The Breast 26 (2016) 25–30

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Does breast composition influence late adverse effects in breast radiotherapy?

Prabhjot Juneja [a, b, c, d], Maria Bonora [e], Joanne S. Haviland [f, g], Emma Harris [a, b], Phil Evans [a, b, h], Navita Somaiah [a, b, *]

[a] The Institute of Cancer Research, London SW7 3RP, UK
[b] The Royal Marsden NHS Foundation Trust, Sutton SM2 5PT, UK
[c] North Sydney Cancer Centre, Royal North Shore Hospital, Sydney 2065, Australia
[d] Institute of Medical Physics, University of Sydney, Sydney 2006, Australia
[e] Centro Nazionale Adroterapia Oncologica, 27100 Pavia, Italy
[f] Faculty of Health Sciences, University of Southampton, Southampton SO17 1BJ, UK
[g] ICR-Clinical Trials and Statistics Unit (ICR-CTSU), Division of Clinical Studies, The Institute of Cancer Research, London SM2 5NG, UK
[h] Centre for Vision Speech and Signal Processing, Faculty of Engineering and Physical Sciences, University of Surrey, Guildford GU2 7XH, UK

ARTICLE INFO

Article history:
Received 14 August 2015
Received in revised form
4 December 2015
Accepted 12 December 2015
Available online xxx

Keywords:
Breast radiotherapy
Toxicity
Breast segmentation
Seroma

ABSTRACT

Background: Large breast size is associated with increased risk of late adverse effects after surgery and radiotherapy for early breast cancer. It is hypothesised that effects of radiotherapy on adipose tissue are responsible for some of the effects seen. In this study, the association of breast composition with late effects was investigated along with other breast features such as fibroglandular tissue distribution, seroma and scar.

Methods: The patient dataset comprised of 18 cases with changes in breast appearance at 2 years follow-up post-radiotherapy and 36 controls with no changes, from patients entered into the FAST-Pilot and UK FAST trials at The Royal Marsden. Breast composition, fibroglandular tissue distribution, seroma and scar were assessed on planning CT scan images and compared using univariate analysis. The association of all features with late-adverse effect was tested using logistic regression (adjusting for confounding factors) and matched analysis was performed using conditional logistic regression.

Results: In univariate analyses, no statistically significant differences were found between cases and controls in terms of breast features studied. A statistically significant association ($p < 0.05$) between amount of seroma and change in photographic breast appearance was found in unmatched and matched logistic regression analyses with odds ratio (95% CI) of 3.44 (1.28–9.21) and 2.57 (1.05–6.25), respectively.

Conclusions: A significant association was found between seroma and late-adverse effects after radiotherapy although no significant associations were noted with breast composition in this study. Therefore, the cause for large breast size as a risk factor for late effects after surgery and optimally planned radiotherapy remains unresolved.

Background

There is good evidence that large breast size is associated with increased risk of late adverse effects after breast conserving surgery and radiotherapy for early stage breast cancer [1–6]. Suboptimal dosimetry in large-breasted women explains at least part of this association [4,5,7]. A randomised trial ($N = 306$) comparing 3D and 2D radiation dosimetry showed that minimisation of unwanted radiation dose inhomogeneity in the breast significantly reduces late adverse effects [8]. However, a study by Goldsmith et al. [3] suggests that residual dose inhomogeneity in patients treated with optimal dosimetry was insufficient to explain the increased risks of late adverse effects associated with large breast size.

Assessment of late adverse effects is made by clinicians, using patient-reported outcomes and from patient photographs as recorded in several breast radiotherapy trials [9–11]. The effects of radiotherapy most easily noticed on photographs are changes in

* Corresponding author. Division of Radiotherapy and Imaging, The Royal Marsden, Downs Road, Sutton, Surrey SM2 5PT, UK. Tel.: +44 (0)2086613460.
E-mail address: navita.somaiah@icr.ac.uk (N. Somaiah).

http://dx.doi.org/10.1016/j.breast.2015.12.004
0960-9776/

size and shape, with breast shrinkage being the commonest effect. There are suggestions that the shrinkage may result from atrophy of adipose cells in the breast. Preclinical studies suggest that radiation induces a significant reduction in both number and mean size of adipocytes with consequent reduction in fat pad weight in mice [12]. In large breasted women, the major component of the breast by volume is adipose tissue [13,14]. This raises the possibility that a higher proportion of adipose tissue in large breasted women may, in some way, be responsible for some of the effects after radiotherapy, particularly breast shrinkage.

The purpose of this study was to test the association of breast composition and fibroglandular tissue distribution with late adverse effects after breast conservation surgery and radiotherapy. This association, if found, could then be used for prediction of late adverse effects of breast radiotherapy.

Methods

Patients

All patients from The Royal Marsden who had participated in The Royal Marsden FAST Pilot and UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (ISRCTN62488883; CRUKE/04/015) [9,10] were identified. The FAST Pilot study recruited 30 patients aged ≥50 years with early invasive breast cancer (tumour size < 3 cm, clear resection margins, negative axillary node status and no requirement for cytotoxic therapy). They were prescribed 30 Gy in five fractions over 15 days to the whole breast using tangential 6–10 MV X-ray beams and three-dimensional dose compensation. The UK FAST Trial recruited 915 women with similar characteristics as above from 18 centres, 75 of which were from The Royal Marsden. Patients were randomly assigned to 50 Gy in 25 fractions versus 28.5 or 30 Gy in 5 once-weekly fractions of 5.7 or 6.0 Gy, respectively, to the whole breast. Both trials collected standardised pre-radiotherapy baseline photographs of the breasts followed by repeat photographs at 2 years post-radiotherapy, along with annual clinical assessments. Change in breast appearance (size and shape) were scored by three observers on a 3-point scale (none, mild or marked change) from the serial photographs at 2 years post-radiotherapy compared with pre-radiotherapy baseline photographs [11].

Inclusion criteria for this study were, treatment at The Royal Marsden, availability of CT planning scan images and a baseline and 2-year photographic assessment of change in breast appearance. All eligible cases with mild or marked change in photographic breast appearance were matched on fractionation schedule, breast size and surgical deficit (both scored as small/medium/large from baseline photographs) to controls defined as having no change in photographic breast appearance at 2 years (Table 1). Where there was more than one possible matched control per case, all of these controls were selected for inclusion in the study. Other known confounding factors such as chemotherapy, lymphatic radiotherapy and radiotherapy boost were exclusion criteria for the FAST Pilot and FAST trials.

Table 1
Summary of patient and treatment characteristics of cases and controls.

	Cases N = 18	Controls N = 36
Age in years		
Median (range)	66 (50–76)	65 (51–77)
Breast size,[a] *n* (%)		
Small	6 (33%)	13 (36%)
Medium	8 (44%)	19 (53%)
Large	4 (22%)	4 (11%)
Surgical deficit,[a] *n* (%)		
Small	7 (39%)	23 (64%)
Medium	7 (39%)	7 (19%)
Large	4 (22%)	6 (17%)
Fractionation schedule, *n* (%)		
Fast pilot trial – 30 Gy in 5 fractions over 3 weeks	5 (28%)	14 (39%)
Fast trial – 50 Gy in 25 fractions over 5 weeks	3 (17%)	8 (22%)
Fast trial – 30 Gy in 5 fractions over 5 weeks	6 (33%)	8 (22%)
Fast trial – 28.5 Gy in 5 fractions over 5 weeks	4 (22%)	6 (17%)

[a] Assessed from baseline photographs.

Breast outlining

The CT data consisted of 3 mm axial slices (GE HiSpeed XQ/I (GE Healthcare Ltd, Buckinghamshire, UK)). On each slice whole breast was delineated by a single clinician (MB). The Hounsfield units of scar and seroma are similar to fibroglandular tissue and therefore these tissues are not easily differentiated using segmentation methods [15]. The contralateral breast was used for the analysis of breast composition and tissue distribution, in order to avoid the effects of post-surgical seroma and scar on breast tissue segmentation. The contralateral whole breast was outlined using anatomical landmarks on planning CT scans for the treated breast as described by Kirby et al. [16].

In some cases a portion of the breast was not contained in the field of view of the CT scanner (see Fig. 1b). These patients were excluded, with some exceptions:

1. In 5 patients for whom only the skin was marginally not contained in the field of view, the anterior/surface margin was brought right up to the visible edge.
2. In 2 patients for which a significant proportion of the contralateral breast was missing but the treated breast had a well-defined seroma, the treated breast and seroma was outlined with the seroma excluded for the breast analysis (Fig. 1b).

Seroma was delineated using previously published guidelines [17]. Examples of whole breast contours marked on a single CT slice are shown in Fig. 1.

Breast tissue automatic segmentation

The whole breast as defined by the clinician on CT scans (see Fig. 1) was segmented into adipose and fibroglandular tissue using an automated segmentation method. Our previous study [15], showed that the fuzzy c-means clustering method with three classes (adipose, fibroglandular, and background) (FCM3) gave the most accurate breast tissue segmentation when validated against expert segmentation. FCM3 was used to find the volume of adipose tissue and percentage breast composition (BC) was calculated for all patient datasets using the following equation:

$$BC = 100 * V_{adi} / V_{tot}$$

where, V_{adi} and V_{tot} are the volume of adipose tissue and whole breast respectively.

Clinician assessment of breast composition, fibroglandular tissue distribution, seroma and scar

Planning CT scan images were assessed by clinicians blind to patients' case/control status. Breast composition and fibroglandular tissue distribution were also ranked by 3 clinicians (AK, MB and NS), and seroma and scar were scored by a single clinician (MB) using the following methods: