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ORIGINAL ARTICLE

Respiratory gating for proton beam scanning versus photon 3D-CRT for breast cancer radiotherapy

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ABSTRACT

Background Respiratory gating and proton therapy have both been proposed to reduce the cardiopulmonary burden in breast cancer radiotherapy. This study aims to investigate the additional benefit of proton radiotherapy for breast cancer with and without respiratory gating.

Material and methods Twenty left-sided patients were planned on computed tomography (CT)-datasets acquired during enhanced inspiration gating (EIG) and free-breathing (FB), using photon three-dimensional conformal radiation therapy (3D-CRT) and scanned proton beams. Ten patients received treatment to the whole breast only (WBO) and 10 were treated to the breast and the regional lymph nodes (BRN). Dosimetric parameters characterizing the coverage of target volumes and the cardiopulmonary burden were compared using a paired, two-tailed Student's t-test.

Results Protons ensured comparable or better target coverage than photons in all patients during both EIG and FB. The heterogeneity index decreased from 12% with photons to about 5% with protons. The mean dose to the ipsilateral lung was reduced in BRN patients from 12 Gy to 7 Gy (RBE) in EIG and from 14 Gy to 6–7 Gy (RBE) in FB, while for WBO patients all values were about 5–6 Gy (RBE). The mean dose to heart decreased by a factor of four in WBO patients [from 1.1 Gy to 0.3 Gy (RBE) in EIG and from 2.1 Gy to 0.5 Gy (RBE) in FB] and 10 in BRN patients [from 2.1 Gy to 0.2 Gy (RBE) in EIG and from 3.4 Gy to 0.3 Gy (RBE) in FB]. Similarly, the mean and the near maximum dose to the left anterior descending artery (LAD) were significantly lower ($p < 0.05$) with protons in comparison with photons.

Conclusion Proton spot scanning has a high potential to reduce the irradiation of organs at risk and other normal tissues for most patients, beyond what could be achieved with EIG and photon therapy. The largest dose sparing has been seen for BRN patients, both in terms of cardiopulmonary burden and integral dose.

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Radiation therapy is a central component in the management of breast cancer reducing both the rate of local recurrence and improving the overall survival [1]. However, the cardiopulmonary radiation burden is a matter of concern due to the risk of heart and lung complications [2,3]. Nevertheless, it has been shown that respiratory gating can reduce the doses to organs at risk (OARs) in breast radiotherapy [4–6], either by increasing the OAR volume as in the case of the lungs or by increasing the anatomical separation between the OAR and the high dose region as in the case of the heart or the left anterior descending (LAD) artery. These reductions would ultimately translate into significant reductions of the iatrogenic side effects in breast cancer patients [7]. However, not all patients comply with the gating procedure and the separation between breast and heart varies from patient to patient. Consequently, some patients may not fully benefit from the potential reductions that can be achieved with respiratory gating in photon radiotherapy.

An alternative for reducing the cardiopulmonary burden is proton radiotherapy due to the finite range of the particles and virtually zero dose deposition beyond their Bragg peak. In particular, intensity-modulated proton therapy (IMPT) using scanned beams represents an interesting option to improve outcome for breast cancer patients [8–10]. However, proton radiotherapy is still an expensive technique in comparison to photon therapy and also quite sensitive to range and setup uncertainties or interplay effects caused by physiological motion [11]. Respiratory gating might be a useful technique to mitigate these factors, but comparatively few studies of its potential exist [12,13]. It is therefore the aim of this study to investigate the additional benefit of proton radiotherapy for breast cancer patients with or

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without respiratory gating in comparison to the corresponding photon techniques.

Material and methods

The study population consisted of 20 patients who received adjuvant radiotherapy for left-sided breast cancer after lumpectomy or mastectomy. The patients were part of a larger cohort retrospectively investigating the potential of audio-coached enhanced inspiration gating (EIG) in photon radiotherapy [14]. Ten patients received treatment to the whole breast only (WBO) and 10 were treated to the breast or the thoracic wall plus the regional lymph nodes (BRN) to have a representative cross-section of patients undergoing adjuvant radiotherapy. All patients were scanned without contrast on a computed tomograph (CT) with 3 mm slices during both EIG and free-breathing (FB). During CT scanning the patients were positioned on a standard breast board (Posiboard-2, Civco Medical Solutions) with both arms placed above the head. The real-time positioning management system (RPM™, Varian Medical Systems) was used to monitor breathing in case of EIG. During EIG the patients breathe deeper than normal, but unlike for deep inspiration breath-hold (DIBH) they do not perform normal breathing between the deep breaths. Also the deep breaths are shorter for EIG compared to DIBH. In this study the patients were audio-coached and inhale and exhale times of approximately 4–5 seconds were used. Image acquisition and irradiation were automatically turned on in an individually preselected part of the inhalation phase, based on the respiration amplitude. Targets and OARs were delineated as described in the original study [14] and reviewed by experienced radiotherapy oncologists according to RTOG guidelines. For WBO patients, the planning target volume (PTV) included the referenced clinical breast at time of CT and the apparent CT glandular breast tissue, with a margin of minimum of 10 mm around the glandular tissue. For BRN patients the PTV was defined either as the referenced clinical breast at time of CT or the part of the thoracic wall where the breast had been located, plus regional lymph nodes. For WBO patients, the PTV was cropped 5 mm from the skin surface. Where appropriate, clinical target volume (CTV)-T was defined as the site of the original tumor, approximately equivalent to a quadrant of the breast. The lungs, heart and LAD were defined as OARs. The delineation of normal tissues was performed with suitable window settings and when necessary was based on linear interpolation between adjacent slices. All volumes of interest were delineated on each EIG and FB CT datasets.

All patients were planned in Eclipse (Varian Medical Systems). For photon plans the analytical anisotropic algorithm was used for dose calculation as described by Edvardsson et al. [14]. For the WBO patients, the photon 3D-CRT plans were created using two tangential 6 MV fields. For dose homogenization, additional fields with lower field weight (6, 10 or 18 MV) were used. For BRN patients, antero-posterior fields were also used for irradiation of the regional lymph nodes. For the posterior field 10 or 18 MV photons were always used and an additional field with lower field weight, shielding for the lung, was added. The patients were subsequently planned with proton scanned pencil beam, using single field uniform dose (SFUD) and IMPT. A three-field technique previously described [10] with beam angles 20°, 60° and 340° has been used in each case. Creating the treatment plans, the goals were that 100% of the CTV-T volume should receive 95% of the prescribed dose, 100% of the PTV volume should receive 93% of the prescribed dose and the volume receiving 105% of the prescribed dose should be minimized, while keeping low the OAR doses. The normalization was 50 Gy (RBE) in 25 fractions as mean dose to the PTV, assuming a relative biological effectiveness (RBE) of 1.1 for protons [15].

Treatments plans were compared in terms of OAR radiation burden using dosimetric parameters representative for international recommendations or for radiobiological models [2,3]. Integral doses were also calculated from average doses and volumes of the delineated structures using volumetric mass densities of 260 kg/m^3 for lungs and 1060 kg/m^3 for other tissues [10].

Target coverage was evaluated in terms of the CTV of the original tumor or the PTV receiving at least 95% of the prescribed dose ($V_{95\%}$) or 93% ($V_{93\%}$) for the PTV. Dose uniformity in the target was determined from the ICRU-recommended [16] near minimum dose, $D_{98\%}$ (the dose to 98% of the volume), near maximum dose, $D_{2\%}$ (the dose to 2% of the volume) and mean dose to the PTV, D_{mean}, as the heterogeneity index (*HI*):

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{\text{mean}}}$$

Differences between parameters were tested for statistical significance using a paired, two-tailed Student's t-test.

Results

Both SFUD and IMPT improved homogeneity in CTV-T and PTV in comparison with photon 3D-CRT in all patients (Tables I, III, and V). Thus, HI decreased from 12% in photon plans to 8.1% and 5.2% in EIG proton plans (SFUD and IMPT, respectively) and to 7.0% and 4.6% in FB proton plans. The volume of the 105% dose hotspot in PTV ($V_{105\%}$) decreased from 3.0–3.5% in photon plans to less than 0.1% in proton plans. The PTV coverage with the 95% isodose was also similarly improved using protons, with best coverage in the IMPT plans.

With respect to OARs, the protons showed potential for decreasing the radiation burden compared to photons (Tables II, IV, and VI). Thus, the mean dose to the ipsilateral lung was reduced in BRN patients from 12 Gy with photons to 7 Gy (RBE) with protons in EIG and from 14 Gy to 6–7 Gy (RBE) in FB, while for WBO patients the values were about 5–6 Gy (RBE) and the difference was not significant. Similarly, the volume of the ipsilateral lung receiving doses above 20 Gy decreased with protons in BRN patients, but not in WBO patients. In contrast, the volume of the ipsilateral lung receiving doses above 10 Gy appeared to increase with protons in WBO patients from 13% to 23% in EIG and from 12% to 19% in FB, while it decreased for BRN patients, 30% versus 27–29% in EIG and 35% versus 23–27% in FB, respectively. It is also interesting to note that $V_{10\,\text{Gy}}$ for lung appeared to be higher in EIG proton plans than in FB proton plans.

Table I. Mean values ± one standard deviation for dosimetric parameters for target coverage for all the patients included in the study.

	Photons	SFUD	IMPT	p-Value SFUD vs. photons	p-Value IMPT vs. photons
Enhanced inspiration gating					
CTV-T					
D_{mean}	50.7 ± 0.6 Gy	50.2 ± 0.1 Gy (RBE)	50.1 ± 0.2 Gy (RBE)	0.0008	0.0004
$V_{95\%}$	99.3 ± 1.1%	100.0 ± 0.1%	100.0 ± 0.0%	0.0274	0.0232
PTV					
D_{mean}	50.0 ± 0.0 Gy	50.0 ± 0.0 Gy (RBE)	50.0 ± 0.0 Gy (RBE)		
$V_{95\%}$	94.5 ± 1.4%	97.7 ± 1.1%	99.3 ± 0.6%	<0.0001	<0.0001
$V_{93\%}$	98.3 ± 0.7%	99.0 ± 0.8%	99.7 ± 0.4%	0.0161	<0.0001
$V_{105\%}$	3.5 ± 2.7%	0.1 ± 0.1%	0.1 ± 0.1%	<0.0001	<0.0001
$D_{98\%}$	46.6 ± 0.3 Gy	47.3 ± 0.7 Gy (RBE)	48.4 ± 0.4 Gy (RBE)	0.0008	<0.0001
$D_{2\%}$	52.6 ± 0.4 Gy	51.4 ± 0.2 Gy (RBE)	51.0 ± 0.2 Gy (RBE)	<0.0001	<0.0001
HI	12.0 ± 0.9%	8.1 ± 1.8%	5.2 ± 1.1%	<0.0001	<0.0001
Free-breathing					
CTV-T					
D_{mean}	50.8 ± 0.5 Gy	50.2 ± 0.1 Gy (RBE)	50.1 ± 0.1 Gy (RBE)	0.0003	0.0001
$V_{95\%}$	99.3 ± 1.1%	100.0 ± 0.0%	100.0 ± 0.0%	0.0231	0.0205
PTV					
D_{mean}	50.0 ± 0.0 Gy	50.0 ± 0.0 Gy (RBE)	50.0 ± 0.0 Gy (RBE)		
$V_{95\%}$	94.1 ± 1.6%	98.4 ± 0.7%	99.7 ± 0.3%	<0.0001	<0.0001
$V_{93\%}$	98.3 ± 0.7%	99.5 ± 0.4%	99.9 ± 0.1%	<0.0001	<0.0001
$V_{105\%}$	3.0 ± 2.5%	0.0 ± 0.0%	0.0 ± 0.0%	<0.0001	<0.0001
$D_{98\%}$	46.7 ± 0.3 Gy	47.7 ± 0.4 Gy (RBE)	48.6 ± 0.2 Gy (RBE)	<0.0001	<0.0001
$D_{2\%}$	52.7 ± 0.4 Gy	51.2 ± 0.2 Gy (RBE)	50.9 ± 0.1 Gy (RBE)	<0.0001	<0.0001
HI	12.0 ± 1.3%	7.0 ± 1.1%	4.6 ± 0.7%	<0.0001	<0.0001

Table II. Mean values ± one standard deviation for dosimetric parameters for the irradiation of organs at risk for all the patients included in the study.

	Photons	SFUD	IMPT	p-Value SFUD vs. photons	p-Value IMPT vs. photons
Enhanced inspiration gating					
Heart					
D_{mean}	1.6 ± 0.8 Gy	0.3 ± 0.2 Gy (RBE)	0.3 ± 0.2 Gy (RBE)	<0.0001	<0.0001
$D_{2\%}$	11.0 ± 12.1 Gy	4.1 ± 2.8 Gy (RBE)	4.0 ± 2.8 Gy (RBE)	0.0136	0.0126
$V_{20\ Gy}$	0.9 ± 1.5%	0.1 ± 0.1%	0.1 ± 0.2%	0.0178	0.0177
$V_{5\ Gy}$	3.7 ± 3.7%	1.6 ± 1.3%	1.6 ± 1.3%	0.0205	0.0228
LAD					
D_{mean}	9.7 ± 9.6 Gy	3.0 ± 1.0 Gy (RBE)	3.1 ± 1.1 Gy (RBE)	0.0031	0.0034
$D_{2\%}$	21.9 ± 16.1 Gy	9.8 ± 2.6 Gy (RBE)	9.8 ± 2.8 Gy (RBE)	0.0021	0.0020
Ipsilateral lung					
D_{mean}	9.0 ± 3.9 Gy	6.7 ± 1.0 Gy (RBE)	6.4 ± 0.8 Gy (RBE)	0.0033	0.0022
$D_{2\%}$	45.4 ± 3.4 Gy	32.6 ± 1.7 Gy (RBE)	33.1 ± 2.0 Gy (RBE)	<0.0001	<0.0001
$V_{20\ Gy}$	16.4 ± 8.1%	11.9 ± 2.0%	10.6 ± 1.2%	0.0103	0.0026
$V_{10\ Gy}$	21.5 ± 10.0%	25.9 ± 4.7%	24.7 ± 3.6%	0.0105	0.0760
Integral dose	76.3 ± 46.6 Gy·kg	52.2 ± 19.6 Gy (RBE)·kg	52.3 ± 19.4 Gy (RBE)·kg	0.0009	0.0010
Free-breathing					
Heart					
D_{mean}	2.7 ± 1.2 Gy	0.4 ± 0.3 Gy (RBE)	0.4 ± 0.3 Gy (RBE)	<0.0001	<0.0001
$D_{2\%}$	25.4 ± 15.4 Gy	5.4 ± 3.4 Gy (RBE)	6.0 ± 3.8 Gy (RBE)	<0.0001	<0.0001
$V_{20\ Gy}$	3.1 ± 2.4%	0.3 ± 0.8%	0.2 ± 0.3%	<0.0001	<0.0001
$V_{5\ Gy}$	7.6 ± 4.2%	2.1 ± 1.5%	2.4 ± 1.6%	<0.0001	<0.0001
LAD					
D_{mean}	22.0 ± 11.7 Gy	3.9 ± 1.0 Gy (RBE)	4.0 ± 0.9 Gy (RBE)	<0.0001	<0.0001
$D_{2\%}$	41.8 ± 8.4 Gy	12.7 ± 3.0 Gy (RBE)	12.8 ± 3 Gy (RBE)	<0.0001	<0.0001
Ipsilateral lung					
D_{mean}	9.7 ± 5.1 Gy	5.7 ± 1.4 Gy (RBE)	5.5 ± 1.1 Gy (RBE)	0.0003	0.0003
$D_{2\%}$	43.7 ± 7.2 Gy	31.8 ± 2.0 Gy (RBE)	32.3 ± 2.2 Gy (RBE)	<0.0001	<0.0001
$V_{20\ Gy}$	18.2 ± 10.9%	11.0 ± 4.7%	9.4 ± 1.8%	0.0018	0.0006
$V_{10\ Gy}$	23.3 ± 13.2%	22.9 ± 6.9%	21.1 ± 4.4%	0.8489	0.3633
Integral dose	79.8 ± 48.1 Gy·kg	51.0 ± 17.9 Gy (RBE)·kg	50.6 ± 17.4 Gy (RBE)·kg	0.0006	0.0006

The largest potential for protons appeared to be the reduction of the cardiovascular burden comparatively with photons in all patients, even without EIG. Thus, the mean dose to the heart decreased by a factor of about four in WBO patients [from 1.1 Gy to 0.3 Gy (RBE) in EIG and from 2.1 Gy to 0.5 Gy (RBE) in FB] and more than 10 in BRN patients [from 2.1 Gy to 0.2 Gy (RBE) in EIG and from 3.4 Gy to 0.3 Gy (RBE) in FB]. Similarly, the mean and the near maximum dose to the LAD were significantly lower ($p < 0.05$) in proton plans in comparison with photon plans. The largest differences in parameters have been seen in BRN patients [mean dose decreased to about 3–4 Gy (RBE) with protons from 15–28 Gy with photons], while for WBO patients the differences between protons and photons were small in the case of FB plans [mean dose to the LAD of 4 Gy (RBE) versus 16 Gy] and almost disappeared in the case of EIG plans [mean dose to the LAD of 3 Gy (RBE) versus 5 Gy].

Protons could also reduce the integral dose in all patients to an average of about 51–52 Gy (RBE)·kg from 76 to 80 Gy·kg in

Table III. Mean values ± one standard deviation for dosimetric parameters for target coverage for the WBO patients included in the study.

	Photons	SFUD	IMPT	p-Value SFUD vs. photons	p-Value IMPT vs. photons
Enhanced inspiration gating					
CTV-T					
D_{mean}	50.7 ± 0.5 Gy	50.2 ± 0.1 Gy (RBE)	50.1 ± 0.2 Gy (RBE)	0.0085	0.0025
$V_{95\%}$	99.6 ± 0.7%	100.0 ± 0.1%	100.0 ± 0.0%	0.1295	0.1136
PTV					
D_{mean}	50.0 ± 0.0 Gy	50.0 ± 0.0 Gy (RBE)	50.0 ± 0.0 Gy (RBE)	0.0055	0.0388
$V_{95\%}$	95.2 ± 1.0%	98.2 ± 0.6%	99.7 ± 0.4%	0.0001	<0.0001
$V_{93\%}$	98.2 ± 0.7%	99.4 ± 0.3%	100.0 ± 0.0%	0.0008	<0.0001
$V_{105\%}$	2.0 ± 1.5%	0.0 ± 0.0%	0.0 ± 0.0%	0.0029	0.0029
$D_{98\%}$	46.6 ± 0.3 Gy	47.6 ± 0.3 Gy (RBE)	48.7 ± 0.1 Gy (RBE)	0.0001	<0.0001
$D_{2\%}$	52.4 ± 0.3 Gy	51.3 ± 0.1 Gy (RBE)	50.9 ± 0.1 Gy (RBE)	<0.0001	<0.0001
HI	11.7 ± 0.7%	7.5 ± 0.7%	4.4 ± 0.3%	<0.0001	<0.0001
Free-breathing					
CTV-T					
D_{mean}	50.7 ± 0.5 Gy	50.2 ± 0.1 Gy (RBE)	50.1 ± 0.1 Gy (RBE)	0.0050	0.0018
$V_{95\%}$	99.5 ± 0.8%	100.0 ± 0.0%	100.0 ± 0.0%	0.0953	0.0910
PTV					
D_{mean}	50.0 ± 0.0 Gy	50.0 ± 0.0 Gy (RBE)	50.0 ± 0.0 Gy (RBE)	0.0063	0.0140
$V_{95\%}$	94.9 ± 1.4%	98.5 ± 0.7%	99.9 ± 0.1%	0.0001	<0.0001
$V_{93\%}$	98.6 ± 0.5%	99.5 ± 0.4%	100.0 ± 0.0%	0.0014	<0.0001
$V_{105\%}$	2.1 ± 1.3%	0.0 ± 0.0%	0.0 ± 0.0%	0.0006	0.0006
$D_{98\%}$	46.8 ± 0.2 Gy	47.7 ± 0.3 Gy (RBE)	48.7 ± 0.1 Gy (RBE)	0.0001	<0.0001
$D_{2\%}$	52.5 ± 0.3 Gy	51.2 ± 0.2 Gy (RBE)	50.8 ± 0.1 Gy (RBE)	<0.0001	<0.0001
HI	11.5 ± 0.9%	6.9 ± 0.9%	4.2 ± 0.3%	<0.0001	<0.0001

Table IV. Mean values ± one standard deviation for dosimetric parameters for the irradiation of organs at risk for the WBO patients included in the study.

	Photons	SFUD	IMPT	p-Value SFUD vs. photons	p-Value IMPT vs. photons
Enhanced inspiration gating					
Heart					
D_{mean}	1.1 ± 0.3 Gy	0.3 ± 0.2 Gy (RBE)	0.3 ± 0.2 Gy (RBE)	<0.0001	<0.0001
$D_{2\%}$	5.4 ± 3.3 Gy	4.9 ± 2.4 Gy (RBE)	4.8 ± 2.2 Gy (RBE)	0.6240	0.5059
$V_{20\ Gy}$	0.3 ± 0.5%	0.1 ± 0.2%	0.1 ± 0.2%	0.2120	0.1837
$V_{5\ Gy}$	2.4 ± 2.7%	1.9 ± 1.1%	2.0 ± 0.9%	0.6117	0.6400
LAD					
D_{mean}	4.9 ± 2.4 Gy	2.8 ± 0.8 Gy (RBE)	2.9 ± 1.0 Gy (RBE)	0.0097	0.0116
$D_{2\%}$	13.9 ± 11.2 Gy	9.3 ± 3.2 Gy (RBE)	9.4 ± 3.5 Gy (RBE)	0.1967	0.1846
Ipsilateral lung					
D_{mean}	5.7 ± 2.0 Gy	6.0 ± 1.0 Gy (RBE)	5.9 ± 0.7 Gy (RBE)	0.5876	0.7308
$D_{2\%}$	43.9 ± 4.2 Gy	32.2 ± 1.7 Gy (RBE)	32.5 ± 2.2 Gy (RBE)	<0.0001	<0.0001
$V_{20\ Gy}$	9.5 ± 4.2%	10.8 ± 2.0%	9.9 ± 1.0%	0.3370	0.7768
$V_{10\ Gy}$	12.8 ± 5.1%	23.0 ± 4.6%	22.5 ± 3.1%	0.0001	0.0001
Integral dose	38.6 ± 8.9 Gy·kg	37.4 ± 6.1 Gy (RBE)·kg	37.6 ± 6.3 Gy (RBE)·kg	0.3930	0.4815
Free-breathing					
Heart					
D_{mean}	2.1 ± 0.8 Gy	0.5 ± 0.3 Gy (RBE)	0.5 ± 0.3 Gy (RBE)	0.0001	0.0001
$D_{2\%}$	18.0 ± 12.5 Gy	6.9 ± 3.6 Gy (RBE)	7.1 ± 3.5 Gy (RBE)	0.0191	0.0197
$V_{20\ Gy}$	2.0 ± 1.9%	0.3 ± 0.3%	0.3 ± 0.3%	0.0116	0.0127
$V_{5\ Gy}$	5.4 ± 2.8%	2.8 ± 1.7%	2.9 ± 1.6%	0.0249	0.0206
LAD					
D_{mean}	16.1 ± 10.1 Gy	3.8 ± 1.0 Gy (RBE)	3.9 ± 1.0 Gy (RBE)	0.0026	0.0029
$D_{2\%}$	39.8 ± 9.9 Gy	12.1 ± 1.9 Gy (RBE)	12.5 ± 2.4 Gy (RBE)	<0.0001	<0.0001
Ipsilateral lung					
D_{mean}	5.4 ± 2.5 Gy	4.9 ± 1.4 Gy (RBE)	4.9 ± 1.1 Gy (RBE)	0.4168	0.4638
$D_{2\%}$	40.2 ± 8.9 Gy	30.8 ± 1.4 Gy (RBE)	31.2 ± 1.0 Gy (RBE)	0.0055	0.0088
$V_{20\ Gy}$	8.9 ± 5.3%	8.6 ± 3.1%	8.3 ± 1.7%	0.8035	0.6870
$V_{10\ Gy}$	11.9 ± 6.4%	18.7 ± 6.2%	18.9 ± 4.8%	0.0020	0.0012
Integral dose	41.0 ± 10.0 Gy·kg	38.1 ± 6.0 Gy (RBE)·kg	38.3 ± 6.0 Gy (RBE)·kg	0.1483	0.1784

the photon plans. BRN patients accounted for most of this difference as for them the proton integral dose represented only 59% and 54% of the photon integral dose in the EIG and FB groups, respectively, illustrating the potential of normal tissue sparing with protons for this patient group. In comparison, proton integral dose in the WBO group was 97% and 93% of the corresponding photon integral doses in the EIG and FB groups, respectively.

Discussion

Respiratory gating has been proposed as a straightforward and cost-effective method to reduce doses to the lung, heart and LAD in photon radiotherapy [7]. It is also thought to reduce uncertainties caused by physiological motion for proton therapy. Nevertheless, the additional benefit of gating to proton therapy has been less explored and to our knowledge

Table V. Mean values ± one standard deviation for dosimetric parameters for target coverage for the BRN patients included in the study.

	Photons	SFUD	IMPT	p-Value SFUD vs. photons	p-Value IMPT vs. photons
Enhanced inspiration gating					
CTV-T					
D_{mean}	50.8 ± 0.7 Gy	50.2 ± 0.2 Gy (RBE)	50.2 ± 0.2 Gy (RBE)	0.0503	0.0525
$V_{95\%}$	98.9 ± 1.5%	100.0 ± 0.1%	100.0 ± 0.0%	0.0976	0.0908
PTV					
D_{mean}	50.1 ± 0.0 Gy	50.0 ± 0.0 Gy (RBE)	50.0 ± 0.0 Gy (RBE)	0.0003	0.0005
$V_{95\%}$	93.9 ± 1.5%	97.1 ± 1.3%	99.0 ± 0.5%	0.0009	<0.0001
$V_{93\%}$	98.5 ± 0.8%	98.5 ± 0.8%	99.4 ± 0.3%	0.8735	0.0071
$V_{105\%}$	5.0 ± 2.9%	0.1 ± 0.2%	0.1 ± 0.1%	0.0005	0.0005
$D_{98\%}$	46.7 ± 0.3 Gy	47.0 ± 0.9 Gy (RBE)	48.2 ± 0.4 Gy (RBE)	0.2271	<0.0001
$D_{2\%}$	52.8 ± 0.4 Gy	51.4 ± 0.3 Gy (RBE)	51.2 ± 0.2 Gy (RBE)	<0.0001	<0.0001
HI	12.3 ± 1.1%	8.8 ± 2.3%	6.0 ± 1.1%	0.0016	<0.0001
Free-breathing					
CTV-T					
D_{mean}	50.8 ± 0.7 Gy	50.1 ± 0.2 Gy (RBE)	50.1 ± 0.1 Gy (RBE)	0.0279	0.0263
$V_{95\%}$	99.1 ± 1.4%	100.0 ± 0.0%	100.0 ± 0.0%	0.1307	0.1231
PTV					
D_{mean}	50.0 ± 0.0 Gy	49.9 ± 0.0 Gy (RBE)	50.0 ± 0.0 Gy (RBE)	0.0003	0.0027
$V_{95\%}$	93.4 ± 1.4%	98.4 ± 0.8%	99.5 ± 0.3%	<0.0001	<0.0001
$V_{93\%}$	98.0 ± 0.8%	99.4 ± 0.4%	99.8 ± 0.2%	0.0003	<0.0001
$V_{105\%}$	4.0 ± 3.1%	0.0 ± 0.0%	0.0 ± 0.0%	0.0026	0.0026
$D_{98\%}$	46.5 ± 0.3 Gy	47.7 ± 0.4 Gy (RBE)	48.5 ± 0.2 Gy (RBE)	<0.0001	<0.0001
$D_{2\%}$	52.8 ± 0.4 Gy	51.2 ± 0.2 Gy (RBE)	50.9 ± 0.2 Gy (RBE)	<0.0001	<0.0001
HI	12.6 ± 1.3%	7.0 ± 1.3%	4.9 ± 0.8%	<0.0001	<0.0001

Table VI. Mean values ± one standard deviation for dosimetric parameters for the irradiation of organs at risk for the BRN patients included in the study.

	Photons	SFUD	IMPT	p-Value SFUD vs. photons	p-Value IMPT vs. photons
Enhanced inspiration gating					
Heart					
D_{mean}	2.1 ± 1.0 Gy	0.2 ± 0.2 Gy (RBE)	0.2 ± 0.2 Gy (RBE)	0.0001	0.0001
$D_{2\%}$	16.7 ± 15.1 Gy	3.2 ± 3.1 Gy (RBE)	3.2 ± 3.1 Gy (RBE)	0.0106	0.0108
$V_{20\ Gy}$	1.6 ± 1.9%	0.0 ± 0.1%	0.1 ± 0.2%	0.0283	0.0298
$V_{5\ Gy}$	4.9 ± 4.3%	1.3 ± 1.5%	1.3 ± 1.5%	0.0148	0.0169
LAD					
D_{mean}	14.6 ± 11.6 Gy	3.2 ± 1.2 Gy (RBE)	3.3 ± 1.2 Gy (RBE)	0.0089	0.0091
$D_{2\%}$	29.9 ± 16.8 Gy	10.2 ± 2.0 Gy (RBE)	10.3 ± 1.9 Gy (RBE)	0.0036	0.0037
Ipsilateral lung					
D_{mean}	12.3 ± 1.8 Gy	7.3 ± 0.6 Gy (RBE)	6.9 ± 0.6 Gy (RBE)	<0.0001	<0.0001
$D_{2\%}$	46.9 ± 1.3 Gy	32.9 ± 1.7 Gy (RBE)	33.6 ± 1.7 Gy (RBE)	<0.0001	<0.0001
$V_{20\ Gy}$	23.3 ± 3.8%	13.1 ± 1.3%	11.3 ± 0.9%	<0.0001	<0.0001
$V_{10\ Gy}$	30.1 ± 4.4%	28.8 ± 2.7%	26.8 ± 2.7%	0.2081	0.0064
Integral dose	114.1 ± 36.6 Gy·kg	67.0 ± 17.0 Gy (RBE)·kg	67.0 ± 16.7 Gy (RBE)·kg	<0.0001	<0.0001
Free-breathing					
Heart					
D_{mean}	3.4 ± 1.1 Gy	0.3 ± 0.3 Gy (RBE)	0.3 ± 0.3 Gy (RBE)	<0.0001	<0.0001
$D_{2\%}$	32.7 ± 15.1 Gy	4.0 ± 2.5 Gy (RBE)	4.8 ± 4.0 Gy (RBE)	0.0001	0.0001
$V_{20\ Gy}$	4.2 ± 2.5%	0.4 ± 1.1%	0.0 ± 0.1%	0.0010	0.0004
$V_{5\ Gy}$	9.7 ± 4.3%	1.5 ± 1.0%	2.0 ± 1.6%	<0.0001	0.0001
LAD					
D_{mean}	27.8 ± 10.5 Gy	4.1 ± 1.1 Gy (RBE)	4.1 ± 0.9 Gy (RBE)	<0.0001	<0.0001
$D_{2\%}$	43.8 ± 6.5 Gy	13.3 ± 3.9 Gy (RBE)	13.2 ± 3.5 Gy (RBE)	<0.0001	<0.0001
Ipsilateral lung					
D_{mean}	14.1 ± 2.4 Gy	6.6 ± 0.7 Gy (RBE)	6.1 ± 0.6 Gy (RBE)	<0.0001	<0.0001
$D_{2\%}$	47.2 ± 1.1 Gy	32.8 ± 2.1 Gy (RBE)	33.5 ± 2.5 Gy (RBE)	<0.0001	<0.0001
$V_{20\ Gy}$	27.8 ± 5.6%	13.5 ± 4.9%	10.4 ± 1.3%	0.0001	<0.0001
$V_{10\ Gy}$	35.1 ± 6.2%	27.1 ± 4.9%	23.3 ± 2.8%	0.0018	<0.0001
Integral dose	118.7 ± 37.9 Gy·kg	64.0 ± 16.4 Gy (RBE)·kg	63.0 ± 16.2 Gy (RBE)·kg	<0.0001	<0.0001

few other similar studies exist comparing intensity-modulated radiation therapy (IMRT) and IMPT plans for WBO patients [12,13]. The present study aimed to add to the existing knowledge by taking additional factors into account for the comparison, including the irradiation of the regional lymph nodes.

The results of our study have shown that proton irradiation could improve target coverage by reducing dose heterogeneity and the size of the coldspots and hotspots for breast cancer patients irrespective of the breathing phase used for the planning CT. These findings are in agreement with findings from other dose planning studies [9–12].

Protons can also reduce the normal tissue irradiation, both in terms of cardiopulmonary burden and integral dose, although the magnitude of the reduction appears to depend on the patient group. Thus, the largest reduction

potential has been seen for BRN patients for whom larger volumes of tissue are involved in photon treatments. This is quite an important result, as BRN patients have not been included in previous studies investigating the additional benefit of gating to proton therapy. For WBO patients, the dose reduction appears to depend on the organ and the irradiation technique. Thus, the mean dose to the ipsilateral lung in the proton plans for WBO patients was 4.9–6.0 Gy (RBE) in the present study, while Mast et al. reported 1.5–1.6 Gy (RBE) [12] and Lin et al. 0.9 Gy (RBE) [13]. Similarly, $V_{20\,Gy}$ was 8.3–10.8% in the present study, 2.5–2.8% in Mast et al. [12] and 0% in Lin et al. [13]. These differences could be explained to a certain extent by the irradiation technique used, with a single field approach in Lin et al. [13] where the main contributor of the dose to the lung is the distal penumbra and multi-field approaches in Mast et al. [12] and in the present study where the dose to the lung comes from a mixture of distal and lateral penumbras. Other differences between the studies originate in the prescribed doses that were 42.56 Gy (RBE) in 16 fractions in Mast et al. [12] and 50 Gy (RBE) in 25 fractions in the present study and in Lin et al. [13]. Last, but not least, differences could also have been caused by the optimization strategies employed. Better sparing of the normal tissues could be obtained if the criteria for target coverage were less prioritized, but this was not the intention in the present study. When comparing the photon plans in WBO patients, the relevant values were similar across studies. Thus, the mean dose to the ipsilateral lung was 5.4–5.7 Gy in the present study employing 3D-CRT versus 5.4–6.1 Gy [12] or 7.3 Gy [13] in photon IMRT. Similarly, $V_{20\,Gy}$ was 8.9–9.5% in the present study, 10.9–12.4% in Mast et al. [12] and 12.5% in Lin et al. [13]. When accounting for the differences in prescribed doses, it appears that the choice of 3D-CRT in the present study produced comparable or even better results than IMRT. This is in agreement with the results of the recent comparison between 3D-CRT and forward planned IMRT on a small group of patients showing similar values for the two techniques [17].

The cardiovascular burden showed a similar pattern, with considerable reduction in the proton plans compared to the corresponding photon plans, although for WBO patients in EIG plans the differences sometimes tended to disappear. Further evaluation of the expected complication rates for the heart was not attempted as the photon dose calculations in the present study were performed using the analytical anisotropic algorithm, while most model parameters are relevant for doses derived from pencil beam convolution calculations [18]. When comparing only WBO patients, the reported values are generally in agreement with those from other studies. Thus, mean dose to the heart in the present study was 1.1–2.1 Gy in photon plans versus 0.3–0.5 Gy (RBE) with protons, while the corresponding values in Mast et al. [12] were 1.5–2.7 Gy and 0.1–0.2 Gy (RBE) and in Lin et al. [13] 1.6 Gy and 0.0 Gy (RBE). Some differences between studies were observed for $V_{20\,Gy}$ and $V_{5\,Gy}$ for this organ, but these could have been caused by the optimization strategies used. A similar pattern of decreasing radiation with protons was also seen for the LAD. However, it has to be mentioned that the maximum doses to this structure in proton plans were below the levels which have been found to correlate with the development of cardiac complications [19].

Similarly, protons could also reduce the integral dose, with most reduction seen in BRN patients. This reduction of the integral dose with protons is expected to decrease the total risk for second cancers, although the distribution of the risks across tissues would depend on the corresponding dose volume histograms.

In proton radiotherapy concerns exist regarding the skin dose in light of worrying reports for worse cosmetic results [20,21]. Nevertheless, clinical studies reporting higher toxicity rates for protons employed one-field techniques with passively scattered proton beams and often hypofractionated schedules. In contrast our study used conventionally fractionated schedules and multiple fields with beam scanning as there are indications that these techniques may reduce skin dose and skin reactions [21,22]. Nevertheless, some field overlapping still occurs and the shape of depth dose curves indicate that protons do not offer the same level of skin sparing as has been seen for photon radiotherapy. However, due to limitations of the treatment planning system in calculating doses to the skin, a direct comparison was not attempted.

Another source of uncertainty is the proton RBE. The 1.1 value used in this study was derived from data relevant to the mid-position of a spread out Bragg peak, while it has been suggested that higher RBE values could be encountered towards the distal part of the range [15]. The difference might be higher for late reacting tissues receiving doses smaller than the nominal fractional dose [23,24] which is the case of the OARs in breast radiotherapy as they are situated in the distal part of the radiation fields. This would mean that the low dose radiation burden from proton therapy might be higher than predicted when a single RBE value is assumed, but quantifying this difference is beyond the purpose of the present study.

Other important sources of uncertainties for protons are the CT-calibration, the physiological motion of the breast during therapy and the resulting range uncertainties. However, Ares et al. [9] reported that the expected impact is quite small for a similar beam arrangement and that in IMPT plans the impact from breast motion with large amplitudes that cover both physiological movement and setup uncertainties is minimal. Furthermore, in the EIG case the expected impact of physiological motion is even smaller as large target movements are avoided by using only an individually preselected part of the inhalation phase.

The cross-comparison of EIG photon plans with FB proton plans confirms the potential of the latter radiation modality to increase plan quality, by improving target coverage and reducing normal tissue radiation burden. From this perspective it appears that protons could be an appealing alternative for those patients who cannot comply with the gating procedure or for whom respiratory gating cannot reduce enough the OAR doses.

In conclusion, the results of the present study indicate that protons have a very high potential to reduce the irradiation of OAR and other normal tissues for most breast cancer patients, beyond what could be achieved with EIG and photon therapy. The largest dose sparing could be expected for BRN patients, both in terms of cardiopulmonary burden and integral dose.

The large dose sparing makes protons an appealing treatment modality for breast cancer patients with coexisting cardiopulmonary and other morbidities that require approaches to reduce the risk for iatrogenic side effects.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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