The Journal of Breast Health
meme sağlığı dergisi

The Journal of Breast Health 2012 Vol: 8 • No: 2
Meme Sağlığı Dergisi 2012 Cilt: 8 • Sayı: 2

RESEARCH ARTICLE/ARAŞTIRMA YAZISI

PRELIMINARY ANALYSIS OF A RANDOMIZED CLINICAL TRIAL COMPARING SHOULDER-ARM MORBIDITY BETWEEN EARLY BREAST CANCER PATIENTS TREATED WITH SHORT COURSE IMAGE GUIDED RADIATION THERAPY AND CONVENTIONAL POST SURGERY RADIATION THERAPY

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KISA SÜRELİ İMAJ KILAVUZLUĞUNDA RADYOTERAPİ VE CERRAHİ SONRASI KLASİK RADYOTERAPİ İLE TEDAVİ EDİLEN ERKEN EVRE MEME KANSERLİ HASTALARDA OMUZ-KOL MORBİDİTESİNİ KARŞILAŞTIRAN RANDOMİZE BİR KLİNİK ÇALIŞMANIN ÖN ANALİZİ

ÖZET

Amaç: Omuz/kol morbiditesi radyoterapinin (RT) ve meme cerrahisinin bilinen bir yan etkisidir. Fakat omuz/kol morbititesi için RT tekniği seçiminin sonuçları açık bir şekilde tanımlanmamıştır. Bu çalışmada, erken meme kanserli hastaların omuz/kol morbiditesinin insidansı ve ayrıca meme kanserine bağlı kolun lenfödemi (MKBL) de muayene edildi ve konvansiyonel (KRT) ve kısa süreli kılavuz eşliğinde RT (KERT) tedavi tekniklerinin karşılaştırılması amaçlandı.

Hastalar ve Yöntem: 3 hafta postoperatif KERT ve 5-7 hafta KRT uygulanan hastaları randomize ettik. Tomo Breast çalışmasında olduğu gibi (onların sonlanım noktaları kardiak ve pulmoner yan etkiler idi). MKBL ve omuz/kol morbiditesi ve MKBL RT'yi takiben bir ile üç ay arasında fiziksel fonksiyon ve common terminology criteria yan etki skalası kullanılarak değerlendirildi. İstatistiksel yöntem olarak ölçümler için t-test ve kategorik veriler için ki-kare testi kullanıldı.

Bulgular: 91 hastanın analizi sonucu en az bir omuz/kol morbiditesi ölçümü yan etki skalasına göre skoru >% 80 deneyimli artış ve %18 oranında MKBL saptandı. Her iki kol hacmi anlamlı ölçüde arttı ve her iki kolda meydana gelen hareket kısıtlılığı anlamlı idi. Bununla birlikte iki tedavi grubunda MKBL insidansında veya omuz/kol morbiditesinde farklılık anlamlı bulunmadı.

Sonuç: Tedaviden sonra bir ve üçüncü aylarda kısa süreli KERT ile KRT karşılaştırıldığında omuz-kol morbiditesinde artış saptanmadı. Uzun süreli takip gerekmesine rağmen sonuçlar kısa süreli tedavi uygulamasını desteklemektedir. Karşı taraf ekstremite morbiditesinin tesadüfi bir bulgu olduğunu göstermek için daha fazla araştırma gerekmektedir.

Anahtar Sözcükler: klinik çalışmalar, rastgele, omuz, kol, morbidite, lenfödem, radyoterapi

ABSTRACT

Purpose: Shoulder/arm morbidity is a known complication of breast cancer surgery and radiotherapy (RT), but the consequences of choosing one RT technology over another for shoulder/arm morbidity are not clearly defined. In this work, we examine early breast cancer patients to compare the incidence of shoulder/arm morbidity, including breast cancer related lymphedema (BCRL) of the arm, between conventional RT and short-course, image-guided RT (IGRT) treatments.

Methods: We randomized patients between post-surgery IGRT over 3 weeks and conventional RT over 5 to 7 weeks, as part of the TomoBreast trial (whose primary endpoint was to assess pulmonary and cardiac toxicities). BCRL and shoulder/arm mobility were assessed prior to and between one and three months following RT, using physical function assessment and common terminology criteria for adverse events. Intention to treat analyses used the matched-pairs t-test for continuous measurements and the chi-squared test for categorical data.

Results: Analysis of the first 91 evaluable patients found that >80% experienced an increase in the adverse event score in at least one shoulder/arm mobility measurement, and 18% had BCRL symptoms. Arm volume on both sides increased significantly and significant impairment of movement occurred in both limbs. However, there was no significant difference in BCRL incidence or shoulder/arm mobility impairment between the treatment groups.

Conclusion: One to three months after treatment, short-course IGRT had not increased shoulder/arm morbidity compared with conventional RT. Although confirmation requires a longer follow-up, the results support the use of a short-course schedule. The incidental finding that morbidity affected the contralateral limb warrants further investigation.

Keywords: clinical trials, randomized, shoulder, arm, morbidity, lymphedema, radiotherapy

Gönderilme Tarihi: 05 Şubat 2012 • **Kabul Tarihi:** 28 Şubat 2012

Introduction

The position and the movement of the scapulae play an important role in shoulder mobility, and, following breast cancer surgery, scapulohumeral and scapulothoracic rhythms are significantly altered. Correspondingly, the most common (1) restrictive sequelae of surgical (2) and radiation therapy (RT) treatment of breast cancer are reduced shoulder range of motion (ROM) and breast cancer-related lymphedema (BCRL) on the operated side (3,4), and subsequent scapulothoracic dysfunction can cause pain and disability in the shoulder girdle (5). Functional impairment and pain in the shoulder girdle following breast cancer surgery can likewise be caused by muscle guarding, muscular and subcutaneous adhesion (6) and fibrosis, in particular of pectoral muscles and fascia (7). Vascular injury or damage to the joints (1), cell damage and promotion of chemical nociceptor stimuli via pro-inflammatory cytokines can also cause reduced ROM and pain (5). Shoulder-arm morbidity may occur early after surgery (8) or years later, and it can become chronic (1), thereby inducing severe and long lasting postural dysfunction (6), functional impairment (7) and decrease in quality of life (8). The extent of morbidity is largely determined by the type of surgery: breast conserving surgery (BCS) and sentinel lymph node dissection (SLND) have been reported to cause less severe shoulder/arm morbidity than total mastectomy (TM) and axillary lymph node dissection, respectively (1,7-12).

RT can also be administered in conjunction with breast cancer surgery as an adjuvant treatment, as it reduces the risk of local recurrence by approximately 33% and increases survival rates after TM. However, adjuvant RT can aggravate shoulder/arm morbidity (2), especially to the lymph node areas (8). Moreover, the incidence and severity of BCRL are increased in patients following RT to the lymph node areas, with a risk ratio of 4.6 relative to patients who did not receive adjuvant RT. This degree of risk is similar to that after treatment with ALND.

Besides causing shoulder/arm morbidity, RT can also lead to the impairment of shoulder mobility, via reduced flexion, external rotation and abduction (1,5,6). However, a recent study by Crosbie et al. (2) concluded that there is a lack of consensus in the literature as to whether RT is major cause of shoulder girdle dyskinesia or whether this dyskinesia leads to further impairment and pain. RT does not cause direct damage to the lymph vessels or lymph nodes over the short term, but it does cause sclerosis of skin, which may obstruct lymph flow and slow down the regeneration and neoformation of lymph vessels (13-16).

As RT technology has advanced, the sequelae resulting from long-term irradiation have generally become less severe (1). Image-guided radiation treatment (IGRT) has decreased the dose of radiation delivered to vital organs relative to conventional RT (17). It might also be expected that IGRT offers an advantage regarding shoulder/arm morbidity. IGRT can be administered in a short course, as short-course RT is an acceptable alternative to conventional RT in terms of efficacy (18-20). However, a larger dose of radiation is delivered per fraction in short-course than in conventional RT, and it has been argued that minor changes in fractionation and dose distribution could be associated with large variations in the risk of developing shoulder/arm morbidity (1,7). Therefore, there is concern that short-course RT could increase the risk of shoulder/arm morbidity compared with conventional RT, and that this might thereby negate the advantages of RT overall.

The TomoBreast randomized, controlled, single-center trial was initiated to investigate pulmonary and cardiac toxicities in women with early primary breast cancer following post-surgical conventional RT or short-course IGRT. In this paper, we describe secondary outcomes of the trial, related to lymphatic and musculoskeletal complications of the upper body. Specifically, we describe the effect of short-course IGRT and conventional RT on BCRL, shoulder/arm mobility and scapula positioning one to three months after the completion of RT, in both the operated and the contralateral arm.

Methods

Selection of patients

The study population was women who participated in the TomoBreast clinical trial, which was approved by the institutional ethics board of the UZ Brussel (ClinicalTrials.gov registration NCT00459628). The trial recruited women aged 18 years or older, presenting with a primary breast carcinoma (stage pT1-3N0M0 or pT1-2N1M0), with pathological nodal status assessed by ALND or by SN. The breast tumors had been completely resected by TM or by BCS and the women were to receive post-surgical RT. Enrollment into the full trial took place between June 2007 and August 2011; for this report we included all evaluable patients who were enrolled between the trial start date and October 1 2010. Women who provided written informed consent were randomly allocated to the control or experimental group by computer randomization balanced by nodal status, type of surgery, and chemotherapy sequence using Efron's biased coin design.

In the control treatment group, a dose of 50 Gy was delivered in 25 fractions over 5 weeks to the chest wall using tangential photon fields, and to the supraclavicular, infraclavicular and axillary nodes in case of pN1 status, using an anterior field matched to the tangential fields. BSC patients received an additional boost of 16 Gy in 8 fractions over 2 weeks to the initial tumor bed using a direct electron field.

In the short course IGRT treatment group, a dose of 42 Gy was delivered in 15 fractions over 3 weeks to the chest wall in case of TM or the whole breast in case of BCS, and to the supraclavicular, infraclavicular and axillary nodes in case of pN1 status, using the IGRT system Tomotherapy®. Patients who had BCS received a simultaneous integrated boost of 9 Gy delivered during the same 15 fractions. Figure 1 summarizes the trial's design.

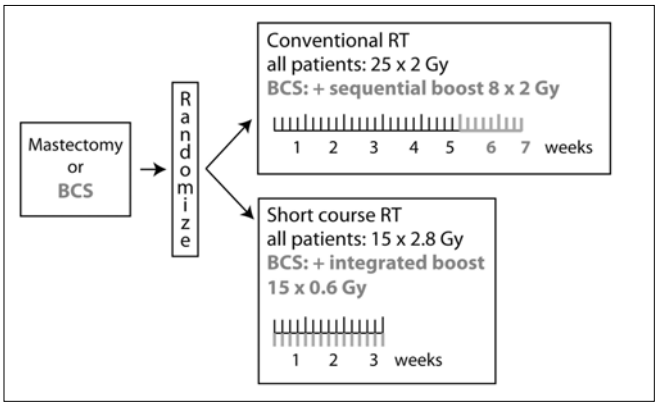

Figure 1. TomoBreast flowchart.

Physical therapy assessment

Assessments were made by a physical therapist prior to RT (baseline evaluation) and 2 ± 1 months after the completion of RT (first follow-up). An assessment was also planned at 3 years, but this is not included in this report.

Baseline patient characteristics and clinical data recorded during the first physical function assessment were the patient's age, weight and height, the chemotherapy and type of surgery received, the side that received the operation, and the dominant side.

For the physical assessment of BCRL, we computed the volume of both arms of each patient from circumferential measurements at 5 locations, using the mean of the frustrum sign and the disc model method.

For the physical assessment of shoulder mobility, we recorded the following measurements with a goniometer (2,6-8,21-23):

1) The maximum range of active forward elevation of the arm (*anteflexion*).
2) The maximum range of active backward elevation of the arm (*retroflexion*).
3) The maximum range of active lateral elevation of the arm (*abduction*).
4) The maximal functional *endorotation* measured by counting the vertebrae between C7 and the most cranial vertebra the patient could reach with her thumb on her back.
5) The *scapular distance* (Lateral Scapular Slide Test), measured as the distance between the spine and the angulus inferior of the scapulae, with the arms elevated 90° in the scapular plane (2,5,11).

With regards to these five measurements, signs of shoulder mobility impairment are indicated by decreased absolute values of abduction, retroflexion, and anteflexion, and by increased values of endorotation and scapular distance.

For the subjective assessment of BCRL, we collected patients' subjective arm symptoms during the physical evaluation. A score of 1 was recorded when any of the following subjective symptoms was present in the operated arm/hand: heaviness, swelling, fatigue, warmth, burning, pain, or when actions required more effort. A score of 0 was recorded when no subjective symptoms were reported (7-9,12,24,25).

To score shoulder/arm morbidity by adverse event grade rather than continuous measurement, we used the common terminology criteria for adverse events, version 3 (CTCAE, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). Grades 1, 2 and 3 adverse BCRL events were defined as 5 - 10%, >10 - 30%, and >30% inter-limb discrepancies in volume, respectively, where inter-limb discrepancy was computed as percent volume difference (PVD = 100 * [volume of affected arm - volume of unaffected arm] / [volume of unaffected arm]). Grades 1, 2, 3, and 4 adverse event related to the functional impairment of shoulder mobility were defined as decreases in ROM (anteflexion, retroflexion and abduction) ≤25%, >25 - 50%, >50 - 75% and >75% from baseline, respectively. In addition, grades 1, 2 and 3 adverse weight gain events were defined as gains of 5 - <10%, 10 - <20%, and ≥20% from baseline, respectively. Grades 1, 2 and 3 weight loss were defined as loss of 5 - <10%, 10 - <20%, and ≥20% of baseline, respectively.

Statistical analysis

The data were verified on a case-by-case basis to identify inconsistencies. Histogram distributions of the measurements were inspected for outliers. A comparison of the evaluable patients' baseline characteristics according to the treatment group was made using Pearson's chi-squared test for contingency tables. Univariate comparisons of continuous measurements according to the treatment group used Welch's t-test to make allowances for unequal standard deviations. Univariate comparisons of pre-RT and post-RT measurements used the matched pairs t-test. To take into account the small number of patients, we pooled all post-RT increases in grade of adverse events into a single group of patients who experienced any increase adverse event grade relative to baseline, versus no increase in adverse event grade relative to baseline. For all analyses, superiority was based on 2-sided P values <0.05.

All statistical computations used JMP v. 9.0.2 (SAS Institute, Cary NC, USA).

Results

Out of 106 patients who participated to the TomoBreast trial between June 14, 2007 and October 1, 2010, 93 received shoulder-arm physical function assessments at baseline and 2 ± 1 months post-RT. One patient had bilateral breast surgery and received bilateral RT, and a further patient had a baseline weight of 150 kg, whereas the weight range of the other patients was 42 - 102 kg. These two patients were excluded, leaving 91 patients available for the analyses. Four cases of physical measurement values were recoded as missing: one patient's scapular distance could not be measured due to lifelong contralateral arm paralysis, another patient was confined to a wheelchair at the time of pre-RT

Table 1. Patients' characteristics.

		Conventional RT	*Short course IGRT*	
	n	**%**	**%**	***p***
Age				0.158
< 50 years old	30	40.0	60.0	
≥ 50 years old	61	55.7	44.3	
Weight pre RT				0.391
< 70 kg	44	43.2	56.8	
≥ 70 kg	30	53.3	46.7	
BMI pre-RT				0.556
< 25 kg/m^2	36	44.4	55.6	
≥ 25 kg/m^2	35	51.4	48.6	
Arm symptom pre RT				0.904
no	62	48.4	51.6	
yes	18	50.0	50.0	
Time interval				0.042
< 16 weeks	53	41.5	58.5	
≥ 16 weeks	38	63.2	36.8	
Chemotherapy				0.251
no	48	56.3	43.8	
yes	43	44.2	55.8	
Type of surgery				0.429
BCS + SN	45	53.3	46.7	
TM + SN	9	66.7	33.3	
BCS + ALND	13	53.9	46.2	
TM + ALND	24	37.5	62.5	
Op. side dominant				0.830
no	49	49.0	51.0	
yes	39	51.3	48.7	
RT regional nodes				0.328
no	63	54.0	46.0	
yes	28	42.9	57.1	

RT: radiation treatment. **IGRT:** image guided radiation treatment. **BMI:** body mass index. **Op:** operated. **BCS:** breast conserving surgery. **TM:** mastectomy. **SN:** sentinel lymph node biopsy. **ALND:** axillary lymph node dissection.

assessment and measurement of retroflexion was therefore impossible, and two further patients had pre-RT measurements of retroflexion exceeding 90°.

Table 1 summarizes the patients' characteristics according to treatment group of the evaluable patients. The two groups were well balanced with regard to age, weight, body mass index (BMI), subjective arm symptoms, type of surgery, and surgery on the dominant arm side, chemotherapy, and radiotherapy to the regional lymph nodes. The time interval between assessments was significantly shorter in the short-course IGRT group because, by design, this group received a shorter course of RT. Baseline pre-RT physical function measurements were similarly well balanced between the two treatment groups (Table 2), and none of the baseline measurements showed a significant difference between the treatment groups, either on the operated side or for the contralateral side (data not shown). The inter-limb PVD at baseline was close to zero in all patients, indicating that there were no patients with BCRL prior to RT in either the conventional RT or the short-course IGRT group (data not shown).

Table 2 shows the mean values for changes in the physical function measurements of BCRL and shoulder/arm mobility that occurred between the pre-RT and the post-RT assessments for all patients, regardless of treatment group. Measurements of the

Table 2. Shoulder/arm changes from pre RT to post RT.

		Pre RT		Post RT		Difference Post - Pre		
Side	***Measurement***	***Mean***	***SE***	***Mean***	***SE***	***Mean***	***SE***	***p diff***
Operated side	Arm volume (ml)	1656.9	38.5	1685.6	39.9	28.7	12.4	0.023
	Abduction (°)	125.9	2.7	121.2	2.6	-4.7	3.1	0.128
	Retroflexion (°)	48.2	1.1	46.2	1.1	-2.1	0.9	0.029
	Anteflexion (°)	140.4	2.1	143.5	1.6	3.1	1.6	0.060
	Endorotation (n vertebra)	7.4	0.2	7.1	0.2	-0.3	0.2	0.105
	Scapular distance (cm)	13.4	0.3	14.0	0.3	0.6	0.2	0.019
Contra-lateral	Arm volume (ml)	1649.0	35.3	1664.9	35.2	15.9	11.8	0.181
	Abduction (°)	133.1	3.2	125.3	3.1	-7.7	3.1	0.015
	Retroflexion (°)	48.9	1.3	46.6	1.3	-2.3	1.0	0.033
	Anteflexion (°)	148.7	2.5	148.3	2.5	-0.4	1.2	0.706
	Endorotation (n vertebra)	7.0	0.2	6.9	0.2	-0.2	0.2	0.279
	Scapular distance (cm)	13.8	0.3	14.3	0.2	0.5	0.2	0.025

RT: radiation treatment. **SE:** standard error. **(°)** degrees.

arm on the operated side revealed a statistically significant increase in arm volume of 28.7 ml at the time of post-RT assessment compared with the pre-RT assessment (p = 0.023). Additionally, shoulder ROM was impaired, with a decrease in retroflexion of 2.1 degrees (p = 0.029; abduction decreased by 4.7 degrees and anteflexion seemed to improve, with a gain of 3.1 degrees, but neither was statistically significant). Scapular distance was significantly impaired (0.6 cm increase, p = 0.019). Measurements on the contralateral side showed an increase in arm volume of 15.9 ml, which did not reach statistical significance. There was a significant impairment of shoulder mobility on the contralateral side, with regard to abduction (-7.7 degrees, p = 0.015), retroflexion (-2.3 degrees, p = 0.033), and scapular distance (+0.5 cm, p = 0.025).

The incidence of increases in shoulder/arm morbidity adverse events of 1 or more grading level from the baseline (after any RT treatment or by treatment group) can be seen in Table 3. Overall, after any RT treatment, the post-RT onset of subjective arm symptoms occurred in 18% (14 of 78) of patients, an increase from the baseline in BCRL (as measured by interlimb discrepancy in volume) occurred in 14% (13 of 91), weight loss occurred in 10% (7 of 69) and weight gain occurred in 20% (14 of 69). On both the operated and contralateral side, after any RT treatment, patients generally experienced a loss of abduction and retroflexion, although this was not the case for anteflexion. No significant differences, however, were observed in adverse event grades between the two treatment groups, except on the contralateral side, which showed significantly less loss of abduction of grade ≥1 in the short-course IGRT group compared with conventional RT (Table 3; p = 0.019, unadjusted odds ratio of 0.36 (=[39.2/64.1]/[60.8/35.9])).

The results of a comparison between the treatment groups, based on continuous shoulder/arm morbidity measurement analyses during the physical function assessments, can be seen in Table 4. The increase in arm volume following RT was smaller in the short-course IGRT group than the conventional group, although this contrast was not statistically significant. On the operated side, the average increase in post-RT arm volume was 49 ml in the conventional RT group vs. 8 ml in the short-course IGRT group (p = 0.101). On the contralateral arm, the average arm volume increase was 27 ml vs. 5 ml, respectively (p = 0.353). There were no consistent trends regarding shoulder/arm mobility outcomes with the exception of abduction, which on the operated side showed no impairment in the short-course IGRT group (0 degree mean loss), whereas a 9-degree mean loss of abduction (not significant) was observed in the conventional RT group (p = 0.169). On the contralateral side, the mean loss of abduction was 1 degree in the short-course IGRT group vs. 14 degrees in the conventional RT group; this contrast was significant (p = 0.029; Table 4).

Discussion

Our results support the notion that RT is an important risk factor for the development of objective and shoulder/arm morbidity and BCRL complications. More than 80% of our patients experienced an increased adverse event score in at least one of four shoulder/arm mobility measurements (arm volume, abduction, retroflexion and anteflexion). Post-RT, 18% of patients experienced subjective BCRL symptoms on the operated side. Subjective arm symptoms are an underestimated problem in clinical practice, and additional research is necessary to understand the biochemical changes in the (sub)dermal tissues(26).

Overall, short-course IGRT caused less severe shoulder/arm mobility problems and BCRL than conventional RT, but the differences between the treatment groups were not statistically significant. The conventional RT group had higher adverse event scores on

Table 3. Incidence of shoulder/arm morbidity changes from baseline.

			Conventional RT (n = 46)	*Short course IGRT (n = 45)*	
Side	***Assessment***	***Number of patients (*)***	***%***	***%***	***p conventional vs. short course***
Combined	Arm symptom				0.283
	No onset	64	51.6	48.4	
	Onset post RT	14	35.7	64.3	
	BCRL				0.146
	None, stable or decrease	78	47.4	52.6	
	Onset or increase	13	69.2	30.8	
	Weight				0.592
	Weight loss ≥5%	7	57.1	42.9	
	Weight change <5%	48	43.8	56.3	
	Weight gain ≥5%	14	57.1	42.9	
Operated side	Abduction				0.116
	No loss	41	41.5	58.5	
	Loss	50	58.0	42.0	
	Retroflexion				0.207
	No loss	37	43.2	56.8	
	Loss	51	56.9	43.1	
	Anteflexion				0.333
	No loss	52	46.2	53.9	
	Loss	39	56.4	43.6	
Contra-lateral	Abduction				0.019
	No loss	39	35.9	64.1	
	Loss	51	60.8	39.2	
	Retroflexion				0.757
	No loss	37	48.7	51.4	
	Loss	50	52.0	48.0	
	Anteflexion				0.205
	No loss	48	43.8	56.3	
	Loss	42	57.1	42.9	

BCRL: breast cancer related lymphedema of the arm. **RT:** radiation treatment. **IGRT:** image guided radiation treatment. **(*)** Totals do not sum to 91 due to missing values.

both sides for all shoulder/arm morbidity measurements (interlimb discrepencies in arm volume, abduction, retroflexion, anteflexion) whereas the short-course IGRT group had lower adverse event scores for all shoulder/arm morbidity measurements. On the other hand, the short-course IGRT group experienced more subjective arm symptoms post-RT than the conventional RT group.

We found that shoulder/arm morbidity also occurred on the contralateral limb. To our knowledge, this is the first report that the contralateral arm requires attention – scoring is usually based on the difference between the operated side and the contralateral side, rather than on separate sides as we have done here. We believe that our approach reveals the true severity of the side-effects of RT on shoulder/arm function – mean post-RT shoulder mobility and arm volume measurements were generally worse than pre-RT measurements on both sides (with the exception of anteflexion on the operated side and endorotation on both sides).

Our study presents several limitations. The study population is part of a population with a high incidence of idiopathic or post-traumatic musculoskeletal shoulder-, neck- and back disorders, but pre-surgical measurements were not available (2,10,27). Because measurements were based on active movements, maximal ROM may not have been reached as a result of pain, anxiety, etc. Patients receiving chemotherapy often have an implanted port-a-cath, which may have restricted full ROM of the contralateral arm (8). As part of the institution's surgical management, operated breast cancer patients receive a prescription for ambulatory

Table 4. Changes in shoulder/arm morbidity measurements post-RT, according to treatment group.

Side	Measurement	Mean difference post - pre	Conventional RT n = 46	Short course IGRT n = 45	p conventional vs. short course
Operated side	Arm volume (ml)	28.7	48.7	8.1	0.101
	Abduction (°)	-4.7	-9.0	-0.4	0.169
	Retroflexion (°)	-2.1	-2.6	-1.5	0.578
	Anteflexion (°)	3.1	0.8	5.4	0.153
	Endorotation (n)	-0.3	0.0	-0.6	0.165
	Scapular distance (cm)	0.6	0.6	0.5	0.877
Contralateral	Arm volume (ml)	15.9	26.8	4.8	0.353
	Abduction (°)	-7.7	-14.4	-0.9	0.029
	Retroflexion (°)	-2.3	-2.2	-2.3	0.970
	Anteflexion (°)	-0.4	-1.7	0.8	0.277
	Endorotation (n)	-0.2	0.2	-0.5	0.029
	Scapular distance (cm)	0.5	0.8	0.3	0.287

RT: radiation treatment. **IGRT:** image guided radiation treatment. **°:** degrees.

physical therapy at the time of discharge. However, we did not record the compliance of patients or their receipt of physical therapy during the study, although their beneficial effects on shoulder mobility and scapula positioning are well known (6,10,1,28). Another limitation of our study is the known lack of reliability of shoulder/arm measurements. The incidence of impaired shoulder mobility should be interpreted with these restrictions in mind.

One strength of the study is its randomized design. Although the lack of reliability of the measurements affects the precision of the estimates and reduces the power of our comparison tests, randomization ensures that measurement errors are expected to be equally distributed between the randomization groups, thereby avoiding comparison biases. Another strength of the study is that the trial was conducted in a single institution. All patients were followed by the same team, which ensures that assessments were consistently performed throughout the trial. We believe that the strengths of the study outweigh its limitations and that the results are robust, at least within the current short follow-up time frame.

Because this is a preliminary analysis, the long-term effects of short-course IGRT cannot yet be demonstrated; however, this technique seems to be less harmful in terms of shoulder/arm mobility and BCRL than conventional RT (1). A follow-up of three years from the end of RT treatment is scheduled as part of the study as most cases of BCRL develop within two years of the operation. A median observation time of nearly four years is considered sufficient for the identification of the majority of cases of BCRL and long-term shoulder function impairment (9). It will be interesting to see if the differences observed in this analysis between treatment groups are confirmed at three years. The finding that shoulder/arm morbidity affected the contralateral side warrants further investigation.

Conclusion

Early assessment of shoulder/arm morbidity shows that short course image guided radiotherapy compares favorably with conventional post-surgery radiotherapy for breast cancer. Intriguingly, significant shoulder/arm morbidity affecting the contralateral limb was observed. Further investigations are required.

Competing interests

The authors declare they have no competing interests.

Authors' contributions

Concept and design (NA, VVH), data acquisition (NA, HVP, GM, HV), data analysis (NA, VVH), interpretation of data (NA, TR, MDR, GS, PL, JL), drafting (NA, HVP, TR, MDR, GS, PL, JL), writing (NA, MDR, VVH), critical revision (MDR, HVP, GM, HV, GS, PL, JL), final approval (all authors).

Acknowledgements

This research is funded by grant SCIE2006-30 from the Foundation against Cancer, foundation of public interest. The Radiation Therapy Department of the UZ Brussel had a research agreement with TomoTherapy Inc. (Madison, USA) and Orfit Industries (Wijnegem, Belgium). The first author is financed by a bursary of the IWT (Foundation for innovation of science and technology). The study sponsors had no involvement in the study design; in the collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication. Eva Swinnen initiated the physical therapy assessments in the first enrolled patients. Ilknur Alsan Cetin provided editorial advice to the manuscript.

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