 ± 0.3	16.7 ± 0.2	17.0 ± 0.2
$D_{5\text{-}95\%}$ (Gy)	2.5 ± 0.2	0.5 ± 0.1	1.5 ± 0.1	1.6 ± 0.2	1.0 ± 0.1	1.4 ± 0.1	2.0 ± 0.3
$D_{99\%}$ (Gy)	14.4 ± 0.3	15.5 ± 0.3	14.5 ± 0.4	14.3 ± 0.5	14.9 ± 0.6	14.0 ± 1.3	14.1 ± 0.5
$V_{95\%}$ (%)	83.4 ± 5.0	99.5 ± 0.9	94.5 ± 2.6	93.5 ± 3.1	97.6 ± 2.2	94.8 ± 2.7	88.7 ± 5.0
$V_{107\%}$ (%)	0.8 ± 1.3	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.4 ± 0.7	0.0 ± 0.0	0.0 ± 0.0
$CI_{95\%}$	2.2 ± 0.2	2.3 ± 0.1	2.0 ± 0.0	2.0 ± 0.1	2.1 ± 0.1	2.5 ± 0.4	3.0 ± 0.3

CTV, clinical target volume; PTV, planning target volume; DCA, dynamic conformal arc; IMRT, intensity-modulated radiotherapy; RA-F, full rapid arc; RA-P, partial rapid arc; IMPT, intensity-modulated proton therapy; 3DC, 3D-conformal treatment. $D_{x\%}$, dose received by the *x*% of the volume; $V_{x\%}$, volume receiving at least *x*% of the prescribed dose; CI, ratio between the patient volume receiving at least 95% of the prescribed dose and the volume of the total PTV.

Table 3
Summary of DVH analysis for organs at risk (including healthy tissue).

	DCA	IMRT	RA-F	RA-P	IMPT	3DC	Electrons
Healthy tissue (16,890 ± 4069 cm^3)							
Mean (Gy)	0.8 ± 0.3	0.8 ± 0.2	0.8 ± 0.2	0.7 ± 0.2	0.3 ± 0.1	1.0 ± 0.5	1.0 ± 0.3
V_{5Gy} (%)	3.6 ± 1.7	3.7 ± 1.3	3.1 ± 1.1	3.0 ± 1.1	2.1 ± 0.6	5.0 ± 2.7	4.7 ± 1.6
DoseInt	13,208 ± 6025	12,611 ± 4763	13,240 ± 4904	11,369 ± 4207	4774 ± 1971	13,590 ± 5109	15,685 ± 4955
Contra-lateral lung (1308 ± 397 cm^3)							
Mean (Gy)	0.4 ± 0.2	0.4 ± 0.1	0.5 ± 0.2	0.3 ± 0.1	<0.01	0.4 ± 0.2	0.3 ± 0.3
$D_{1\%}$ (Gy)	1.0 ± 0.4	1.7 ± 0.3	1.6 ± 0.4	1.0 ± 0.3	<0.01	1.7 ± 0.4	0.6 ± 0.2
V_{3Gy} (%)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0	0.0 ± 0.0	0.0 ± 0.0
Contra-lateral breast (385 ± 160 cm^3)							
Mean (Gy)	0.4 ± 0.2	0.3 ± 0.2	0.5 ± 0.2	0.2 ± 0.1	<0.01	0.5 ± 0.3	0.1 ± 0.2
$D_{1\%}$ (Gy)	1.1 ± 1.0	1.0 ± 0.6	1.5 ± 0.3	0.7 ± 0.2	<0.01	1.2 ± 0.4	0.2 ± 0.3
V_{3Gy} (%)	0.4 ± 1.4	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0	0.0 ± 0.0	0.0 ± 0.0
Ispi-lateral lung (1268 ± 256 cm^3)							
Mean (Gy)	1.3 ± 0.6	1.4 ± 0.6	1.6 ± 0.6	1.3 ± 0.5	0.2 ± 0.1	1.5 ± 0.6	2.7 ± 1.1
$D_{1\%}$ (Gy)	7.4 ± 1.9	7.6 ± 1.8	7.4 ± 1.7	7.1 ± 1.9	4.5 ± 2.8	8.8 ± 3.0	12.1 ± 3.1
V_{3Gy} (%)	14.2 ± 9.2	14.1 ± 8.8	19.6 ± 9.3	13.0 ± 6.2	1.8 ± 1.4	13.9 ± 8.4	30.2 ± 14.4
V_{10Gy} (%)	0.3 ± 0.3	0.4 ± 0.3	0.2 ± 0.3	0.2 ± 0.3	0.2 ± 0.3	0.8 ± 0.9	5.2 ± 3.8
Ipsi-lateral breast (441 ± 243 cm^3)							
Mean (Gy)	9.3 ± 1.5	9.1 ± 1.5	8.1 ± 1.2	8.2 ± 1.1	7.8 ± 1.8	10.5 ± 1.5	9.6 ± 1.7
$D_{1\%}$ (Gy)	17.2 ± 0.2	16.2 ± 0.1	16.7 ± 0.2	16.7 ± 0.2	16.6 ± 0.3	16.6 ± 0.2	16.8 ± 0.2
$D_{50\%}$ (Gy)	9.2 ± 2.5	8.8 ± 2.4	6.8 ± 1.7	7.2 ± 1.7	6.8 ± 3.3	11.2 ± 2.3	10.4 ± 4.6
V_{15Gy} (%)	28.2 ± 7.8	28.2 ± 7.5	23.2 ± 6.2	23.5 ± 6.1	26.0 ± 7.1	34.1 ± 7.7	40.4 ± 10.7
Heart (288 ± 65 cm^3)							
Mean (Gy)	0.8 ± 0.7	0.8 ± 0.7	0.8 ± 0.6	0.7 ± 0.7	<0.01	0.9 ± 0.7	1.5 ± 1.4
$D_{1\%}$ (Gy)	2.5 ± 1.6	2.7 ± 1.7	2.7 ± 1.4	2.5 ± 1.7	0.1 ± 0.1	3.0 ± 1.7	5.1 ± 4.7
V_{5Gy} (%)	0.2 ± 0.6	0.7 ± 1.8	0.1 ± 0.3	0.3 ± 0.9	0.0	0.3 ± 0.8	7.9 ± 11.5
Skin (80 ± 25 cm^3)							
Mean (Gy)	6.8 ± 1.4	6.5 ± 1.5	5.3 ± 1.1	5.4 ± 1.1	5.8 ± 2.0	7.5 ± 1.4	7.2 ± 1.6
$D_{1\%}$ (Gy)	16.0 ± 1.9	15.4 ± 1.8	14.6 ± 1.9	14.5 ± 1.9	15.3 ± 2.0	15.5 ± 0.5	16.4 ± 0.2
$D_{50\%}$ (Gy)	6.2 ± 1.3	6.2 ± 1.4	4.4 ± 1.0	4.5 ± 1.0	5.4 ± 2.5	7.5 ± 1.7	5.2 ± 5.1
V_{15Gy} (%)	8.0 ± 5.5	6.7 ± 5.9	2.4 ± 2.9	2.4 ± 3.1	4.8 ± 4.5	4.2 ± 2.6	31.1 ± 8.3

DoseInt, integral dose, [Gy cm^3 10^5] $D_{x\%}$, dose received by the *x*% of the volume; $V_{x\%}$, volume receiving at least *x*Gy of the prescribed dose.

Discussion

The present study addressed a comparative analysis of several techniques with photons, electrons, and protons, to irradiate the tumor bed after surgery in deep-seated early-stage breast cancer patients. The rationale for this investigation was to search for treatment techniques with better physical characteristics than conventional EB or 3DC photon beams.

Concerning electrons, the study design required the same dose prescription definition to be applied to all techniques. This is different from the usual prescription definition for electrons defined by the 100% or 90% as a minimum dose within the PTV. The strategy of applying the same prescription to all techniques is necessary to perform an appropriate quantitative comparison between competing treatments and is standard in planning investigations.

Single portal 9–12 MeV EB, with a 2–3 cm safety margin around the tumor bed has several limitations. Indeed, high EB energies are required to optimally cover deep-seated PTVs while overdosing the skin, the heart, the breast, and the underlying lung. However, in the *EORTC* Trial 22881–10882 the 10-year risk of severe fibrosis in the tumor bed region increased significantly with higher EB energies. [25,26]. Therefore, only superficial tumors may be optimally

treated with EB. Furthermore, it has been suggested that clinical delineation of the target volume based only on the surgical scar may frequently miss the target, thereby impairing local control [27]. Fiducial markers placed around the lumpectomy cavity can be easily identified with imaging techniques such as CT, thus helping to optimize treatment planning and dosimetry with potentially better local control and cosmetic results [28].

In our study the CTV was defined as the area of architectural distortion inside the breast surrounded by surgical clips around the resection cavity, and thereafter a 1.0-cm expansion was used for PTV definition, similar to the method described by Kirova et al. [29]. There is no wide agreement between tumor bed and PTV margin definition among authors [30]. For instance, CTV can be defined by expanding the excision cavity with 15 mm and subtracting from this expansion the tumor-free resection margin. The PTV would then be created by adding an extra 5 mm margin to the CTV as described by multiinstitutional Dutch guidelines [31].

Although not defined as an explicit planning objective, satisfactory PTV coverage was obtained with all technical alternatives though DCA was somewhat suboptimal with $V_{95\%}$ below 85% while a 93% was exceeded with all optimized photon techniques. Conformation (CI_{95}) was better with RA, followed by DCA. 3DC photons and EB showed the worst CI. The drawback of dynamic conformation techniques is mostly the risk of missing the target if suboptimal treatment set-up occurs or patient immobilization fails. Image-guided radiotherapy with respiratory gating or frozen respiration may be the best-proposed solutions to overcome this problem.

In addition to radiation-induced pneumonitis, worsening of preexisting cardiovascular lesions leading to death has been reported after radiation therapy for early-stage breast cancer, especially in women with left-sided and inner quadrant breast tumors [32–34]. Reducing the irradiated volume of lung and heart, without compromising the target volume irradiation, has the highest priority when planning radiotherapy for breast cancer. In the present study the mean dose to the ipsi-lateral lung was extremely low with all techniques (i.e.,<3 Gy for the lung). Nevertheless, boosting with photons allowed to reduce by a factor of ~2.6 the volume of the lung receiving >3 Gy compared to EB. Furthermore, for left breast-sided tumors, EB delivered the highest dose to the heart compared to all other photon-based and IMPT treatment techniques.

The incidence of permanent late skin changes (telangiectasia, fibrosis, and breast retraction) is related with high radiation doses to the skin, especially in areas with brisk acute moist reaction [35,36]. Micro-vessels in the upper portion of the dermis (1–5 mm), if damaged, are responsible for the cutaneous late effects observed after radiotherapy. In our study, the optimal skin dose-sparing effect obtained with RA improved the less efficient skin sparing effect with DCA or static field IMRT and most of all of EB. This skin dose reduction with RA may positively influence long-term cosmetic effects in these patients.

Few investigations exist in the literature comparing different external beam techniques with photons, electrons or protons. Most of the recent investigations addressed the issue of simultaneous integrated boost (SIB) or of intraoperative boost techniques. Both methods are not coherent with our investigations and therefore direct comparisons cannot be performed although a natural expansion of the present investigation would be the application of rotational techniques to SIB. Also not completely consistent with our study, the concept of Partial Breast Irradiation (PBI) is considered in several studies with both internal and external beams. Among these, Kainz et al. [37] and Moon et al. [38] investigated the role of Helical Tomotherapy also in comparison with other techniques. Moon proved that all photon-based approaches and protons achieved acceptable coverage of targets but at the price of higher dose exposure of lungs and heart for Tomotherapy, while Kainz proved that Tomotherapy might be adequate in sparing all structures with the exclusion of the contra-lateral breast.

A widely accepted alternative to EB for boosting the tumor bed has been, and still is, brachytherapy (BT) [39]. Low-dose rate BT with Ir-192 sources is most frequently recommended for patients with large breasts and/or deep-seated tumors [40]. This technique needs, however, a specialized infrastructure and hospitalization [41]. Furthermore, fibrosis, breast retraction, and suboptimal cosmetic results are not rare events after BT. MammoSite is a special BT technique based on an inflatable device conceived to fill the tumor cavity after lumpectomy in order to irradiate from inside the breast tissue surrounding the tumor bed [42]. However, this technique may have several drawbacks such as skin sparing limitations, a risk of leakage and/or rupture of the balloon, local pain during and after treatment, and a fair incidence of seroma and local infections [43,44].

In summary, boosting the tumor bed in early-stage breast cancer with optimized photon or proton beams may be preferred to EB in breast cancer patients with deep-seated targets. The marked OAR dose-sparing effect may allow for a potential long-term toxicity risk reduction and better cosmesis. Because of their wide availability, IMRT, DCA and RA may play a relevant role in the management of boosting the tumor bed after lumpectomy. IMRT may present a slight dosimetric advantage even though differences are within uncertainties of inter-patient variability and of different algorithms used for calculations. On the other hand, other arguments such as total treatment time and complexity of set-up with multiple static fields may recommend simpler approaches such as DCA and possibly RA. Management of moving organs was briefly addressed above and patient coaching should also be a part of the treatment preparation.

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Dr. L. Cozzi acts as Scientific Advisor to Varian Medical Systems and is Head of Research and Technological Development to Oncology Institute of Southern Switzerland, IOSI, Bellinzona.

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