Comparison of prone and supine positioning for breast cancer radiotherapy using REQUITE data: dosimetry, acute and two years physician and patient reported outcomes

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Objective

Most patients receive whole breast radiotherapy in a supine position. However, two randomized trials showed lower acute toxicity in prone position. Furthermore, in most patients, prone positioning reduced doses to the organs at risk. To confirm these findings, we compared toxicity outcomes, photographic assessment and dosimetry between both positions using REQUITE data.

Methods

REQUITE is an international multi-centre prospective observational study that recruited 2069 breast cancer patients receiving radiotherapy. Data on toxicity, health related quality of life (HRQoL) and dosimetry were collected, as well as a photographic assessment. A matched case control analysis compared patients treated prone (n=268) versus supine (n=493). Exact matching was performed for the use of intensity modulated radiotherapy, boost, lymph node irradiation, chemotherapy and fractionation, and nearest neighbour for breast volume. Primary endpoints were dermatitis at the end of radiotherapy, and atrophy and cosmetic outcome by photographic assessment at 2 years.

Results

At the last treatment fraction, there was no significant difference in dermatitis ($p=0.28$) or any HRQoL domain, but prone positioning increased the risk of breast oedema ($p<0.001$). At 2 years, patients treated in prone position had less atrophy ($p=0.01$), and higher body image ($p<0.001$) and social functioning ($p<0.001$) scores. The photographic assessment showed no difference in cosmesis at 2 years ($p=0.22$). In prone position, mean heart dose (MHD) was significantly lower for left-sided patients (1.29Gy vs 2.10Gy, $p<0.001$) and ipsilateral mean lung dose (MLD) was significantly lower for all patients (2.77Gy vs 5.89Gy, $p<0.001$).

Conclusion

Prone radiotherapy showed lower MLD and MHD compared to supine position, although the risk of developing breast oedema during radiotherapy was higher. At 2 years the photographic assessment showed no difference in cosmetic outcome, but less atrophy was seen in prone treated patients and this seems to have a positive influence on the HRQoL domain of body image.

Keywords: Breast cancer, prone position, radiotherapy toxicity, health-related quality of life, dosimetry

Introduction

Whole breast irradiation (WBI) after breast conserving surgery (BCS) results in better overall survival, but the benefit is partly undone by secondary heart disease and lung cancer.[1–4] Several methods to reduce organs-at-risk (OAR) dose have been developed including deep inspiration breath hold (DIBH), prone positioning and better planning techniques.[5] Usually, WBI is performed in supine position, but several studies have found better dosimetric results when treating in prone position, especially in patients with larger breasts.[6–9] A recent comparison of supine DIBH and prone position with free breathing found prone as the optimal position in 62% of patients, most notably for lung dose.[10] Besides better dosimetry, other advantages have been described, including lower rates of acute and late toxicity.[11–15] Two randomized trials compared the acute toxicity between both positions for large breasted women and both studies found a reduction in de rate of acute toxicity.[14,16] Of these two trails, one trial also reported a reduction in late toxicity, but no results on quality of life.[15]

REQUITE (www.requite.eu) is a large prospective multicentre cohort study of patients undergoing radiotherapy for breast, prostate or lung cancer.[17] Over 2000 breast cancer patients were included and prospective data collection was done using standardized case report forms. Very detailed information is available for each individual patient including, but not limited to, fractionation, treatment techniques, and breast volume. To confirm the advantages of prone positioning, we performed a matched case-control analysis using data from the REQUITE breast cohort.[17] Our analysis compares the differences between prone and supine positions for toxicity and patient reported health related quality of life (HRQoL), both acute and at 2 years. In addition, a dosimetric comparison was performed.

Materials and methods

Study population

REQUITE is an international multi-centre study using prospective standardized data collection with the aim to validate prediction models for late toxicity. From April 2014 until March 2017, the study recruited 4438 patients in 26 hospitals, of which 2069 were breast cancer patients (99% of target). The inclusion criteria were patients suitable for adjuvant radiotherapy (RT) after breast conserving surgery including patients receiving (neo-)adjuvant chemotherapy, with the last cycle at least 2 weeks before the start of WBI. All patients had planned potentially curable RT according to the local regimes. The choice of treatment position was based on the local treatment protocol. Exclusion criteria were mastectomy, prior RT in the same region, bilateral breast cancer, male breast cancer, partial breast irradiation, breast implants and bilateral breast cancer. Follow-up was for at least 24 months, with longer follow-up encouraged. More detailed

information on the REQUITE study and the patient characteristics of the breast cancer cohort can be found in a recent publication.[17]

Matching

Before matching, fractionation schedules were categorized as normofractionation (above 20 fractions), moderate hypofractionation (10-19 fractions), and strong hypofractionation (1-9 fractions). Each patient treated in a prone position was matched with 1 or, if possible, 2 patients treated in supine position, selected by means of a propensity scoring method without replacement. An exact method was used for lymph node irradiation (LNI), boost, intensity modulated radiotherapy (IMRT), chemotherapy and fractionation schedule, and a nearest neighbour method for breast volume.[18–21]

Data collection

For the analysis, three time-points of interest were chosen: baseline, end of RT (acute toxicity) and 24 months after the end of RT. At baseline, demographics, comorbidity and treatment data were collected, including dosimetry. The physician assessed toxicity was assessed at all three time-points using the following Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 terms: atrophy, oedema, skin ulceration, telangiectasia (inside and outside tumour bed), skin induration (inside and outside tumour bed), erythema, arm lymphoedema, pain and skin hyperpigmentation. Patient reported HRQoL data were collected at all 3 time-points using two standardized questionnaires from the European Organisation for Research and Treatment of Cancer (EORTC): the EORTC QLQ C30 [22] and breast specific QLQ BR23 [23] questionnaires. Since not all HRQoL questions are relevant in the comparison of prone and supine position, only the following scales were retained for the analysis: Physical Functioning, Social Functioning, Fatigue and Pain (QLQ C30), Body Image, Breast

Symptoms and Arm Symptoms (QLQ BR23). A photographical assessment of breast cosmesis was done before RT and after 2 years using the BCCT.core software.[24] Dosimetry data were collected centrally through standardized operating procedures. The dosimetric analysis contained data on mean heart dose (MHD), mean lung dose (MLD), maximum skin dose, and the skin volume receiving a dose of >107% of the prescribed dose.

Objectives

The goal of the current analysis was to compare prone and supine positioning for 3 domains: 1) toxicity and cosmesis, 2) HRQoL and 3) dosimetry. Toxicity and HRQoL were separated in acute (at the end of RT) and late reactions (2 years). Before any analysis, to account for multiple testing, three primary endpoints were chosen: 1) acute dermatitis, 2) atrophy at 2 years and 3) photographic assessment at 2 years. Desquamation and ulceration were only analysed in the acute setting. Atrophy, telangiectasia, fibrosis and hyperpigmentation were compared at 24 months. All toxicity measurements were dichotomized in no toxicity versus grade 1 or higher toxicity, except for acute dermatitis which was dichotomized between grade 1 or lower and grade 2 or higher toxicity (because 87% of all patients developed at least grade 1 dermatitis).

Statistical analysis

R studio version 3.2.6 was used for all statistical analyses and data visualisation. To compare acute toxicity, acute and 24-months HRQoL and 24-months photographic assessment, the difference between baseline scores and the score after RT were calculated. A deterioration was defined as a worsening of at least one grade for physician assessed toxicity or cosmesis, and as a negative change of at least 10 points for HRQoL.[25] For the 24 months toxicity assessment, the baseline was not

substracted. Cosmesis and toxicity outcomes were analysed using a Chi-Square test. HRQoL scores and dosimetry were compared using the Mann-Whitney U test. For the primary endpoints, an alpha level of 0.05 was chosen. To avoid type I errors due to the multiple tests, the Bonferroni correction was used for all secondary endpoints and for comparison of the baseline characteristics.

Results

Figure 1 gives an overview of the available data and the matching procedure, data was available for 2069 patients with missing data for one of the matching variables in 61 patients. In total, 2008 patients after BCS were matched, 292 were treated in prone and 1716 in supine position. After matching (exactly for LNI, boost, IMRT, chemotherapy and fractionation category, and nearest neighbour for breast volume) the number of patients was reduced to 761 (268 in prone and 493 in supine position). Table 1 shows the baseline characteristics before and after matching. Most patients treated in prone position were included in treatment centre A, whereas treatment centres B & C provided 45% of patients treated in supine position. After matching, statistically significant differences remain for age (57 vs 61 year, $p<0.001$), and treatment centre ($p<0.001$).

Toxicity and cosmesis

Figure 2 gives an overview of acute and 2-years toxicity. For acute toxicity, the proportion of patients experiencing at least one grade of deterioration is significantly higher for oedema (48% in prone vs 31% in supine, $p<0.001$). The primary endpoint of the proportion of patients with a deterioration (≥2 grades) for dermatitis is not statistically significant (16% vs 20%, $p=0.28$). At 2 years, the proportion of patients experiencing breast atrophy (primary endpoint) is significantly lower: 45% in prone and 56% in supine position ($p= 0.013$). For the secondary endpoints, the proportion of

patients with at least grade I toxicity is not significantly different between both treatment positions. The photographic assessment, included in Table 2, found no difference in the risk of worse cosmesis at 2-years compared to baseline, both for arms on the hips and arms up.

Health related quality of life

Figure 3 shows improvements or deteriorations of HRQoL from baseline, both acute and after 2 years. After RT, no significant difference in HRQoL between prone and supine position is found. At 2 years, body image ($p=0.001$) and social functioning ($p=0.001$) are significantly better in patients treated in prone position, with fewer patients experiencing a deterioration and a higher proportion of patient experiencing an improvement. The difference in body image compared to baseline is weakly correlated with the difference in social functioning (Spearman correlation coefficient $rs=0.34$).

Dosimetry

Figure 4 shows the MHD for left and right-sided patients and the ipsilateral MLD. On the one hand, the median MHD for left-sided patients is 1.29Gy in prone position and 2.10Gy in supine position ($p<0.001$). On the other hand, for right-sided patients median MHD is significantly higher in prone (0.60Gy vs 0.40Gy, $p<0.001$). A 3.11Gy lower median MLD is found for prone position, compared to supine position (2.77Gy vs 5.89Gy, $p<0.001$).

Discussion

The dosimetric advantages of prone positioning have been known for a long time, yet the application in daily clinical practice remains limited.[6–8,10,26] Other potential advantages, like reduced toxicity and improved HRQoL remain underreported. Only

one randomized controlled trial (RCT) has compared acute and late toxicity between prone and supine position in women with large breasts.[11–13] This RCT showed positive results at all three time-points (acute, 2 years and 5 years). The risk of acute toxicity, measured both at the end of WBI and 1 to 2 weeks thereafter, was lower for prone compared to supine positioning for the following toxicity domains: desquamation (or ulceration), dermatitis and oedema.[12] Recently a second single blind RCT confirmed the lower risk of desquamation after WBI in prone position.[14] In contrast, the present analysis of acute toxicity did not find any advantage for prone positioning. On the contrary, prone positioning resulted in a significantly higher risk of oedema. However, acute toxicity was only measured at last day of irradiation, while it is known the highest rates of acute toxicity are seen 2 to 8 weeks after irradiation, depending on fractionation.[27,28] Also, fraction of patients treated in prone positioning is radiotherapy centre dependent and most prone patients were included from a single institution, hence resulting in a risk of bias due to scoring differences between institutions. Finally, previous RCTs only allowed patients with large breast sizes, which is a risk factor for acute toxicity.[6,18,19,29] In contrast our analysis included patients of all breast sizes, like small breasted patients with a low risk of acute toxicity in both positions. A hypothesis for the increased risk of oedema is the increased gravitational pull in prone position. The higher rate of oedema did not result in any differences in the acute patient reported outcomes.

In contrast to the acute toxicity results, our 2-year results do confirm the lower risk of breast atrophy (45% vs 56%, p= 0.013) found in the only RCT reporting late toxicity, despite our analysis including patients with small breasts.[11] However, these findings were not confirmed in the photographical assessment. All RT centres took photographs which were assessed centrally using the BCCT.core software.[30] The

HRQoL items body image and social functioning were significantly better in prone position at 2 years. The better patient satisfaction with their body image could be a result of the lower risk of atrophy. Besides a weak correlation with body image (rs =0.34), the difference in social functioning might be due to other differences. These factors influencing HRQoL include age (supine patients are on average 4 years older), use of hormone therapy, cultures between treatment centres or other factors not used in matching, due to the choice for toxicity as the primary endpoints.[31,32]

The current analysis supports the reduced MHD and ipsilateral MLD in prone compared to supine position. [6–8,10] Median MHD for left-sided patients is 39% lower in prone compared to supine position. The 0,81Gy difference in MHD between both positions should lead to a 6 percent reduction in the increase in the rate of major coronary events after radiotherapy, according to Taylor et al.[2] In contrast to the MHD reduction for left-sided patient, prone resulted in a 0.2Gy higher median MHD for right sided patients. Nevertheless, the median MHD in both positions for right-sided patients is low (0.6Gy in prone, and 0.4Gy in supine position). Besides heart disease, a second cause radiation-related mortality in breast cancer patients is secondary lung cancer. A SEER analysis even found that for women treated between 1983 and 1992, there was evidence for secondary lung cancer mortality, but not for cardiac mortality.[4] Taylor et al. found an excess relative risk for lung cancer of 0.11 per Gy.[33] The risk is most prominent after the first decade. In prone-treated patients, the median ipsilateral MLD was more than halved from 5.89 to 2.77 Gy.

A recent analysis comparing prone free breathing with supine DIBH, found a dosimetric gain for prone position in 62% of patients.[10] The UK HeartSpare Stage IB Study also compared prone free breathing and supine DIBH, using a cross-over design in patients requiring left-sided WBI with an estimated breast volume of at least

750cm³.[34] The authors concluded that supine DIBH resulted in better heart sparing and higher set-up accuracy, and was preferred by patients. Nevertheless, prone resulted in a 10-fold decrease in ipsilateral MLD (3.73Gy vs 0.34Gy, $p<0.001$). Hence, the question becomes: should the focus be on MHD or MLD reduction, in particular for smokers?[4,33] The most promising technique is probably the combination of prone position with DIBH, a combination which has been described to be feasible and of great potential.[27,35,36] Unfortunately, data on DIBH were not collected in the REQUITE study.

Despite the advantages of prone position, implementation of the technique in daily clinical practice remains limited. Only 2 centres in the REQUITE study used the prone position on a regular basis. Potential reasons for the limited use of the prone position are the superiority of supine DIBH over prone free breathing for MHD (even though prone DIBH probably is the most optimal technique), the greater set-up errors in prone position resulting in larger PTV margins, the misconception that the benefits of prone position only apply to patients with large breast size and prone positioning being less comfortable for patients. Since prone positioning is more complex, training for the technologists is required, but after being accustomed to the technique, treatments can be given in 20 minutes or less.[34,37]

The main limitation of the current analysis is the overrepresentation of patients from one single treatment centre, contributing for 67% of all prone patients, which could have biased the results. The other 7 out of 9 main participating centres treated only a very limited percentage of patients in a prone position (less than one in ten). This could introduce bias due to differences in target volume contouring, field arrangement and treatment planning. Furthermore, physician assessed toxicity has been shown to be highly susceptible to interobserver variability.[38] Another limitation is the difference

in age, with supine-treated patients being on average 4 years younger. This discrepancy was accepted since literature does not show a strong connection between age and acute toxicity.[19,22,39] In contrast, age does impact HRQoL and late toxicity which could influence the results.[40] Nevertheless, scoring was done prospectively using standardized instruments at specific intervals and dichotomized to minimize inter-observer discrepancies.[17] Also, observer independent measurements were included like HRQoL and photographic assessment.

Our current findings indicate prone could be superior to supine positioning for late toxicity and dose to the organs at risk: it lowers the risk of atrophy at 2 years, improves body image at 2 years and lowers ipsilateral MLD and MHD for left-sided patients. Contrary to previous studies that reported lower acute toxicity, the REQUITE data indicate a higher risk of breast oedema at the end of RT. Overall, we endorse the use of prone positioning for WBI.

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Conflict of interest

Ghent University owns the patent application entitled Radiotherapy Board and Couch [WO2015144654A1] filed on March 25, 2014 for which LV is listed as inventor. The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

Raw data were generated by the REQUITE consortium. Derived data supporting the findings of this study are available from the corresponding author VV on request.

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Table 1. Baseline characteristics of patients treated in prone and supine positions, before and after propensity score matching.

Table 2. Photographic assessment at 24 months of deterioration of cosmesis compared to baseline for the photographs with a) both arms on the hips and b) both arms elevated.

Figure 1. CONSORT diagram.

Figure 2. Comparison of physician assessed toxicity between prone and supine positions. A) Proportion of patients with a deterioration in toxicity at the end of radiotherapy compared to baseline with one category (oedema, ulceration and breast pain) or two categories for dermatatis. B) Proportion of patients experiencing grade I or higher toxicity at 2 years after radiotherapy.

Figure 3. Proportion of patients, treated in prone or supine position, experiencing an improvement or deterioration of at least 10 points compared with baseline at A) the end of radiotherapy and B) 24 months after radiotherapy.

Figure 4. Mean heart dose, shown separately for left- and right sided breast cancer patients, and ipsilateral mean lung dose for all patients.

Table 1. Baseline characteristics

	Before matching			After matching		
	Prone	Supine	p-value	Prone	Supine	p-value
	N (%)	N (%)		N (%)	N (%)	
	N=292	N=1716		N=268	N=493	
Patient characteristics						
Age – years, mean	58	58	0.52	57	61	<0.001*
BMI – mean	27	26	0.86	27	27	0.63
Breast volume – cc, mean	775	811	0.23	799	782	0.64
Smoking			0.76			0.94
Never	171 (58)	955 (56)		153 (57)	282 (57)	
Former	86 (30)	499 (29)		80 (30)	140 (28)	
Current	35 (12)	240 (14)		35 (13)	61 (12)	
Unknown	0 (0)	22 (1)		0	10 (2)	
Treatment center						
Centre A	203 (70)	83 (5)	<0.001	179 (67)	21 (4)	<0.001*
Centre B	41 (14)	58 (3)		41 (15)	28 (6)	
Centre C	7 (2)	428 (25)		7 (3)	152 (31)	
Centre D	7 (2)	337 (20)		7 (3)	42 (9)	
Other centers	34 (12)	810 (47)		34 (13)	250 (51)	
Treatment characteristics						
Axillary surgery			<0.001*			0.03
Sentinel node biopsy	236 (81)	997 (58)		215 (80)	304 (62)	
Axillary lymph node dissection	13 (4)	114 (7)		13 (5)	26 (5)	
ALND + SNB	13 (4)	167 (10)		12 (4)	31 (6)	
No axillary surgery	14 (5)	149 (9)		14 (5)	42 (9)	
Unknown	16 (5)	289 (17)		14 (5)	90 (18)	

Chemotherapy			0.73		0.69
Neo-adjuvant	24 (8)	165 (10)		23 (9)	37 (8)
Adjuvant	65 (22)	366 (21)		47 (18)	78 (16)
No chemotherapy	203 (69)	1185 (69)		198 (74)	378 (77)
Hormone therapy			<0.001*		0.008
Tamoxifen	145 (50)	600 (35)		138 (51)	204 (41)
Aromatase inhibitor	88 (30)	705 (41)		77 (29)	195 (40)
None	56 (19)	403 (23)		50 (19)	92 (19)
Unknown	3 (1)	8 (0)		3 (1)	2 (0)
Anti Her2 directed therapy			0.01		0.17
Yes	35 (12)	131 (8)		27 (10)	36 (7)
No	252 (86)	1572 (92)		236 (88)	455 (92)
Unknown	5 (2)	13 (1)		5 (2)	2 (0)
Radiotherapy details					
Fractionation schedule			<0.001*		0.33
1 – 9 fractions	24 (8)	24 (1)		11 (4)	11 (2)
10 – 19 fractions	221 (76)	706 (41)		210 (78)	390 (79)
20 or more fractions	47 (16)	986 (57)		47 (18)	92 (19)
Lymph node irradiation			0.02		0.96
Yes	22 (8)	212 (12)		22 (8)	41 (8)
No	270 (92)	1504 (88)		246 (92)	452 (92)
Boost			0.75		0.59
Yes	200 (68)	1159 (68)		177 (66)	316 (64)
No	92 (32)	557 (32)		91 (34)	177 (36)
IMRT			<0.001*		0.54
Yes	198 (68)	803 (47)		175 (65)	311 (63)
No	94 (32)	913 (53)		93 (35)	182 (37)

Axillary lymph node dissection, BMI body mass index, ER estrogen receptor, IMRT intensity modulated radiotherapy, SNB sentinel node biopsy. * Significant after Bonferroni Correction $p<0.003$

Table 2. Photographic assessment at 24 months

	Prone (N= 198)	Supine (N= 390)	p-value
	n (%)	n (%)	
A) Arms on the hip			
No deterioration	148 (75)	275 (71)	0.50
1 category worse	37 (19)	89 (23)	
2 categories worse	12 (6)	26 (7)	
B) Arms up			
No deterioration	144 (73)	284 (73)	0.22
1 category worse	49 (25)	83 (21)	
2 categories worse	5 (3)	21 (5)	