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A SYSTEMATIC REVIEW OF METHODS TO IMMOBILISE BREAST TISSUE DURING ADJUVANT BREAST IRRADIATION

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Abstract

Greater use of 3D conformal, Intensity Modulated Radiotherapy (IMRT) and external beam partial breast irradiation following local excision (LE) for breast cancer has necessitated a review of the effectiveness of immobilisation methods to stabilise breast tissue.

To identify the suitability of currently available breast (rather than thorax) immobilisation techniques an appraisal of the literature was undertaken. The aim was to identify and evaluate the benefit of additional or novel immobilisation approaches (beyond the standard supine, single arm abducted and angled breast board technique adopted in most radiotherapy departments). A database search was supplemented with an individual search of key radiotherapy peer-reviewed journals, author searching, and searching of the grey literature. A total of 27 articles met the inclusion criteria.

The review identified good reproducibility of the thorax using the standard supine arm-pole technique. Reproducibility with the prone technique appears inferior to supine methods (based on data from existing randomised controlled trials). Assessing the effectiveness of additional breast support devices (such as rings or thermoplastic material) is hampered by small sample sizes and a lack of randomised data for comparison.

Attention to breast immobilisation is recommended, as well as agreement on how breast stability should be measured using volumetric imaging.

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1.0 INTRODUCTION

Breast cancer affects a substantial proportion of the population, over 41,000 women were diagnosed with breast cancer in England in 2010 accounting for over 30% of all female cancers (1). For many of these women the primary treatment is local excision (LE) followed by external beam radiotherapy to the whole breast. Traditionally this has been given using basic tangential radiotherapy beams. New technology employing complex approaches such as 3D conformal and Intensity Modulated Radiotherapy (IMRT) provide the opportunity to spare sensitive structures that lie close to the breast. However, IMRT requires greater accuracy in patient alignment. Set up inaccuracies (anterior-posterior and superior-inferior systematic displacements) have dosimetric consequences that vary depending on initial breast volume, breast gradient, standard or IMRT based techniques and magnitude of error(2) and may increase the risk of a loco-regional recurrence(3).

Furthermore, interest in partial breast radiotherapy is increasing with a number of Phase III clinical trials ongoing. Partial breast irradiation requires greater treatment accuracy to ensure an adequate dose distribution across the target volume and to reduce long-term side effects. Poor congruence between the dose distribution planned and that delivered (because of movement of the breast) may lead to poor clinical outcomes (4).

 Survival rates following LE and radiotherapy are good with local recurrence generally low (survival 79-98% at 4-5 years, local recurrence 0.3-10% (5-9)) hence more women are surviving and having to live with the side effects of therapy.

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Furthermore, the interim data from some of the Phase III clinical trials using partial breast radiotherapy has raised concerns over worse than expected cosmetic outcomes (10;11) causing at least one of these trials to close early. Accurate and effective delivery of radiotherapy requires a robust means of stabilisation of the breast and yet this important issue has not been fully considered. Hence, it is pertinent given developments in breast radiotherapy at this time to investigate methods to immobile the breast during treatment.

In the UK most centres rely on the use of permanent tattoos marked on the patient and laser systems aligned to the machine. However, accuracy using this approach can be problematic (12) and the use of permanent tattoos is of concern to many patients(13). In addition, women with large or pendulous breasts are more difficult to position accurately and may need special immobilisation methods if accuracy is to be comparable to smaller breasted women.

To identify methods of breast stabilisation currently being used and the accuracy of each method a review of the literature was undertaken.

1.1 AIMS

The review focused on the adjuvant treatment of early breast cancer using external beam radiotherapy. The overarching aim was to identify and evaluate the benefit of additional or novel immobilization approaches (beyond the standard supine, single arm abducted and angled breast board technique adopted in UK radiotherapy departments). The following questions were central to the review:

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1. Beyond the standard supine breast board technique what methods have been used to immobilise breast tissue in patients given radiotherapy for early stage breast carcinoma?

2. What were the levels of reproducibility (in terms of random and systematic errors) compared with standard positioning (without immobilisation)?

3. What was the impact of the immobilisation device on skin doses or cosmetic outcome?

4. What problems were identifiable with currently available methods of immobilisation?

The review did not aim to address the impact on set-up accuracy of different on-treatment imaging methods.

2.0 METHOD

The review was based on a literature search of Medline, CINHAL, ScienceDirect, National Research Register, ISI Web of knowledge as well as broad Google scholar web search and individual search of key radiotherapy peer-reviewed journals, and author searching. A search of the grey literature was also conducted (Index to Theses and a search of conference papers).

Table 1 below indicates the key terms, alternatives and key word combinations used in the database searches.

Studies were included if they fulfilled the following criteria:

- The primary focus of the research considered the immobilisation or positioning of the breast for early stage disease.

- Radiotherapy technique was external beam (partial or whole breast irradiation)

- Studies that considered radiotherapy alone or in combination with other adjuvant therapies.

- English language only (although English language abstracts of non-English articles were reviewed for relevance)

Studies focusing on brachytherapy, treatment using electrons alone or protons alone, or where the primary focus was advanced stage disease were not included in the review. Similarly, where only an abstract was available or if the study was a dosimetric analysis from a planning study alone, with no accuracy or cosmetic outcome data, the study was not included. Studies where the primary focus was a comparison of on-board imaging, or surface registration devices for set-up purposes were also excluded from the review. Articles were included from 1989 onwards to ensure as much data as possible could be retrieved.

HP completed the search process. A quality assessment tool was used for each article identified from the search and a further data repository tool used to tabulate extracted data in preparation for data synthesis. Review of the titles and abstracts identified from the search was undertaken to identify any possible duplicate studies including reports that followed up earlier studies.

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Data was extracted and assessed for quality by HP and independently assessed by DG using electronic forms to allow easy data storage and retrieval. Agreements between assessment reviewers occurred in 26 out of the 27 article reviews. The disagreement on article 2(14) was discussed and resolved(15) through joint discussion and review.

An adaptation of the Scottish Intercollegiate Guidelines network (SIGN) checklists(16) were used for quality assessment using the guidelines from the Centre for Reviews and Dissemination(15).

Data synthesis was primarily via descriptive analysis of the extracted data which is collated and presented in tabular format (see Tables 2 and 3 in the results section).

Once a final agreed set of research studies was identified for inclusion each full paper was reviewed and assessed for quality using the quality assessment tools identified above (quality assessment undertaken by HP and DG independently).

3.0 RESULTS

Figure 1 indicates the number of included articles in the review from the hits identified from the database search as well as those articles included via other identification routes. The articles reviewed on supine and prone positioning are tabulated in Table 2 and 3 below, the quality assessment identified in the final column indicates the assessment made in relation to the attempts to minimise bias in the results and conclusions. Using an adaptation of the SIGN checklists the quality assessment is based on a sliding scale (++ to -) with ++ representing high

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quality (based on study design ie whether patients were randomised, and efforts to minimise opportunities for bias) ' + ' was chosen as the minimum quality standard on which conclusions were drawn.

3.1. METHODS AVAILABLE FOR IMMOBILISATION

Immobilisation of breast tissue is often reserved for women with large or pendulous breasts. Barrett-Lennard and Thurston (2008) surveyed radiotherapy centres across continents to identify methods used to immobilise patients with large or pendulous breasts; ten different immobilisation techniques were identified(17).

1. Prone breast board
2. Supine breast board
3. Thermoplastic shells
4. Adhesive tape
5. Wireless bra
6. Breast ring
7. Breast cup
8. Stocking
9. Vacuum bags (bags filled with polystyrene balls with air evacuated to mould the shape of the patient's body)
10. L-shaped breast plate (a plate that stands on the bed and supports the breast laterally)

Of the 17 responding centres (10 returned from Australia, 5 New Zealand and 2 from UK) the most commonly applied techniques were prone positioning, and a supine breast board system. The prone breast technique was rated as the most effective at immobilising the breast although this is a subjective assessment, no quantitative data is available to support reproducibility. The breast board was rated most user friendly along with the prone technique, although it is unclear if the user is the therapist or the patient. Thermoplastic devices, stockings, and an L-shaped breast plate were considered least user-friendly. The breast boards and prone breast platform were considered highly re-usable, L-shaped, breast ring and vacuum bags were also reusable. In terms of patient comfort, the wireless bra was rated as most comfortable with the L-shaped device and breast cups rated least comfortable (but it is not clear if this is the health care professional rating this on the patient's behalf). Considering therapist rated effectiveness, reproducibility, ease of use, patient comfort, skin dose, reduction of skin folds, patient positioning and cost the methods rated highest were the vacuum bags and the breast cups; however, the survey sample was small, only from 3 countries and hence the data may be of limited value.

A review of set up errors across six treatment sites by Hurkmans et al(18) evaluated eight studies of breast radiotherapy set up verification. Immobilisation methods included in the review of breast radiotherapy techniques included hemi-body cradles, plastic masks, foam supports and arm supports. The results presented in the review did not show a reproducibility advantage when using the additional immobilisation devices compared with reproducibility achieved using no immobilisation. Four of the

studies included in the review by Hurkmans et al (18) are included in this review as they met our inclusion criteria and are discussed in the section below.

3.1.1.SUPINE IMMOBILISATION METHODS

Research published related to immobilisation with the patient in the supine position (14;19-31) includes 14 articles that focus primarily on immobilisation of the thorax through the use of support cushions, vacuum bags or arm-pole devices with only 8 of these papers specifically testing immobilisation of breast tissue itself. Of these 14 articles reviewed only 5 were considered of sufficient quality to be of value in identifying suitable interventions for retaining a reproducible set-up(14;19-21;25). Only one of the 5 best quality articles specifically tested an immobilisation device for positioning the breast rather than just the thorax(14). The remaining 4 papers meeting the minimum quality standard tested variations of traditional positioning techniques using a breast board, vacuum bag device, support cushions and different arm-pole arrangements(19-21;25); these are discussed in more detail below.

A randomised comparison(19) between a hard foam support cushion and no immobilisation identified an improvement in accuracy with the use of the support cushion (average simulator to treatment errors of 8.4 mm vs 6.1 mm). Similarly, treatment to treatment errors were improved with the use of a support cushion (mean difference in error 2 mm, p=0.001). Patient height, weight and age appeared to influence positional accuracy without the support cushion. However, with the hard foam support cushion only the patient's thoracic circumference appeared to influence set-up accuracy (correlation 0.18 p=0.023).

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Two studies (Graham et al and Nalder et al) compared traditional positioning with vacuum bag methods. In terms of patient reported comfort the arm rest system was superior. Inter-fraction accuracy was the same for both systems at 21 mm (95% CI 17-26 for arm rest patients and 17-24 mm for the vacuum bag)(20). The armrest system appeared to consistently result in larger lung depths being included in the tangential beams. At the dual simulations the median lung depth was 15 mm for the vacuum bag and 20 mm for the armrest system, this difference was maintained during treatment (median 16 mm vs 20 mm p=0.01)(20). The authors indicate this may be a chance finding in this small sample (n=30). However, it has been shown that the greater arm abduction that occurs with a vacuum bag positioning lifts the rib cage thus reducing the amount of lung (and heart in the tangential fields)(32). Skin folds were reduced with the arm-rest system compared with the vacuum bag making this system more desirable especially where nodal irradiation may be required.

A second study comparing arm-pole positioning with vacuum bag systems further supports the data above(21) random and systematic errors were similar for both the vacuum bag system and the control group (traditional breast board). In the anterior-posterior direction systematic errors in Central Lung Depth (CLD) of less than 2mm were identified. Random errors were similarly very small (<3mm for both techniques in the AP direction). Caudo-cephalic shift (CCD) demonstrated greater discrepancies between techniques across both random and systematic errors (mean difference in systematic errors =0.8 mm, random errors-the mean difference between groups was 0.4 mm). Average random and systematic errors remain small across both techniques (0.4-1.8 mm for systematic errors and 2.2-3.2 mm for random errors)(21).

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A further randomised study by Goldsworthy et al(25) comparing single arm abducted on an arm-pole versus both arms abducted confirmed a hypothesis that using double arm abduction increases patient stability when a breast board device is employed. The population systematic error for CLD was halved by using a double or bi-arm technique (compared with a single arm technique- 2.3 mm vs 4 mm respectively p=0.005).   Population random errors were small for both techniques (1.6 mm vs 2.1 mm in favour of the bi-arm technique p=0.055). Similarly, for CCD the bi-arm technique improved set up accuracy for both population systematic errors (2.4 mm vs 3.6 mm p=0.056) and population random errors (2.4 mm vs 2.6 mm p=0.056); mean difference in accuracy between the techniques was generally small (0.2-1.7 mm).

 As the studies conducted in this field tend to be pilot or feasibility studies it is difficult to assess the scientific quality of the research in the same way as full experimental designs. For this reason, all studies irrespective of the quality standard will be mentioned in this section to allow the opportunity to identify potentially useful immobilisation procedures. However, the results for some of the following studies should be viewed with caution given the study designs and small sample sizes.

Eight studies report methods or materials that could be used to immobilise the breast or chest-wall(14;22-24;26,28-29;31). One technique utilises the lateral decubitus position with the patient's affected breast positioned in Styrofoam(24). In this study four women with very large breasts (ie cup size EE), were rolled generally by 5 degrees with the affected breast placed in a styroform cut out, and also immobilised in an alpha cradle. A major disadvantage with this technique is the

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inability to match any nodal fields where required. All 4 women developed moist desquamation in the infra-mammary fold at the end of treatment, accentuated by contact with the styroform foam; tests showed that the surface dose increased from 40% to 80% with the addition of the styroform. The cosmetic results were ranked as excellent in three and good in the fourth; although it is unclear at what time point following treatment completion cosmetic assessment was undertaken and no positional accuracy data is presented.

A PVC ring device was tested by Bentel et al in 56 patients(22). The ring consisted of a hollow PVC tube wrapped around the base of the breast (and supported by a Velcro strap). Acute and late toxicity was assessed retrospectively using patient case notes. Breast size was correlated with outcomes such as cosmetic result. Four different rings were used and surface doses were measured under the ring on a phantom; although only one ring type was used on a patient sample. Moist desquamation occurred in 60.7% of patients (34 out of 56 patients) the most common site was the infra-mammary fold; indicating limited effectiveness of the positioning device as an aid to reduce the self bolusing effect that can occur in women with larger breasts. A key aim in this patient group would be to reduce the impact of breast overhang that causes a loss of skin sparing and hence increased skin toxicity in the breast fold. The ring used for the 56 patients studied caused a surface dose of approximately 85%, a different ring tested on the phantom but not used on patients showed a lower surface dose around 80%. Surface dose in an open field without the ring was extrapolated as 35% of the dmax; indicating a large increase in skin dose with the use of the immobilisation ring. Dimensions of the

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moist desquamation were not recorded but noted to span over several centimetres. Treatment interruption was required in 9% of cases; 2 patients did not complete treatment. Incidence of moist desquamation was higher in those patients with breast area greater than the mean (although this mean size is not quoted p=0.08). Patient weight did not appear to have any association with incidence of moist desquamation. Late sequalae included pain in 4 patients, induration in 7 (grade 1) changes in breast size in 14 cases and hyperpigmentation in 23. Cosmesis was scored as either excellent (50%) or good (50%) the irradiated breast was almost identical to the un-irradiated side or there were minor but acceptable differences. No accuracy data is provided, and no patient characteristics data, so it is not clear what range of breast sizes were studied, or what prospective data was collected using formalised criteria, and there was no survey of patient's experience of comfort or dignity.

An investigation by Latimer et al of a number of materials (including a standard garden hose) identified polymethyl methacrylate (a clear acrylic) as causing the least increase in surface dose compared with other materials tested(14). The acrylic micro-shell horse-shoe design presents a very cost-effective approach to the problem of breast immobilisation. This can be re-used and adapted for large and small breasts, is fairly straight forward to produce more when needed, and a small area of the breast is in contact with the acrylic meaning skin toxicity will be limited to a fairly small area. However, the micro-shell still produces higher skin doses than no device in the order of 9%. In this study there was no measure of patient satisfaction using the device or measure of target reproducibility and subsequent cosmetic outcome (14).

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Carter et al(27) reports a retrospective case series of 20 patients treated in a customised foam cradle, with the ipsilateral arm elevated and the shoulders raised by approximately 10 degrees. Average displacement for the CLD was -1.2 mm with displacements up to 2 cm reported. Reproducibility with the customised cradle appears good but there is no control group for comparison and no patient characteristics reported so it is difficult to be clear about the impact of the cradle alone. A further two studies report outcomes from using plastic masks for immobilising the breast(28;29). Reproducibility with the use of a plastic mask appeared acceptable, approximately 3 mm in the ventro-dorsal direction. The non-randomised study by Creutzberg et al(28) included 31 patients treated using tangential beams. Seventeen patients were treated flat without a breast board but with plastic fixation to the breast, the remaining 14 were treated without fixation (5 flat and 9 raised on an inclined breast board). Ventro-dorsal displacements were lower with the fixation (3.2 mm vs 4.6 mm). However, CLD discrepancies were greater for those positioned in the masks and this was considered by the authors to be a result of difficulties positioning the breast within the mask on a daily basis. A case series by Valdagni et al(29)of 20 patients irradiated in plastic masks showed good reproducibility in both ventro-dorsal and cranio-caudal directions, although 20% had errors greater than 10 mm requiring re-simulation. Both studies involving plastic masks/fixation(28;29) lack information on patient characteristics (such as breast size or volume) that would be beneficial to understanding any sub groups that may benefit from this type of immobilisation.

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A more recent study by Strydhorst et al (23) investigated the impact of the use of a thermoplastic shell to immobilise the breast or chest-wall. This study involved a single cohort of patients that were part of a larger study investigating tomotherapy for breast irradiation in high risk patients. Only 8 patients were analysed in the immobilisation device. Of these patients 5 had undergone mastectomy and 3 LE (across both right and left sides). CT planning was undertaken under normal breathing conditions. Measurements were taken at maximum inhalation and exhalation for external contour and lung from the CT images and the difference between the two breathing positions was measured. Total displacement over the course of the respiratory cycle was measured in 3 transverse planes for each patient at the mid-breast and then 5.1 cm above and below this point. The authors conclude that for 7 out of 8 patients the thermoplastic immobiliser restricted intra-fraction motion associated with breathing in the AP direction below 2 mm. However, without comparable data from a control group it cannot be determined if the thermoplastic reduced this motion, this may have occurred without the immobilisation based on how the measurements were taken. In addition, it could be argued that patients with a mastectomy are easier to reproduce than those who have undergone a LE, so the data may not be fully applicable to the population of concern. The inter-fraction movements identified that patients were not reliably positioned within the shells on a daily basis and hence this method is not acceptable as a method for improving daily reproducibility especially in the cranio-caudal direction where both random and systematic errors were around a centimetre or greater(23).

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An older study by Zierhut et al (26) investigating thermoplastic immobilisation in 7 patients using a repeated measures design, assessed set-up with and without the thermoplastic immobilization. Immobilisation was via thermoplastic over the breast that was attached to the breast board. With the thermoplastic device in position the mean ventro-dorsal shift was 0.3 cm +/- 0.29 cm, CCD was 0.41 cm +/- 0.53 cm. Surface dose was increased from 47% (+/- 6%) to 64% (+/- 12%) using the thermoplastic. Maximum skin reaction was dry desquamation in 6 patients and moist desquamation in 1. Cosmetic outcome at 1.5 years was reported as good but there was no indication of the assessment method used for cosmesis. In terms of acute skin reactions no comparator group was provided and no indication of location or the size of the dry and moist desquamation.

A final study investigated the benefits of treating women with large breasts in a commercially available bra/bustier (31). The authors assessed rate of acute radiation dermatitis as the primary endpoint, no accuracy or reproducibility data was collected. The results indicate the commercial bra increased the rate of dermatitis compared with no bra (grade 2 dermatitis occurred in 90% of cases with a bra compared with 70% of cases without a bra p=0.003). Dosimteric analysis of 12 cases within this study(31) identified a decrease in the volume of heart irradiated with use of the bra (volume decreased by 63% p=0.002) indicating that the bra may lift tissue away from the chest wall. However, it is not clear how cases were selected for this sub analysis so the data maybe unreliable.

3.1.2.PRONE IMMOBILISATION METHODS

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The remaining 11 papers included in Table 3 investigated immobilisation in the prone position (33-43). Of these 11 studies 6 were scored at the '+' or '++' quality standard (35, 37-39, 42- 43) and will be discussed below.

It is not uncommon for additional positioning aids to be used for positioning in the prone position either to support the treated breast or to aid comfort and decrease pressure on the contra-lateral breast. Becker et al (42) compared two positioning pads for use during prone irradiation, identifying that a foam support if in the beam path would substantially increase the surface skin dose compared with a helium filled Mylar bag. This data showed the importance of care in the use of foam supports identifying that the surface skin dose may rise threefold when the foam pad is in contact with the patient's skin, although this data did not account for any contribution from exit doses(42).

One of the proposed advantages of the prone technique is the reduction in intra-fraction motion due to minimization of patient breathing. Morrow et al (39) compared intra-fraction motion on 3 prone cases with 3 cases treated in the supine position. These results showed that motion was reduced from 2.3 mm (+/- 0.9 mm) in the supine position to -0.1 mm (+/- 0.4 mm) in the prone position. However, without detail on patient characteristics across the two positions it was not possible to determine how representative this small sample was of the population under study, or whether there was balance of relevant characteristics between techniques. Intra-fractional motion in the prone position was minimal on average -0.1 mm for the three cases studied. For supine cases average motion was higher (2.3 mm), but still less than 3 mm, hence it is questionable whether the differences observed were clinically

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significant? In the same study inter-fraction motion was measured on a larger sample of 15 prone cases (no supine comparison group) with movement up to 1.65 cm identified in both AP and SI directions.

The largest of the studies investigating positional accuracy in the prone position was a single centre retrospective study by Stegman et al(35) that reviewed the data of patients treated over a 12 year period (n=245 patients, 248 breasts median age = 60yrs range from 30-83yrs). Initially, only patients with large, pendulous breasts were eligible for prone-whole breast irradiation (WBI). Later, the indications for prone-WBI were broadened to include patients with significant co-morbid cardiopulmonary disease, extensive tobacco use, and patient or physician preference. This means the sample in terms of potential skin reactions is likely to be heterogeneous. Median breast area was 68 cm^2 (range, 10.5–229.6 cm^2). Bra sizes were available for the 56 patients included in the original retrospective analysis of the prone-WBI by Grann et al(34). The median bra size was 41D (range, 34D–44EE), corresponding to a median breast area of 99 cm^2 (range, 52.5–229.6 cm^2). Planning for the majority of cases was via parallel opposed co-planar beams, and dose distributions taken only on the transverse central axis, the median hot spot was 106% (inter-quartile range 104-108%). Shifts were only made in 4.4% of cases following portal imaging indicating good reproducibility of the technique. Median follow-up for living patients was 4.9 years (range, 4 months to 11.9 years). In all, 119 patients (48%) were followed for a minimum of 5 years.

Early in the series, 12 patients (4.9%) complained of mild-to-moderate chest wall or rib pain during treatment that was managed conservatively; one patient discontinued

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treatment. Two patients (0.8%) sustained rib fractures while being positioned on the prone board. Six patients (2.4%) required treatment breaks. There were no reported cases of radiation pneumonitis or cardiac related events (although follow up maybe too short to detect cardiac events). In terms of local recurrences and overall survival the authors compare the data of the prone technique with that of Early Breast Cancer Trialists' Collaborative Group (EBCTCG) data (44) which is likely to be a comparison of dissimilar groups, (for example, it is not clear how comparable the data is in terms of patient ages, or number of involved lymph nodes). The authors did not recommend prone irradiation for elderly and morbidly obese patients due to difficulties getting the patients onto the breast board. Treatment accuracy was reported as good but this was based on the number of treatment shifts and this would depend on local protocol. If acceptable margins of error were high, shifts would not be employed so this data tells us little about treatment accuracy (in terms of random and systematic errors). Due to the retrospective nature of the study there was no data on patient comfort or how often the attempted prone position was abandoned. The authors claimed good dose homogeneity within this series yet patients were only planned on a single plane (ie central axis) so there was no data regarding volume homogeneity. Skin toxicity levels were low but no cosmesis data was reported during follow up so this data was not available. The authors measured breast area but did not correlate skin toxicity with breast size to identify the impact.

Of the studies meeting the quality standard only three were randomised comparisons of prone versus supine positioning. The largest of these studies was a two phase study by Varga et al (43) the first phase was a dosimetry analysis, the

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second phase was a feasibility study (n=20 and n= 41 respectively). The results of the dosimetry analysis identified a significantly better planning target volume (PTV) coverage with the supine versus prone positioning (89.2% vs 85.1% respectively for dose range 47.5-53.5Gy) but reduced lung doses in the prone position (although dose to the heart did not show comparable benefits in the prone position). In phase II of this study positional changes were required in 20.3% of both supine and prone cases, although the size of the displacements on average were larger with the prone position (vector displacement 8 mm vs 6.6 mm respectively p= 0.02). Population systematic errors were small for both positions (<1 mm), random errors were less than 3mm in supine position and just over 3mm in prone position. Positional accuracy showed a time trend in the prone position with accuracy improving as treatment progressed. No such time trend was determined in the supine position, although positional accuracy in the supine position was significantly related to lower patient weight, body mass index, waist size, separation and volume of ipsilateral breast.

Patients undergoing supine breast irradiation had significantly lower rates of radiation dermatitis grade 1 and 2 (55% vs 38% grade 1, 35% vs 19.5% grade 2, prone vs supine respectively p=0.025). No association was identified between acute skin reactions and PTV dose homogeneity or set-up errors. However, this could be a reflection of the relatively small sample size (n=41) given set-up errors were small it is likely that a larger sample would be needed to demonstrate statistically significant correlations between skin toxicity and positional errors.

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The second randomized study by Kirby et al was a cross-over design (n=25)(38) and supports the previous study indicating a possible decrease in positional accuracy with the prone position. Population systematic and random errors were greater in the prone position (1.3-1.9 mm supine vs 3.1-4.3 mm prone p=0.02 for systematic errors and 2.6-3.2 mm supine and 3.8-5.4 mm prone p= 0.02 for random errors). Positional accuracy was worse for CCD (mean displacement 0.1 mm vs 3.6 mm supine vs prone p= 0.02). The data also demonstrated decreased motion from respiration with the prone positioning supporting previous data(39). The final randomised study from Veldeman et al (37) used a within subjects design (n=10) to measure differences between prone and supine positioning. No significant differences were seen in dose parameters for heart doses between the prone and supine position; although could this just be a reflection of the small sample size? As identified by other studies the lung dose was lower in the prone than the supine position. In all ten cases the systematic error exceeded 3mm in the vertical direction (in both supine and prone position) in 60% of cases the systematic error was worse in the prone position. In two cases where the patients had the largest breasts both have larger errors in the prone compared with the supine position. Random errors were high for both techniques especially in the lateral axis where errors were approximately 7mm for both techniques.

4.0 CONCLUSIONS

A variety of techniques are used globally to position patients for whole breast irradiation. Commonly supine systems employ an armrest and angled board system

or use a vacuum bag system. Where the supine positioning method is employed the use of an additional support cushion may enhance treatment accuracy(19). Accuracy in terms of random and systematic errors are similar when the traditional breast board and arm-pole system is compared with a vacuum bag system(20-21). Using a bi-arm (double arm up) technique also increases patient stability and hence treatment accuracy but the reduction in error between single arm versus double arm is small (0.2-1.7 mm) and it may be questioned whether this statistically significant difference is clinically relevant(25); although a bi-arm technique has other advantages including the potential to decrease the volume of lung or heart within the treatment field(32). Using a standard breast board and arm pole system or a vacuum bag system in the supine position can allow adequate chest wall reproducibility in terms of random and systematic errors (20-21,25) with population errors of less than 3 mm achievable for CLD. Systems currently available for immobilising breast tissue show limited success with large increases in surface doses (in the region of 17-20% compared to doses without the device (24,26) except for the acrylic micro-shell which showed limited increases in surface dose (9% increase). Without corresponding data on breast tissue reproducibility with the addition of the breast devices it is not possible to assess overall effectiveness.

The prone breast position offers an alternative to supine positioning especially for women with larger breasts; potentially allowing for reductions in cardiac doses. However, where adequate data on reproducibility are reported population random and systematic errors appear larger than those achievable with supine positioning and are generally over 3 mm in all directions (38).

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Advantages and disadvantages of the supine versus the prone technique are presented in Table 4 below.

In terms of assessing the suitability of current immobilisation methods for use with conformal or IMRT technology, the following points need to be considered:

1. There is limited data available in the literature on supine breast immobilisation devices beyond the standard arm-pole or vacuum bag techniques.

2. There are few high quality randomized trials from which to draw accurate data on breast immobilisation effectiveness.

3. There are dignity issues with both supine and prone methods but prone positioning may be significantly less dignified.

4. For supine positioning techniques accuracy may be dependent on patient size measured either by body mass index (BMI), weight or breast volume/separation, hence these patients may need additional positional support to ensure comparable treatment accuracy and subsequent outcomes.

5. Methods used to report positional error and cosmetic outcome vary, making comparison across studies difficult.

6. Random and systematic errors are defined for chest wall positioning only with no measure of breast tissue movement that may influence cosmetic outcome. With advances in technical delivery and greater use of 3D conformal and

IMRT techniques and the availability of x-ray volumetric imaging accuracy in breast tissue positioning (rather than position of the lung or chest wall) should be included in research reporting reproducibility for breast irradiation?

Recommendations

Radiotherapy positioning for supine whole breast irradiation have been fairly unchanged for the last 20 years. While great efforts have been made in other anatomical sites to ensure accurate radiotherapy delivery (such as prostate and lung) the technical positioning for breast radiotherapy has not kept pace with these developments. It may be argued that high local control rates at the cost of generally low toxicity and good cosmesis were achievable using basic parallel opposed radiotherapy beams, hence complicated positional methods have been unwarranted. However, recent improved understanding of the adverse consequences of cardiac irradiation and the greater use of 3D conformal and IMRT techniques now necessitates greater attention to the reproducibility not only of the thorax but also of the breast tissue itself in order to ensure good cosmetic outcomes, especially in women with larger or more pendulous breasts and maintenance of good local tumour control. Advantages and disadvantages of both supine and prone methods exist and the choice for adopting one approach versus the other may depend on local preferences. However, the data from the randomised studies comparing prone versus supine techniques show the prone technique to have worse reproducibility than the existing supine techniques. The ability to make decisions on the adequacy of each approach or of the effectiveness of additional support devices (such as rings or thermoplastic material) are hampered by small sample sizes and a lack of

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randomised data for comparison. Additional variations in the reporting of population

errors, and skin toxicity make comparisons across studies difficult. In order for breast

radiotherapy to keep pace with the developing technological innovations it is

necessary for positioning and immobilisation research to meet the relevant

standards for other health technology assessment research. Only 11 out of the 25

studies reviewed met our minimum quality standard because of design flaws that

may have introduced opportunities for bias. The use of adequately powered RCTs,

standard reporting of errors(45) and toxicity scales as well as additional reporting of

breast tissue reproducibility using volumetric x-ray imaging (where available) would

greatly improve practitioners' ability to implement the findings of reproducibility

studies within this field.

Figure Legends

Figure 1. Flow diagram of included articles

Tables

Table .1. Key Words and Key Word combinations

Table 2 Immobilisation Literature (Supine Position)

Table 3 Immobilisation Literature (Prone Position)

Table 4 The Advantages and Disadvantages of Supine vs Prone Positioning for Breast Irradiation

Table .1. Key Words and Key Word combinations

FACETS	KEYWORDS	MEDLINE SUBJECT HEADINGS
Patients with early stage breast cancer	Breast Carcinoma, breast tumour, breast tumor, breast cancer, invasive carcinoma	Breast neoplasms
Immobilisation	Positioning, accuracy, geographical miss, reproducibility, immobilisation, device, mask	
Radiotherapy	radiotherapy, radiation treatment, Radiation Therapy, external beam	radiotherapy

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Table 4 The Advantages and Disadvantages of Supine vs Prone Positioning for Breast Irradiation

	SUPINE TECHNIQUES	PRONE TECHNIQUE
	Advantages	**Advantages**
1	Ease of set up	Narrowing of breast shape makes gaining a homogenous dose easier
2	Tried and tested technique that staff are familiar with	Organs at risk may be separated from the breast tissue leading to reductions in lung volume
3	Can match nodal fields to chest wall fields when required	Respiration while prone is limited reducing intra-fractional movement
4	Higher patient satisfaction	
	Disadvantages	**Disadvantages**
1	Gravity effect on women with large breasts can	PTV often doesn't include the chest wall which

	mean there is a loss of skin sparing inferiorly	may be a problem depending on the position of the original tumour.
2	Immobilisation of breast tissue may be difficult in women with large or pendulous breasts with unknown effects on subsequent cosmesis.	Not possible to match on nodal fields
3		Difficult for patients to climb onto the platform-some rib fractures reported
4		Accuracy not as good as supine positioning.

Key for Table 2 below:

Scf= Supraclavicular field

QA= quality assessment of the study

NM= not measured

CLD= Central lung distance,

CCD= caudo-cephalic distance

VB= Vacuum Bag

Table 2 Immobilisation Literature (Supine Position)

Author+ year	Description	Accuracy	n	Materials Used on the breast	Skin reactions	Advs/disad	QA
Latimer JG, Beckham W, West M, Holloway L, Delaney G. - 2005(14)	A micro-shell vs two other breast rings	Not measured	8	Polyacrylic micro-shell shaped into a horse-shoe	Micro shell increased surface dose by 9%, other devices increased by 22%	• Shaped to reduce skin dosage, • Reusable • expandable capacity	**+**
Carter, D.L., Marks, L.B., & Bentel, G.C. 1997.(27)	Retrospective review	CLD variability average= -1.2mm	20	Alpha Foam cradle	Not applicable	• No patient demographic available so unable to assess impact of patient size on reproducibility • No control group for comparison	**-**
Thilmann C, Adamietz IA, Saran F, Mose S, Kostka A, Bottcher HD.- 1998(19)	Comparison between a positioning support cushion and no immobilisation.	Mean error without support 8.4mm vs 6.1mm.	55	Foam	Not observed	Accuracy significantly improved with support (72% more comfortable)	**+**
Graham P, Elomari F, Browne L.- 2000.(20)	Randomisation to armrest or vacuum bag immobilisation.	lung exposure (mean SD): Vac-bag 0.21cm (95% CI 0.17-0.26) Arm-rest 0.21cm (95% CI 0.17-0.24)	30	None thorax stabilisation	less skin folds present in armrest	armrest more comfortable, vacuum bag allowed less lung exposure, no difference in stability and set-up time	**+**

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Nalder CA, Bidmead AM, Mubata CD, Tait D, Beardmore C-2001 (21).	Comparison of standard breast board and vacuum bag attached to a breast board.	mean and SD of the systematic errors (mm) : **With VB** AP -1.8 (2.9) **No VB** AP -1.7(2.8) SD of the random errors: **With VB** AP 2.6 **No VB** AP 2.2	17	Not stated	n/a	• Minimal improvements found using the VB • Majority found the VB more comfortable	**+**
Bentel GC, Marks LB, Whiddon CS, Prosnitz LR. - 1999(22)	Patients with large and/or pendulous breasts underwent radiotherapy using a breast ring; comprised of a hollow tube and fitted around the breast in contact with the skin.	n/a	56	PVC tube (other material of tube tested was nylon)	Moist desquamation in 60.7% Surface dose under the ring approximately 85% of D_{max} dose .Without ring surface dose 35%.	• Reduce skin folds and lateral movement in supine position- no quantitative data. • Good cosmetic outcome reported	**-**
Strydhorst JH, Caudrelier JM, Clark BG, Montgomery LA, Fox G, MacPherson MS. 2011 (23)	Assessment of the effect of a thermoplastic immobilisation device on minimising breast/chest wall movement during chest wall/breast irradiation	Inter-fraction motion: average random error Left/rt= 4mm Sup/inf= 12mm and AP= 4.5mm Intra-fraction motion: av =1mm	N= 8	Thermopla-stic shell	Not measured	Inter-fraction motion appears large which would indicate this method of immobilisation does not work well.	**-**
Cross MA, Elson HR,	Feasibility study to assess the	Not measured	N= 4	Styrofoam block plus alpha cradle	all developed moist	Conclude lateral decubitus position	**-**

Aron BS. 1989(24)	usefulness of the lateral decubitus position for women with very large breasts.				desquamation inferiorly due to contact with styroform foam, surface dose increased from 40- 80%	feasible for women (cup size EE). technique does not allow matching of an scf	
Goldsworthy SS, Sinclair NN, Tremlett JJ, Chalmers AA, Francis MM, Simcock RR 2010(25)	RCT comparing positioning on a breast board with either both arms abducted (intervention group) or single arm abducted. (control group)	CLD systematic error mean= -1.7mm vs -1.9mm p=0.06, population systematic error 4mm vs 2.3mm p=0.005 in favour of intervention. Population random error 2.1mm vs 1.6mm p=0.055	50	Traditional breast board with armpole device	not measured	The use of bi-lateral arm abduction resulted in smaller set up errors than the single arm positioning, although differences small.	+
Zierhut D, Flentje M, Frank C, Oetzel D, Wannenmacher M.-1994(26)	A repeated measures design to test the usefulness of a thermo plastic immobilisation device. Patients were treated in the thermoplastic but simulation data available with and without the device.	AP mean deviation= 3mm with the device. sup-inf 4.1mm	7	Thermoplastic	Surface dose increased from 47% to 64% on patients, on the phantom the surface dose was increased from 51-64% (of the maximum dose). The increase in skin dose was 17%	The increase in skin dose was 17%	-
Chopra, S., Dinshaw, K.A., Kamble, R., & Sarin, R.	A case series	Displacements: Sup-inf = 1.3mm Med-lat= 1.3mm Ant-post= 4.4mm	5	Vacuum bag immobilisation	Not measured/Not applicable	Patient demographics not reported, no control group for comparison	-

2006(30)							
Creutzberg, C.L., Althof, V.G.M., Huizenga, H., Visser, A.G., & Levendag, P.C. 1993.(28)	Non-randomised trial 1) patients lying flat with plastic mask(n=17) 2) patients no mask (n=14)9 on inclined wedge, 5 lying flat	Ventral-dorsal displacement: With mask= 3.2mm Without mask= 4.6mm	31	Plastic mask vs no mask And flat vs inclined on a wedge	Not measured	Not clear the criteria for allocation (except for those with additional nodal fields), no patient demographic data	-
Valdagni, R. & Italia, C. 1991(29)	Case series	Ventral-dorsal shift = 2.7mm (+/- 2.2mm) Craniocaudal shift= 1.9mm (+/- 1.8mm)	20	Plastic mask immobilisation		No control group for comparison. Patient demographic data, no information on observer reliability	-
Keller, LMM et al 2013 (31)	A commercially available bra/bustier compared with no bra	Not measured	N= 246	Commercial bra using thin plastic stays	Bra- 90% of cases grade 2 dermatitis No bra- 70% (p=0.003)	Baseline characteristics were uneven across control and intervention (ie more cases with larger breast cup size in the intervention group), no randomisation between control and intervention	-

Table 3 Immobilisation Literature (Prone Position)

Author+ year	Description	Accuracy	n	Materials	Skin reactions	Limitations	Results-Advs/disad	Variables	QA
Stegman LD, Beal KP, Hunt MA, Fornier MN, McCormick B. 2007(35) (Memorial Sloan-Kettering Cancer Center, New York)	Retrospective study patients treated between 1992 and 2004	No data on random and systematic errors	245	Prone breast board	Prone position: Grade ≥3acute dermatitis and oedema 4% of patients - Chronic Skin and subcutaneous tissue toxicity grade≥ 2 4.4% , 13.7% respectively –	No comparison supine group Breast sizes measured but not used to look at relationships with skin morbidity scores.	improved dose homogeneity and reduced cardiac and lung dose.	Local recurrence, disease-free survival, overall survival, skin toxicity	+
Grann A, McCormick B, Chabner ES, Gollamudi SV, Schupak KD, Mychalczak BR et al. 2000(34)(Memorial Sloan-Kettering Cancer Center, New York)	A feasibility report using a prototype prone breast board for patients with breast sizes of 34D–44EE.	Not stated/not measured	56	Prone breast board	1 pt Grade III moist desquamation, 80% grade I/II erythema, 72% mild oedema, Overall cosmetic outcome excellent or good	Tumours close to the c/wall not eligible for prone irradiation. No assessment of inter-rater reliability. No supine comparison.	Dose homogeneity improved in the prone position dose to OAR is minimised (not quantified in this paper)	Skin reaction Cosmetic outcome	-

Veldeman L, Speleers B, Bakker M, Jacobs F, Coghe M, De Gersem W et al. 2010(36) Ghent University Hospital, Ghent, Belgium	Supine and prone dosimetry plans compared using a repeated measures design, patients treated in the prone position	Systematic errors high in the first 6 patients, improved with later patients, mean =5mm in the vertical direction, random errors 4.2mm, 2.6mm and 3.2mm in x, y and z axis respectively.	18	Prone breast board	13/18 developed grade 1-2 erythema (CTC), subcutaneous oedema reported in 9/16 cases	Technique changed slightly after 6 cases, no supine treatment comparator for set up times or treatment precision.	Dose homogeneity similar for both supine and prone- 13.9% vs 15.1% p=0.1). Lung volume lower in the supine but dose to the lung was lower in prone position (0.7 vs 8.3 % V20 p<0.001). heart doses significantly lower in the prone position.		-
Mahe MA, Classe JM, Dravet F, Cussac A, Cuilliere JC. 2002(33)	To evaluate the prone-position technique for breast irradiation using a plexiglas breast board.	The isocentre needed to be moved superiorly by 0.5-1 cm in 50% of cases indicating a systematic error.	35	plexiglas platform	Only I-II acute skin reactions observed at top of breast (in approx 33% of cases).	3 patients unable to climb onto the breast board or lie in prone position. Chest pain and	Breast and C/W treated to 98% of the prescribed dose in all cases.	Patients with large breast size (defined as over 37 inches chest size or bra cup size C and above).	-

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						discomfort with the untreated breast			
Kirby AM, Evans PM, Helyer SJ, Donovan EM, Convery HM, Yarnold JR 2011(38)	RCT of supine vs prone positioning	Systematic error Ant/Post Supine=1.8mm Prone=3.4mm Random error Ant/Post Supine=2.6mm Prone=4.2mm	25	Prone platform and standard supine wedge based arm-rest system	Not measured	Cosmetic outcome data not possible to measure because of study design,	Prone position greater set-up inaccuracy and slightly worse patient satisfaction scores, treatment times comparable.	Age Patient epigastrium size Patient bra cup sizes	**+**
Morrow NV, Stepaniak C, White J, Wilson JF, Li XA 2007(39)	Measurement of inter-fractional variability of patients treated prone and an assessment of intra-fractional movement associated with breathing (comparing prone with supine positioning)	Intra-fractional movement Prone av =-0.1mm Supine av = 2.3mm Inter-fractional movement prone ranged from 0.01cm-1.65cm on a per patient basis	N=6 n=15	Prone breast board	NM	Sample size is small and standard random and systematic errors not calculated so difficult to compare across studies	Prone positioning reduces intra-fractional motion due to breathing compared with supine positioning	Inter-fractional and intra-fractional movement	**+**
Mitchell J, Formenti SC,	Prospective analysis of	Inter-fractional error mean	10	Prone breast	NM	Only systematic	Prone positioning	Inter-fractional systematic	**-**

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DeWyngaert JK 2010(40)	prone positioning no supine comparison	AP= 0.8mm, SI=0.4mm Intra-fractional displacement =1.3mm		board		error calculated	achieves acceptable inter and intra-factional errors with a resultant CTV to PTV expansion of 1.4cm	errors and intra-fractional errors	
Croog VJ, Wu AJ, McCormick B, Beal KP 2009.(41) Sloan kettering	retrospective review of cases treated in the prone position using simplified IMRT	No accuracy data provided	128	Prone breast board	Majority of reactions for dermatitis, erythema or purities were grade 0/ 1 14% of patients reported grade 2 dermatitis	No cosmetic outcome data reported no inter or intra-rater reliability reported	prone positioning with sIMRT is an acceptable treatment in terms of acute skin toxicity	RTOG skin toxicity	-
Becker SJ, Patel RR, Mackie TR. 2007(42)	A phantom study to measure the skin surface dose that may occur in prone breast irradiation when a positional foam support cushion is used.	n/a	n/a phantom study	Comparison of a nylon coated foam pad with a helium filled mylar bag	Surface doses increased substantially when the foam support was touching the skin surface (increased 300% compared	Doses calculated do not account for exit dose and this is likely to reduce total skin doses measured.		Surface dose	+ +

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					with no pad)				
Varga Z, Hideghqty K, Mezo T, Nikolqnyi A, Thurz£ L, Kahbn Z. 2009.(43)	Two phase study (phase I dosimetry analysis, Phase II randomised comparison of prone vs supine positioning)	Vector displacement 8mm vs 6mm (prone vs supine p=0.02)	Phase 1=40 Phase 2=61	Prone breast board vs supine breast board (15^0 incline both arms up and thermoplastic to contralateral breast up to chin	Grade 1 dermatitis 55% prone vs 38% supine Grade 2 35% (prone) vs 19.5% (supine)			Dose to contralateral breast Ipsilateral lung and heart doses Systematic and random errors Skin toxicity	**+**
Veldeman L, De Gersem W, Speleers B, Truyens B, Van Greveling A, Van den Broecke R, et al. 2012(37)	Within subjects design	Systematic error Lat and long axis < 2mm for both prone and supine Vertical axis Supine= 2.8mm Prone= 7.22mm	10	Prone breast board vs supine (arms raised)	Not measured		Random errors are high for both techniques especially in lateral direction (≈7mm)	Time taken to set-up Reproducibility Dose-volume comparisons Respiration	**+**

sIMRT= Simplified Intensity Modulated Radiotherapy

R/L= Right /Left, S/I= Superior/inferior

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CTC= Common Toxicity Criteria

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