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Original paper

Normal tissue sparing potential of scanned proton beams with and without respiratory gating for the treatment of internal mammary nodes in breast cancer radiotherapy

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ABSTRACT

Proton therapy has shown potential for reducing doses to normal tissues in breast cancer radiotherapy. However data on the impact of protons when including internal mammary nodes (IMN) in the target for breast radiotherapy is comparatively scarce. This study aimed to evaluate normal tissue doses when including the IMN in regional RT with scanned proton beams, with and without respiratory gating. The study cohort was composed of ten left-sided breast patients CT-scanned during enhanced inspiration gating (EIG) and free-breathing (FB). Proton plans were designed for the target including or excluding the IMN. Targets and organs-at-risk were delineated according to RTOG guidelines. Comparison was performed between dosimetric parameters characterizing target coverage and OAR radiation burden. Statistical significance of differences was tested using a paired, two-tailed Student's *t*-test. Inclusion of the IMN in the target volume led to a small increase of the cardiopulmonary burden. The largest differences were seen for the ipsilateral lung where the mean dose increased from 6.1 to 6.6 Gy (RBE) ($P < 0.0001$) in FB plans and from 6.9 to 7.4 Gy (RBE) ($P = 0.003$) in EIG plans. Target coverage parameters were very little affected by the inclusion of IMN into the treatment target. Radiotherapy with scanned proton beams has the potential of maintaining low cardiovascular burden when including the IMN into the target, irrespective of whether respiratory gating is used or not.

1. Introduction

The adjuvant loco-regional radiotherapy (RT) for breast cancer (BC) has contributed to a reduction of recurrence rate and improved disease-free survival rate [1], the absolute benefit being reduced due to unwanted doses to organs-at-risk (OAR), e.g., heart and lungs. This is also illustrated by the controversial topic on whether to include the internal mammary nodes (IMN) in the target due to the closeness to the heart and the associated risk for cardiac morbidity [2]. Drugs used in the systemic treatment settings, e.g., anthracyclines, trastuzumab, lapatinib, may also contribute to heart toxicity [3]. BC patients are a group of patients where the large majority is cured and additionally many become long-term survivors as the 5-years survival is well over 80% [4] and therefore radiation induced toxicity should be reduced to a minimum. Hence, much focus during the last years has been on minimizing the risk for normal tissue toxicity.

Proton therapy has the potential of reducing unwanted radiation bath to OAR through the physical properties of protons and several dose planning studies have explored their potential for BC [5–11]. Two newly published dose planning studies compared photon and proton plans for both free breathing and respiratory gating for patients candidates for local RT [12,13]. The studies showed that proton plans could significantly reduce doses to the heart and the left anterior descendent artery (LAD) even without respiratory gating. It should be noted that Ares et al. [6] showed in their dose planning study that the more complex the target the more obvious the benefit was from using protons. This may further expand the future indication for proton RT as several clinical studies have now shown that including the IMN in regional RT not only significantly improves disease free survival (DFS) but also indicates a better overall survival (OS) in stage I-III breast cancer [14]. However, so far there has been a shortage of data showing the impact of protons with or without respiratory gating when including the IMN. The aim of this study was to evaluate the effect on doses to normal tissue when including the IMN to the regional lymph

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Table 1
The effect for target coverage and OAR burden of including the internal mammary nodes (IMN) in the treated region for free breathing (FB) or enhanced inspiration gating (EIG); average ± standard deviation for all the patients included in the study.

		FB		EIG		P-values		
		w/o IMN	w IMN	w/o IMN	w IMN	FB w/o IMN vs FB w IMN	EIG w/o IMN vs EIG w IMN	FB w IMN vs EIG w IMN
PTV	$V_{95\%}$ [%]	99.5 ± 0.3	99.4 ± 0.4	99.0 ± 0.5	98.6 ± 0.6	0.8141	0.0009	0.0008
	$V_{93\%}$ [%]	99.8 ± 0.2	99.8 ± 0.2	99.4 ± 0.3	99.3 ± 0.3	0.2976	0.1751	0.0015
	$D_{98\%}$ [Gy (RBE)]	48.5 ± 0.2	48.4 ± 0.3	48.2 ± 0.4	48.0 ± 0.4	0.1526	0.0010	0.0005
	$D_{2\%}$ [Gy (RBE)]	50.9 ± 0.2	51.0 ± 0.2	51.2 ± 0.2	51.2 ± 0.2	0.0094	0.3252	0.0244
	HI [%]	4.9 ± 0.8	5.2 ± 0.8	6.0 ± 1.1	6.4 ± 1.3	0.0010	0.0066	0.0012
Heart	D_{mean} [Gy (RBE)]	0.3 ± 0.3	0.4 ± 0.3	0.2 ± 0.2	0.2 ± 0.2	0.0050	0.0546	0.0001
	$D_{2\%}$ [Gy (RBE)]	4.8 ± 4.0	6.2 ± 4.0	3.2 ± 3.1	2.6 ± 2.7	0.0021	0.0366	0.0001
	$V_{5\ Gy\ (RBE)}$ [%]	2.0 ± 1.6	2.6 ± 1.7	1.3 ± 1.5	1.0 ± 1.2	0.0055	0.0870	0.0001
LAD	D_{mean} [Gy (RBE)]	4.1 ± 0.9	3.8 ± 1.1	3.3 ± 1.2	2.6 ± 1.2	0.1576	< 0.0001	0.0198
	$D_{2\%}$ [Gy (RBE)]	13.2 ± 3.5	12.0 ± 2.3	10.3 ± 1.9	9.7 ± 2.4	0.2706	0.0352	0.0290
Lung ipsilateral	D_{mean} [Gy (RBE)]	6.1 ± 0.6	6.6 ± 0.7	6.9 ± 0.6	7.4 ± 0.6	< 0.0001	0.0033	< 0.0001
	$V_{20\ Gy\ (RBE)}$ [%]	10.4 ± 1.3	11.5 ± 1.7	11.3 ± 0.9	12.6 ± 1.2	< 0.0001	< 0.0001	0.0038
	$V_{10\ Gy\ (RBE)}$ [%]	23.3 ± 2.8	24.1 ± 3.3	26.8 ± 2.7	26.8 ± 3.4	0.0028	0.9876	0.0007
Lung contralateral	D_{mean} [Gy (RBE)]	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.0518	0.0782	0.5114
	$D_{2\%}$ [Gy (RBE)]	1.1 ± 1.1	1.2 ± 0.9	1.0 ± 0.9	1.3 ± 0.8	0.8602	0.1237	0.7183
Breast contralateral	D_{mean} [Gy (RBE)]	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.1	0.0 ± 0.1	0.6098	0.1156	0.2051
	$D_{2\%}$ [Gy (RBE)]	0.6 ± 0.5	0.5 ± 0.5	0.7 ± 0.6	0.6 ± 0.6	0.3846	0.1230	0.1028
Spinal cord	D_{mean} [Gy (RBE)]	0.3 ± 0.2	0.3 ± 0.2	0.9 ± 0.5	0.7 ± 0.5	0.0403	0.0041	0.0224
	$D_{2\%}$ [Gy (RBE)]	4.0 ± 3.2	3.4 ± 2.3	8.1 ± 5.2	6.9 ± 5.5	0.2775	0.1115	0.0754
Body	*ID [Gy (RBE)·kg]*	63.0 ± 16.2	64.6 ± 15.5	67.0 ± 16.7	64.7 ± 15.8	0.0099	0.0005	0.8635

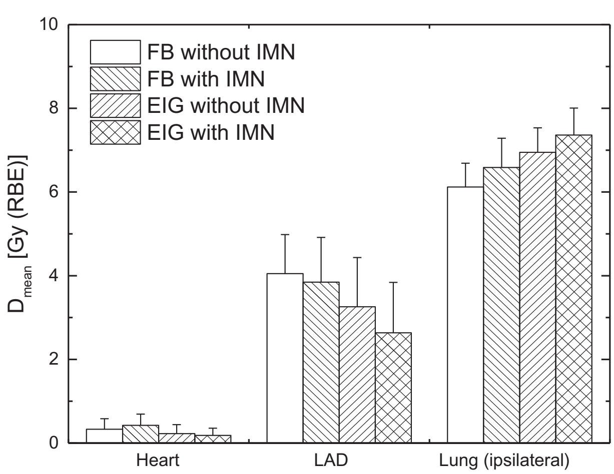

Fig. 1. Mean organ doses for the planning approaches considered (average ± standard deviation for all the patients included in the study).

nodes as a target for adjuvant loco-regional RT with scanned proton beams with and without respiratory gating.

2. Material and method

The study was performed on computed tomography (CT) datasets acquired for ten left-sided BC patients during enhanced inspiration gating (EIG) and free-breathing (FB) who were randomly selected from a larger cohort retrospectively investigating the potential of audio-coached EIG for photon treatment [15]. During EIG, the breathing was monitored using the real-time positioning management system (RPM™, Varian Medical Systems) and the patients were audio-coached to breathe deeply, with inhale and exhale times of approximately 4–5 s. The patients were positioned on a standard breast board (Posiboard-2, Civco Medical Solutions) with arms placed above the head and were CT-scanned without contrast with 3 mm slices during both EIG and FB. In EIG, image acquisition took place in an individually preselected part of the inhalation phase, based on the respiration amplitude.

The patients were planned for treatment to the breast or the thoracic wall plus the regional lymph nodes with or without the IMN. Targets and OARs were delineated according to RTOG guidelines. 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 5 mm medially and 5 mm laterally, and including the regional lymph nodes. A clinical target volume (CTV)-T was defined where appropriate, as the site of the original tumor, approximately equivalent to a quadrant of the breast. The lungs, heart and LAD were defined as OARs, reflecting the practice at our institutes. The delineation of OARs was performed on the CT images with suitable window settings and linear interpolation between adjacent slices was used when necessary. All volumes of interest were delineated on both EIG and FB CT datasets by the same user.

The patients were subsequently planned with proton scanned pencil beam in Eclipse (Varian Medical Systems), using intensity modulated proton therapy (IMPT) with spot sizes between 7 and 12 mm (full width at half maximum) as a function of energy. A three-field technique previously described [7,13] with fields angled at 20^0, 60^0 and 340^0 has been used and the plans were devised to deliver 50 Gy (RBE) in 25 fractions as mean dose to the PTV, assuming a relative biological effectiveness (RBE) of 1.1 for protons [16]. The goals of treatment planning followed the recommendations of the Swedish Breast Cancer Group (SweBCG) aiming to deliver 95% of the prescribed dose to 100% of the CTV-T, and 93% of the prescribed dose to 100% of the PTV, while keeping the OAR doses as low as possible [17]. According to these recommendations, no specific constraints were used for the LAD as there