Radiotherapy for Early Breast Cancer: Virtual Simulation and Patient Alignment

Sairanne Wickers

University College London

Thesis submitted for the degree of

Doctor of Philosophy

April 2025

Acknowledgements

I would like to express my thanks to my supervisors, Professor Mark Gaze and Professor Gary Royle, for their guidance and support throughout my research. I also wish to thank my committee members, Professor Heidi Probst, Dr Yatman Tsang and Lucy Shepherd for their insightful feedback, invaluable advice and constant encouragement.

I am grateful for the financial support from the University College London Hospitals Charity Cancer Fund, The Society and College of Radiographers, Macmillan Cancer Support, and Cancer Research UK RadNet City of London, which made this research possible.

I would also like to acknowledge my colleagues within UCLH and beyond (too many to list, but from every corner of our multidisciplinary team), for their constant support, insight and encouragement. From helping me navigate the medical device regulations, introducing me to those with specialist knowledge to guide me over the next research hurdle, identifying funding streams affiliated with my research, and being there to talk through my data until somehow the right statistical test would pop into my head.

Most importantly, I would like to thank the patients that took part in my research and were so generous with sharing their experiences.

Finally, I wish to thank my family and friends for their unwavering support and encouragement.

Declaration

I, Sairanne Wickers confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:

Date: January 2025

Abstract

Introduction

Breast cancer radiotherapy relies heavily on virtual simulation (VS). Some retained elements of two-dimensional simulation are incompatible with modern practice, increasing inefficiency and impacting body image.

Aims and Objectives

Aim 1: Identify VS heart and lung dose surrogates to support optimum target coverage, pre-treatment pathways and modality selection.

Aim 2: Investigate the impact of permanent Indian-ink tattoos and evaluate an alternative that is visible and acceptable for people of all skin colours.

Methods

Correlations between the percentage of heart/lung in the VS-fields and heart/lung dose was performed. Linear regressions of a model-building cohort determined VS thresholds for clinically relevant tolerance parameters. A validation cohort confirmed the clinical model.

A national survey and thematic analysis was conducted to investigate the impact of Indian-ink tattoos following breast cancer radiotherapy. A randomised controlled trial was conducted to evaluate the feasibility of non-permanent natural-coloured ink pigments. Data collected and analysed included application and alignment time, radiographer-assessed visibility, equipment acceptance, and pain scores.

Results

Accurate heart and lung dose VS surrogates were identified (R^2= *>0.9*). Threshold values to meet clinically relevant dose levels, and equations to estimate heart/lung dose were provided and validated for 40Gy in 15-fraction and 26Gy in 5-fraction schedules.

Permanent Indian-ink tattoos negatively impacted 51% of respondents (n = 205), affecting clothing choices (15%) and serving as a constant negative reminder (31%), due to the unnatural-colour and permanent high-visibility. 6% were positively impacted, feeling proud of their survivorship. The randomised

controlled trial confirmed that natural-coloured non-permanent tattoos are feasible in terms of visibility, application/alignment time, pain and radiographer acceptance.

Discussion

This project was the first to identify and validate predictive VS heart and lung dose surrogates and conducted the largest survey investigating the impact of Indian-ink tattoos. This supported the randomised controlled trial that has identified a feasible alternative.

Conclusion

The ability to predict heart and lung dose during VS supports efficient planning and early indication if tangential radiotherapy might be associated with an unacceptably great risk of late morbidity.

The impact of Indian-ink tattoos and confirmed feasibility of natural-coloured, semi-permanent tattoo pigments as an alternative, has provided the reassurance to industry and other stakeholders that this unmet need warrants investment to obtain the regulatory medical device certification of a wider range of radiotherapy tattoo pigments.

Impact Statement

Introduction

Practicing as a therapeutic radiographer for 25 years has afforded me the opportunity to develop several techniques whilst transitioning from two-dimensional to three-dimensional planning, driven by huge leaps in technological and computational capability. Breast cancer survival and quality of life have also improved, with radiotherapy advances attributed to this alongside the optimisation of surgical and systemic interventions. Ten-years as a consultant breast radiographer have provided the opportunity to combine the technical skills and knowledge gained during my pre-treatment role, with the highly privileged insight into what matters to our patients before, during and after treatment.

Heart and lung dose surrogates

The virtual simulation dose surrogates identified in my research have been implemented as standard-of-care in my department. No patients have field border or isocentre changes due to unexpected heart/lung dose during dose optimisation. Dosmietrists and physicists that have worked elsewhere, regularly comment on previously associating breast planning with late-stage changes due to heart/lung doses exceeding tolerance, causing inefficiency and delays to treatment. The release of resources no longer ‘wasted’ has supported technique development and implementation of intensity modulated arc therapy (IMAT) boosts in deep inspiration breath hold (DIBH), monoisocentric nodal delivery, DIBH internal mammary node radiotherapy, IMAT DIBH for complex cases and recruitment to the PARABLE trial (photon and proton arms) at my centre.

Within my role of the PARABLE trial working party, I identified early during protocol development that waiting for final planned heart dose to confirm trial eligibility was inefficient and not required. My clinical example of dose surrogates was reviewed favourably, and as a result centres are not required to produce an optimised plan if using an approved method for heart dose estimation.

In terms of international impact (with regard to proton beam referral pathways), I identified the value of accurately estimating photon heart dose from diagnostic computer tomography (CT) scans; as having to ‘fail’ photon planning prior to a proton beam referral adds several weeks to the treatment pathway. A working party was formed and is evaluating several models. The current limitation is the

wide confidence intervals of these models, but with advances in Artificial Intelligence models, I am confident that this will be possible.

Non-permanent natural-colour radiotherapy tattoos

Indian-ink tattoos are used internationally for a wide range of treatment sites. For white/lighter skin they are permanently highly visible, and on brown/black skin, can be very difficult to locate during treatment, reducing dignity. A minority with surface guidance technology can perform tattoo-less radiotherapy.

My research is the largest to investigate the impact of permanent Indian-ink tattoos following breast radiotherapy. The negative impact and verbatim quotes presented do not support the persistent minimisation by the radiotherapy team. The NEAT trial conducted in this project demonstrates the feasibility (in terms of visibility and planning/treatment times) of natural-coloured ink pigments for radiotherapy tattoos. Together, these have challenged industry to increase the range of radiotherapy tattoo ink pigments, having previously assumed that they are inconsequential to patients. This has facilitated an exciting opportunity for the Translational Research Office at UCL, industry partners Biotic Phocea (only medical device licence holders for a limited radiotherapy ink pigment range) to work with me and have each entered into a knowledge-sharing agreement to progress this work. Several charitable organisations, including Macmillan and Black Women Rising, have also provided support for natural-coloured tattoos that are visible on all skin colours and acceptable to patients. This has resulted in successful grant funding and access to the community members for effective and insightful patient and public involvement.

Conclusion

Utilising my close patient interaction, technical knowledge, and relationships forged with industry, academic and charitable partners during my career, I was able to efficiently conduct my research into the two areas I had identified with an unmet need. I was then able to rapidly implement my findings into clinical practice (with regard to the dose surrogates) and establish knowledge sharing agreements with Stakeholders in terms of medical device development (with regard to new radiotherapy ink pigments), both of which have a potential international impact.

UCL Research Paper Declaration

UCL Research Paper Declaration Form: referencing the doctoral candidate's own published work(s)

1. **For a research manuscript that has already been published**

   a) What is the title of the manuscript?

   i). Identifying surrogates for heart and ipsilateral lung dose to guide field placement and treatment modality selection during virtual simulation of breast radiotherapy.

   ii). Permanent Indian ink tattoos for breast cancer radiotherapy: A United Kingdom study of the emotional impact on patients following radiotherapy.

   b) Please include a link or doi for the work:

   i). https://doi.org/10.1016/j.clon.2020.12.005

   ii). https://doi.org/10.1016/j.radi.2024.08.004

   c) Where was the work published?

   i). Clinical Oncology

   ii). Radiography

   d) Who published the work?

   i) and ii). Elsevier Ltd

   e) When was the work published?

   i). April 2021

   ii). October 2024

   f) List the manuscripts authors in the order they appear on the publication:

   i). [redacted]

   ii). [redacted]

   g) Was the work peer reviewed?

   i) and ii). Yes

   h) Have you retained the copyright?

   i) and ii). No

   i) Was an earlier form of the manuscript uploaded to a preprint server (e.g. medRxiv)? If yes, please give a link to the doi – N/A

   If 'No', please seek permission from the relevant publisher and check the next box next to the below statement:

- ✓ I acknowledge permission of the publisher named under 1d to include in this thesis portions of the publication named as included in 1c.

Taken from Elsevier website: "Pay-to-read, where articles are free to publish, but usually require a subscription or payment to read. When publishing subscription the author typically transfers copyright to the publisher. However, each author retains the right to re-use the article for certain personal and scholarly purposes, including the creation of some derivative works, without permission from, or payment to, Elsevier."

2. **N/A**

3. **For multi-authored work, please give a statement of the contribution covering all authors:**
   i). [redacted]

4. **In which chapter(s) of your thesis can this material be found?**

   i). Chapters 2 and 3

   ii). Chapters 4, 5 and 6

e-Signatures confirming that the information above is accurate (this form should be co-signed by the supervisor / senior author unless this is not appropriate):

Candidate:

Date: January 2025

Supervisor:

Date: January 2025

Table of Contents

List of Figures

Page No.

List of Appendices

Page No. A:

Chapter 1

Introduction

1.1 Introduction

Over 55,000 women are diagnosed with breast cancer every year in the United Kingdom, with approximately 33,000 referred for adjuvant radiotherapy (1). Post-operative radiotherapy is indicated for most patients following breast conservation and for those with large, locally advanced, or node positive disease post mastectomy (2). Adjuvant radiotherapy for early breast cancer reduces the risk of local recurrence by 70%, avoiding one cancer death for every four local recurrences it prevents (3). Breast radiotherapy therefore represents a significant proportion of the total radiotherapy caseload; in some centres constituting up to 50% of the total number of new patient referrals.

Radiotherapy technique development and implementation relies heavily on the availability and allocation of radiotherapy resources such as the radiotherapy workforce (therapeutic radiographers, clinical oncologists, dosimetrists and physicists), planning and treatment room capacity, and access to specialist equipment. Advances in the quality of radiotherapy delivery for a cancer sub-type is therefore highly sensitive to the size of that specific patient cohort. Inevitably, the success of providing an optimum breast radiotherapy service, even if this requires only a minimal increase in resource allocation per patient, is vulnerable to underinvestment and underdevelopment.

The balance between increasing radiotherapy quality and improved patient outcomes by increasing the complexity of planning and treatment delivery, with the impact this has on resources, must not be overlooked by National Health Service (NHS) commissioners, those developing national radiotherapy guidelines, and radiotherapy service managers when rationalising limited resources. Conversely, improvements in the efficiency of any component of the radiotherapy pathway for a large patient cohort will have a significant positive impact in terms of releasing resources for technique development and improving patient outcomes for the ever-increasing surviving population. We must also acknowledge the population-effect in terms of any intervention that reduces the rate or severity of toxicity (for example cardiac disease) or other outcome

measure (for example, body image satisfaction), as even if modest, will benefit many thousands of people following breast cancer treatment.

Members of the oncology workforce not involved in the breast radiotherapy pathway may be forgiven for assuming that my work is the product of research conducted a decade or two ago, if based solely on the appraisal of my thesis title. However, breast radiotherapy stands alone from all other cancer sub-types, not only due to the high number of referrals received throughout all radiotherapy departments, but also due to the methods employed to facilitate the production of the final dosimetric plan for treatment delivery.

The evolution of the pre-treatment pathway since the adoption of three-dimensional planning at the turn of the century, has taken a tangential path for breast cancer radiotherapy compared to all disease subgroups. Unlike all other radical treatment sites, pure, volume-based planning has not, and likely will not be universally adopted for all breast radiotherapy patients for many years to come. A hybrid virtually simulated field-based-volume approach is widely used, and as a result can be inefficient and ineffective in terms of the pre-treatment pathway. The reasons for this is multifactorial, and will be discussed in greater depth within this introductory chapter.

The continued use of some ‘hangovers’ of two-dimensional practice to three-dimensional planning have not translated well or been re-evaluated. This is the binding theme of the research that I have conducted and will present in this thesis under the title of *Radiotherapy for early breast cancer: Virtual simulation and patient alignment*. I have identified two elements of current practice that are strongly rooted in the principals of two-dimensional fluoroscopy simulation, that I consider to be out-dated and ineffective. Firstly, the use of two-dimensional heart and lung parameters to justify field border reduction and target volume compromise; and secondly, the requirement to apply permanent unnatural coloured skin alignment marks (radiotherapy tattoos) to the chest as a record of the irradiated field borders.

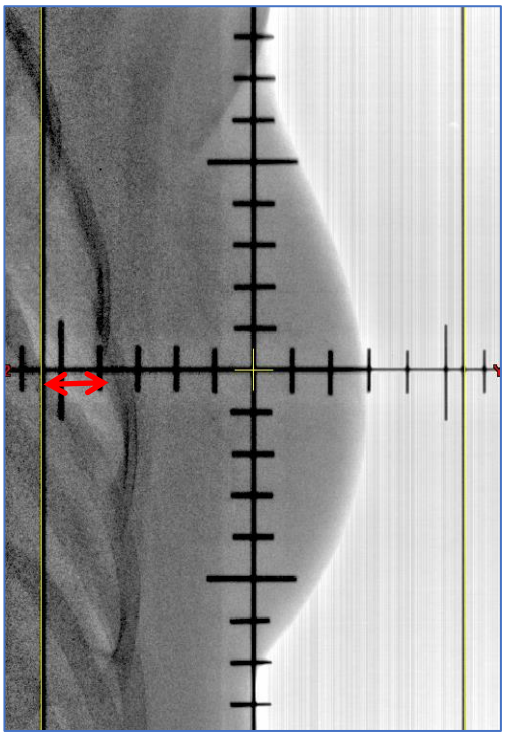
I will present solutions and adaptations (that I have identified through my research) to these widely utilised elements of breast radiotherapy planning that I consider feasible and important. This relates not only to the optimisation of the pre-treatment pathway, but also to patient outcomes in terms of the impact on body image of permanent unnatural coloured skin marking, that despite the justification for permanence now being null and void, persist in practice with no regard to the impact on quality of life when patients transgress into survivorship post-treatment. The combination of quantitative technical research and qualitative patient experience-based research, I think is an apt reflection of the varied role and skills required to be a Therapeutic Radiographer, of which I am very proud to be.

1.2 Breast radiotherapy planning

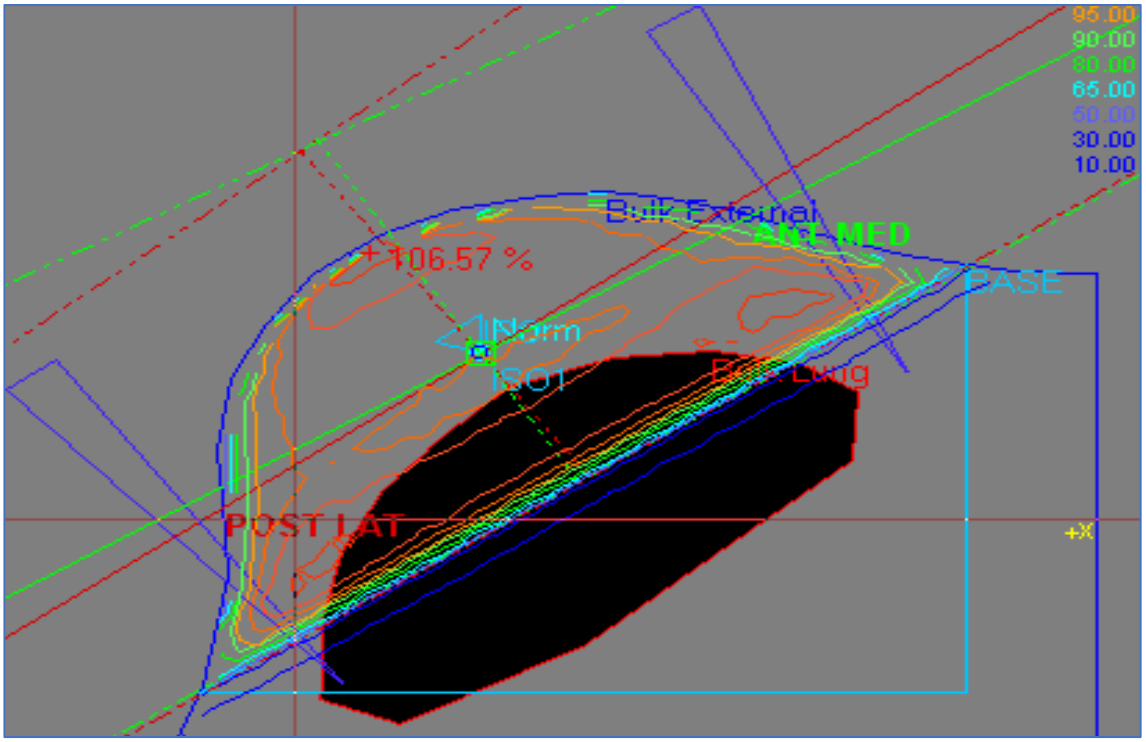
1.2.1 Radiotherapy technique evolution

Radiotherapy planning techniques and treatment delivery have evolved significantly over the last two decades, due to both hardware and software developments of the pre-treatment, planning and treatment technologies. This has facilitated the delivery of more complex conformal radiotherapy, with greater ability to spare normal tissues and optimise dose to the target volumes. The catalyst for the greatest change was borne from the replacement of two-dimensional fluoroscopy simulation, with three-dimensional computed tomography planning at the turn of the century. This was supported by the ever-growing advances in computational capability. Two-dimensional simulation was rapidly superseded by three-dimensional virtual simulation, whereby dose could be optimised throughout the entire treatment field as opposed to on just a single axial slice, aided by the delineation of clinical targets volumes and organs at risk (figures 1&2).

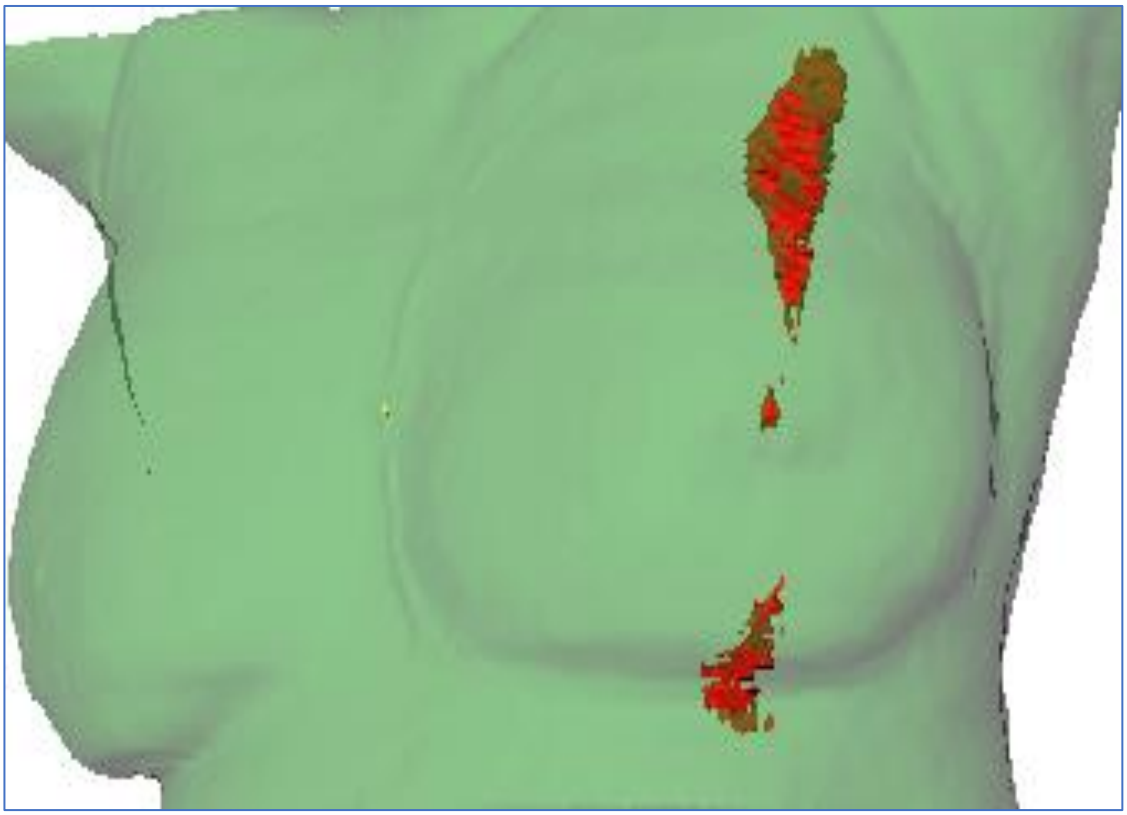
Figure 1: Two-dimensional fluoroscopy simulation and simple dose calculation for breast radiotherapy



2D fluoroscopy simulation image of the medial tangential breast field.
Arrow = Central lung depth often used as a field placement tolerance

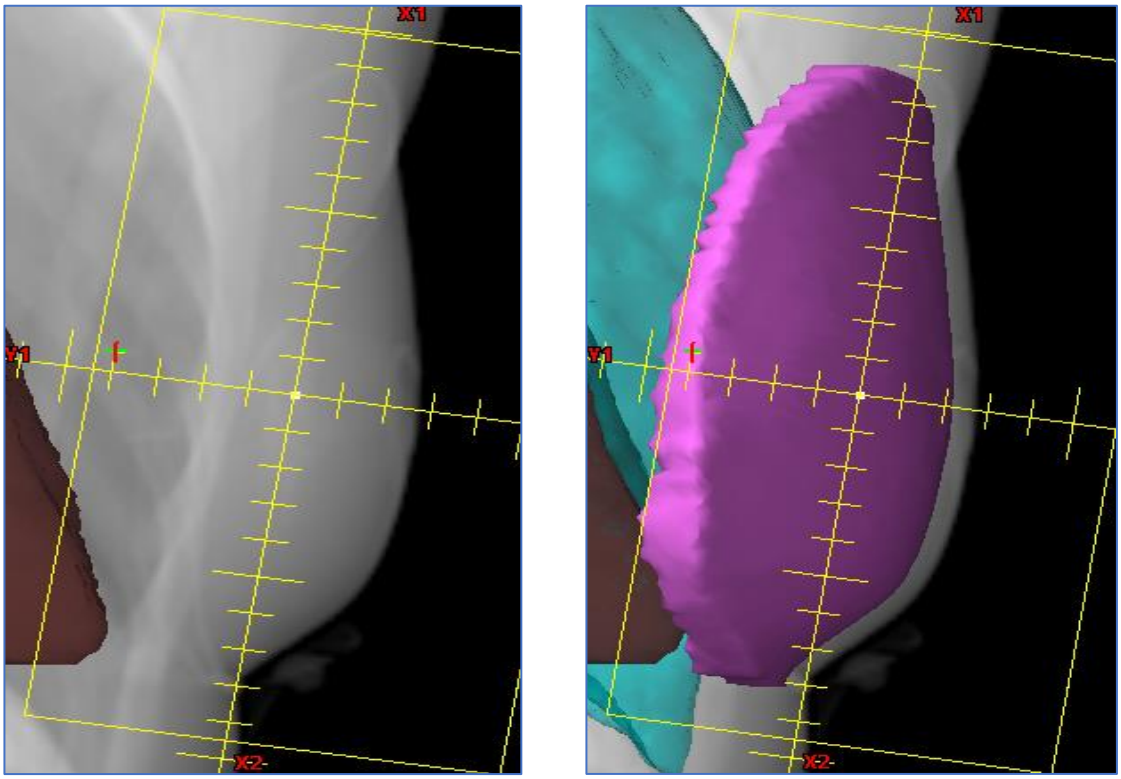


2D dose optimisation - Single axial slice digitised from manually contoured central slice with standard Hounsfield Units assigned for body and lung density. Lung contour approximated from the central lung depth measurement according to the 2D fluoroscopy simulation image of the medial field.

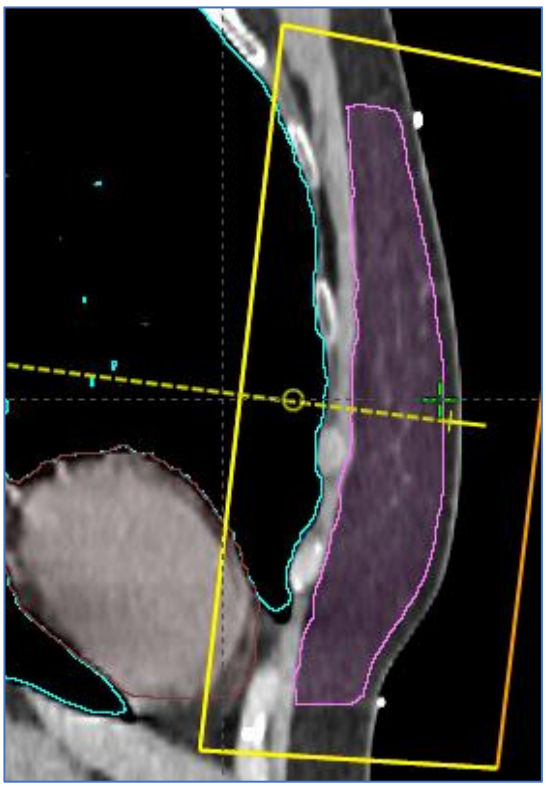


Impact of single slice 2D dose optimisation when applied to 3D CT data set. Red volume represents dose >107%, exceeding ICRU 50/62 dose levels, contributing to increased skin toxicity and poor breast cosmesis.

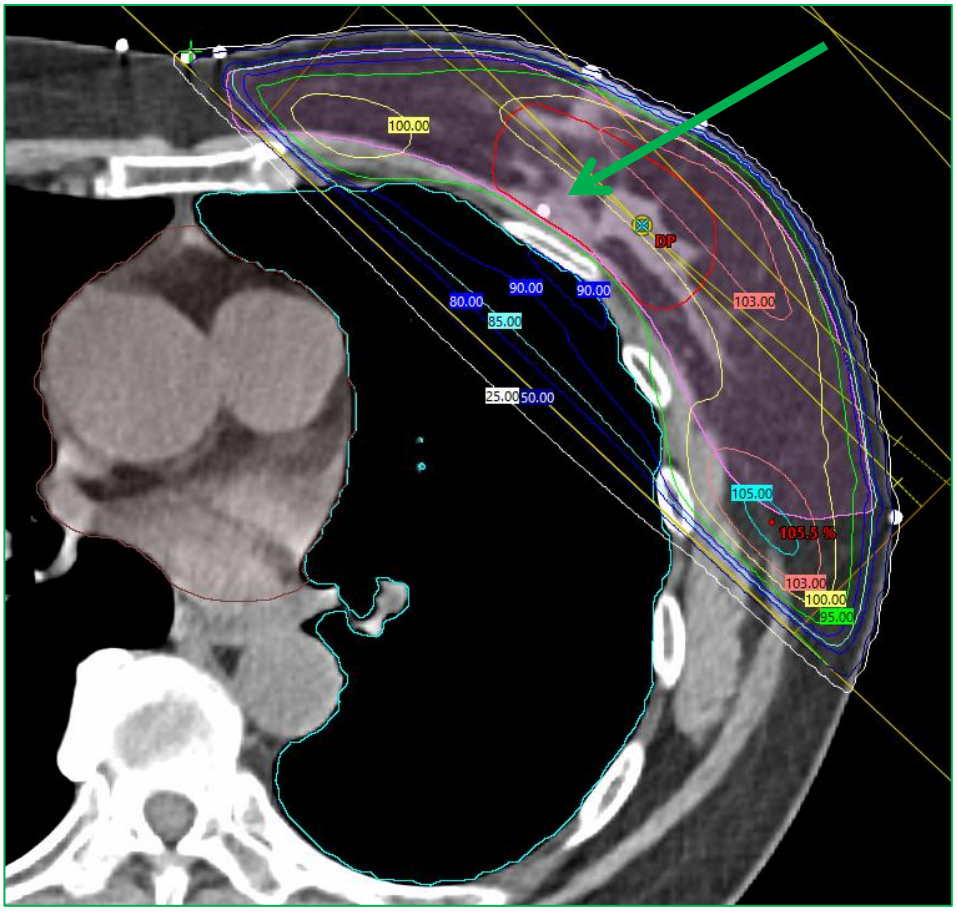
Figure 2: Three-dimensional CT virtual simulation and dose calculation for breast radiotherapy

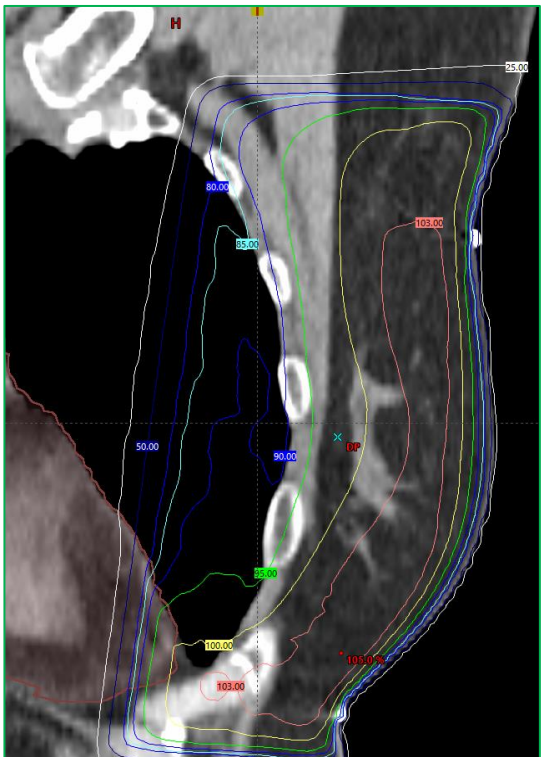


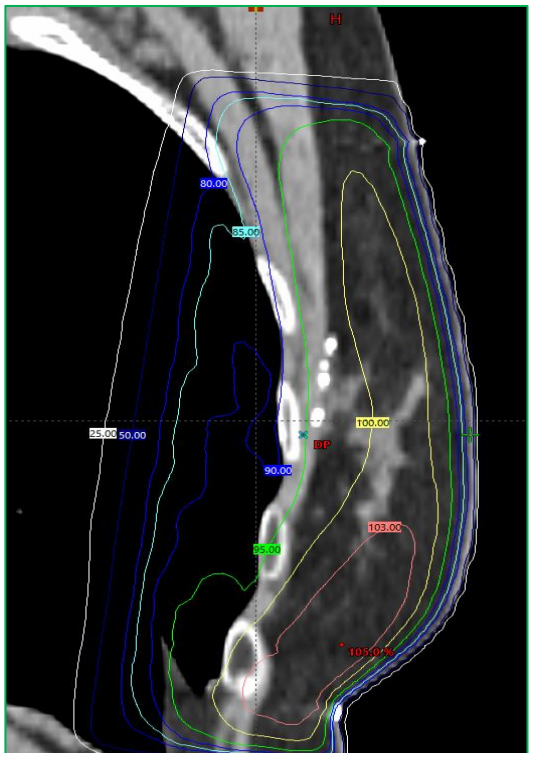
Digitally reconstructed radiograph (DRR) with 3D clinical target volume and organs at risk (OARs) delineated and displayed in relation to the virtually simulated medial tangential field : Pink: Breast CTV, Maroon: Heart, Blue: Ipsilateral lung.



Sagittal cross section demonstrating soft tissue delineation according to CT data to aid field localisation.
Radiopaque markers represent palpated breast tissue.







Axial, coronal and sagittal CT views demonstrating the optimised 3D dose distribution. Arrow: Surgical clip marking the excision cavity, Red: Tumour bed CTV, Pink: Whole breast CTV, Maroon: Heart, Blue: Ipsilateral lung, Yellow: Tangential field.

For the majority of treatment sites, virtual simulation has since become redundant, replaced with volume-based planning, whereby the target volumes (gross tumour volume and clinical target volumes) and organs at risk are delineated on the CT dataset (often supported by the registration of diagnostic MRI and PET-CT images) by the clinical oncologist. The isocentre placement and field parameters are subsequently defined by the radiotherapy dosimetrist and optimised with either forward or inverse planning techniques to meet pre-specified dose objectives (targets) and constraints (organs at risk).

Breast radiotherapy planning however, still largely relies on virtual simulation for the localisation of the tangential fields in terms of defining the treatment isocentre, field parameters, gantry angles and use of multi-leaf collimators to shape the beam. This is performed by the referring radiotherapy consultant and pre-treatment radiographers prior to sending the plan for dose optimisation. This is due to the ability of this efficient technique and beam arrangement to cover the target, avoid organs at risk, and provide effective patient set-up for this large patient cohort (4). The dose to the virtually simulated fields is three-dimensionally optimised according to International Commission on Radiation Units and Measurement requirements (5,6), ensuring that the dose is homogeneous, the target is not under-dosed, and that 'hotspots' within the plan are removed. This not only improves the tumour control probability, but also reduces the risk of poor cosmetic outcome which is associated with dose inhomogeneity (figure 1 & 2).

A weakness of this method of planning, is that whilst organ at risk doses can be reported on the final dosimetric plan dose volume histograms (DVH's), they cannot be optimised to meet dose constraints without amendment of the isocentre and tangential field placement. Relocating the isocentre of virtually simulated fields at the point of plan optimisation introduces inefficiencies to the pre-treatment pathway. Therefore, the ability to predict organ at risk doses at the point of virtual simulation can be highly valuable in avoiding such late-stage changes which may delay patients starting their adjuvant radiotherapy and increase the resource burden of this large patient cohort.

1.2.2 Workforce and skill mix

In response to an increasing cancer incidence and the declining oncology medical workforce, culminating in a 10% (and growing) vacancy rate of clinical oncologists (7,8), skill mix and role extension of therapeutic radiographers has been an important response in meeting demand and improving radiotherapy services (9–12).

As recognised in the Department of Health's Cancer Reform Strategy (13), the high workload of breast cancer radiotherapy has supported the UK-wide implementation of advanced practice therapeutic radiographers, with similar strategies emerging globally. Where successfully implemented, therapeutic radiographers are leading the virtual simulation and volume delineation of breast cancer radiotherapy which has streamlined the pre-treatment process, whereby the clinical decision-making of field localisation can be performed in the absence of the clinical oncologist. The appointment of consultant radiographers has further pushed the boundaries of non-medical oncologic patient management, with particular success in the growing number of consultant breast radiographers demonstrating a positive impact on radiotherapy services (14).

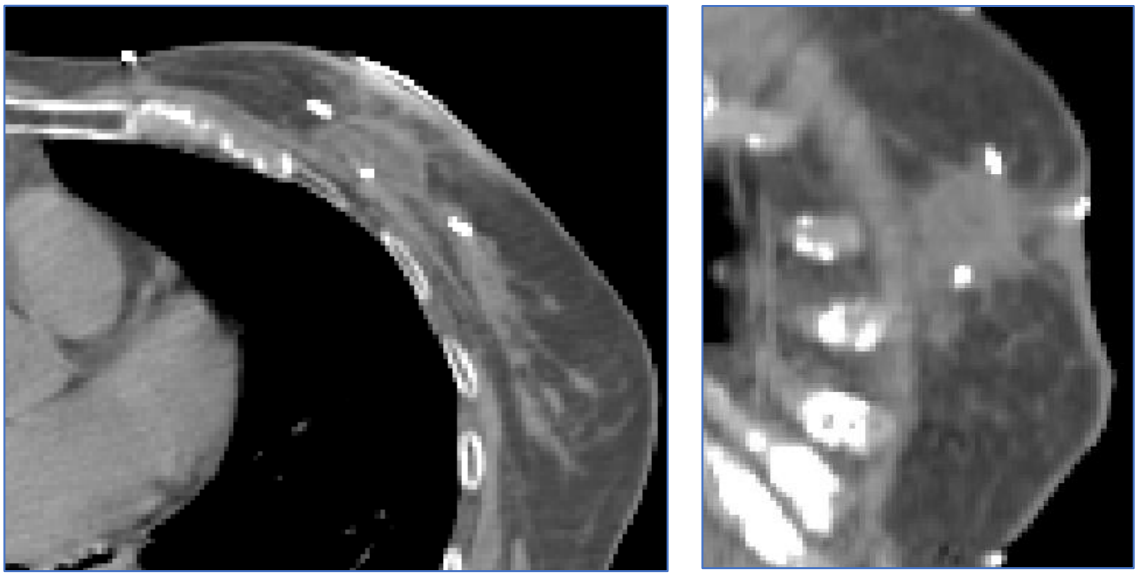
1.2.3 Target volume delineation

Breast radiotherapy has increased in complexity in recent years in terms of target volume delineation and subsequent treatment delivery.

The first widely implemented change in the UK was instigated by the IMPORT High trial which, through successful collaboration with the British Association of Surgical Oncology, realised the ability to accurately delineate the tumour bed by standardising the use of circumferential demarcation surgical clips for all patients undergoing breast conservation (15,16) (figure 3). Demarcating the excision cavity is not only important when aiming to effectively dose escalate the tumour bed, but also to avoid the risk of target miss with the whole breast fields (17–19). The standardisation of excision cavity clips was particularly timely with the increased use of oncoplastic surgical techniques, which results in the excision

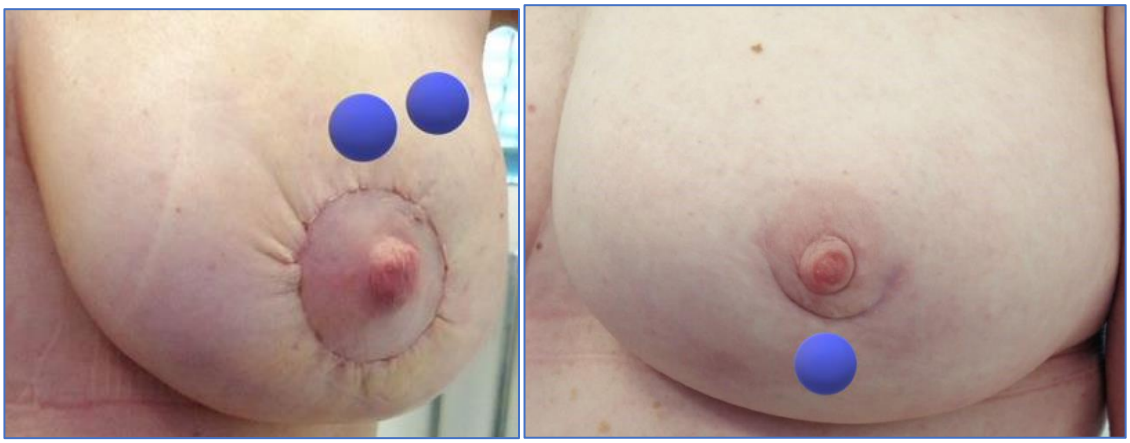
scar (previously used to localise the tumour bed for 'clinically marked-up' electron boost) being located remotely from the excision cavity (17) (figure 4).

Figure 3: Radiopaque clips to the breast conserving surgery tumour bed excision cavity



Axial (left) and coronal (right) views demonstrating paired titanium clips demarcating the excision cavity

Figure 4: Oncoplastic surgery remote scar placement

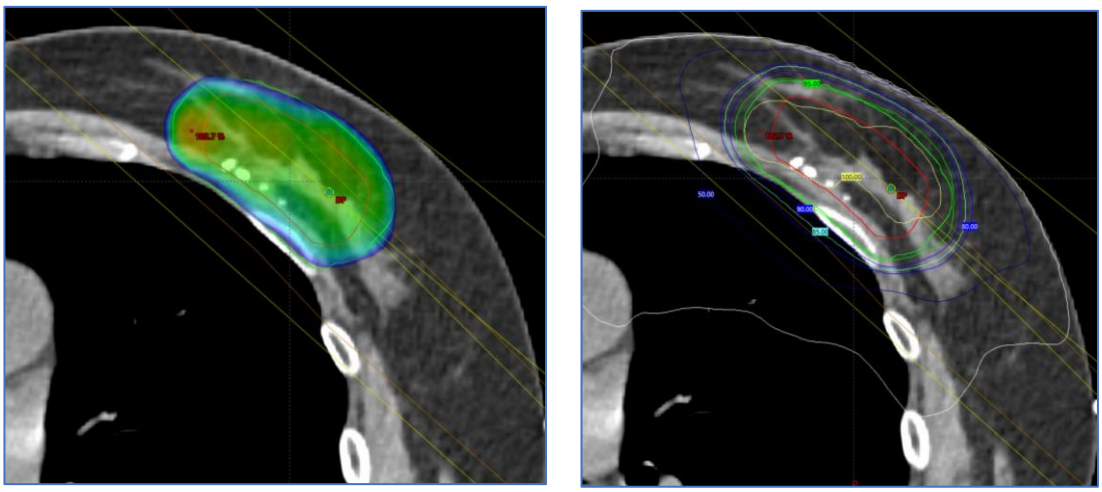


Images: Presented with permission of Consultant Oncoplastic Surgeon Mr [redacted]. Blue markers: tumour location. Right image shows cosmetic result following removal of 60 mm tumour and glandular mobilisation.

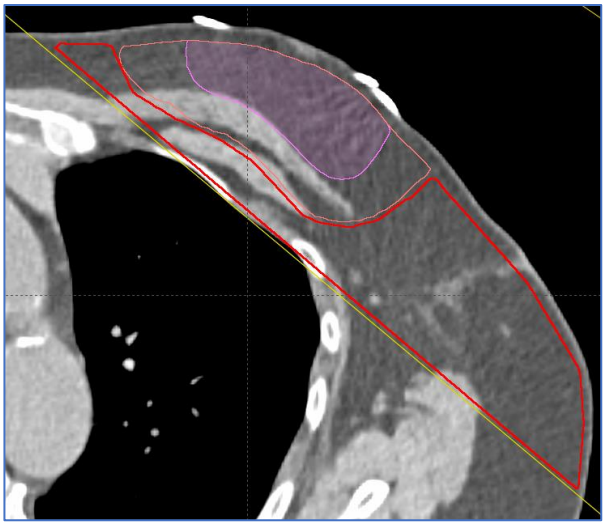
Delineating the tumour bed clinical target volume (surgical clips and any CT-defined architectural change), enables three-dimensional corrective treatment verification, smaller planning target volumes, and more conformal dose boosting of the tumour bed with intensity modulated radiotherapy (figure 5a*)*. This reduces the normal tissue complication probability by reducing the volume of normal tissue irradiated, and also improves local disease control. This may in part explain the lower-than-expected local recurrence rates reported in the control arms of modern studies where such techniques were employed (17,20,21).

Prior to the implementation of excision cavity delineation, there was minimal target voluming for breast radiotherapy, with the radiation dosimetrist aiming for uniform dose optimisation across the entire rectangular tangential beams. This results in unnecessary use of segment and boost fields to deliver the prescription dose to the soft tissues that are incidentally within the tangential field but not part of the target (i.e., not breast tissue) *(*figure 5b). With the ability to accurately localise the tumour bed, practice has expanded to include the delineation of the whole breast (breast conserving surgery) or chest wall (post mastectomy) targets. This enables the radiation dosimetrist to conform and shape the dose within the tangential fields; minimising the dose to those tissues within the field aperture that are not included within the planning target volume (figure 5c).

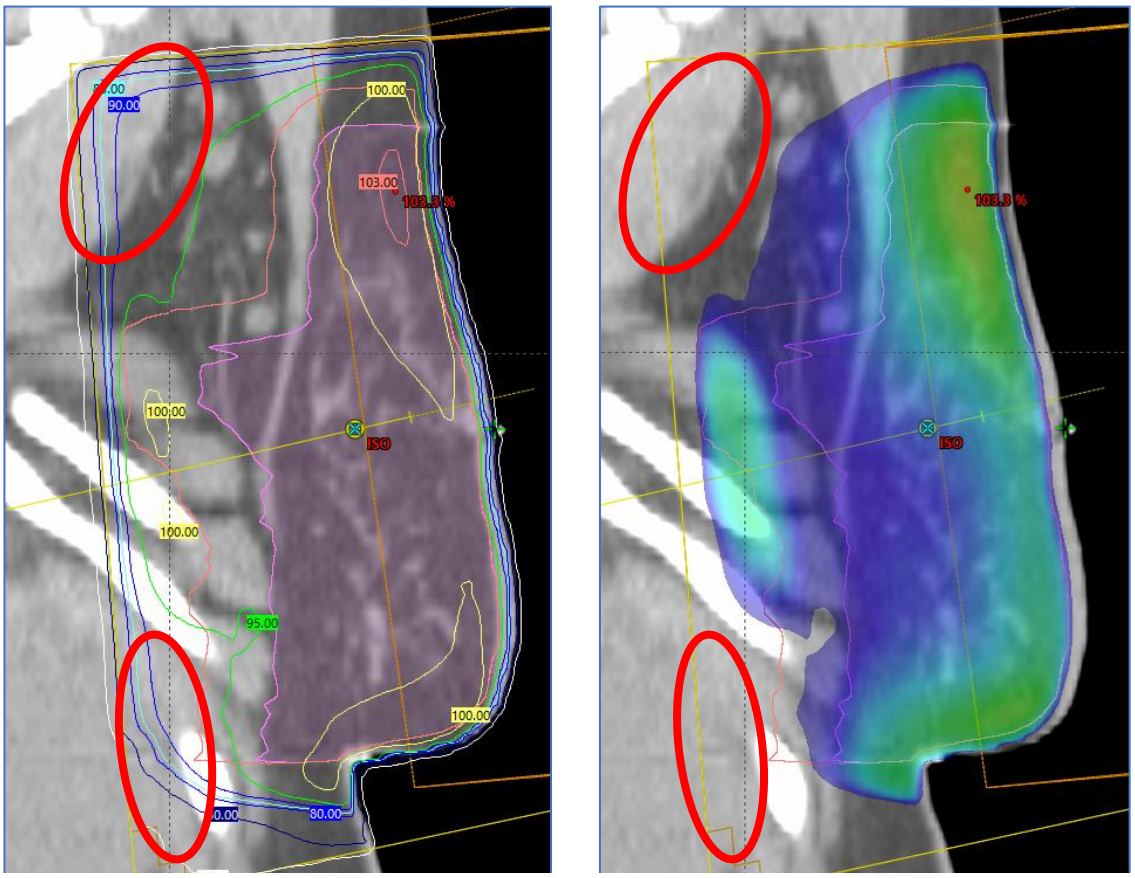
Figure 5: Tumour bed delineation, target volume dose conformality and normal tissue sparing



5a: Highly conformal IMAT boost dose conformity to the excision cavity PTV (dose colour wash, left), and low dose to the surrounding non-boost target (isodose lines, right).



5b: Whole breast CTV (pink) and PTV (peach) delineation avoids the unnecessary dose optimisation of achieving prescription dose to the entire field perimeter (yellow). Non-target tissue highlighted here in red (delineated not required in planning process).



5c: Dose prescription (green isodose line / blue colourwash) delivered to PTV (peach). Soft tissues incidentally within radiation field (red) do not require dose prescription. target tissue highlighted here in red (delineated not required in planning process).

A second significant change to practice is in response of three highly influential publications that reported an increase in disease-free and overall survival when including the internal mammary nodes (IMN) in the radiotherapy target volume (22–24). The benefit to survival of irradiating the internal mammary nodes is likely

to be greatest (up to 10%) in those patients with 4 or more involved axillary nodes (N2 disease), with a meta-analysis suggesting that the true benefit to overall survival may be even greater with modern radiotherapy techniques whereby the rate of excess death related to radiation-induced cardiac mortality is less (25). As a result, in 2016 the Royal College of Radiologists published guidelines recommending the inclusion of the ipsilateral IMN in a subset of high-risk patients; which was subsequently incorporated into the NICE breast cancer guidelines in 2018 (updated in 2024), which recommended that IMN radiotherapy should be considered for node positive patients (26,27).

The high-risk patients identified as benefiting from IMN irradiation by the RCR and NICE criteria represent between 13 and 18% of breast radiotherapy referrals (28). The impact on workforce, capacity and equipment resources is high and multifactorial. The time to delineate the regional nodal targets is significantly greater, with additional training requirements to ensure competency of both clinical oncologists and specialist radiographers. The development and implementation of artificial intelligence in the form of auto-segmentation is showing promise, although is not yet at the stage of replacing the human role of accurate delineation and interpretation of multi-source imaging data.

More complex planning and treatment techniques are required in acknowledgement of the higher failure rate of achieving the more complex breast radiotherapy dose objectives and constraints when using a conventional tangential approach (29). As described above, the consequence of the new indication for a relatively large patient cohort, was the slow and inconsistent implementation of IMN irradiation across the UK; demonstrated by less than 15% of patients receiving radiotherapy to the IMN in whom it was indicated in 2021; five years after the RCR recommendation (30).

1.2.4 Organs at risk

For breast radiotherapy, the dose-limiting organs influencing field placement are most commonly the ipsilateral lung, and for left-sided cases, the heart. A tangential field arrangement is generally successful in achieving ipsilateral lung

and heart tolerance doses that are not commonly associated with a high incidence of acute or chronic side effects. However, due to the high incidence of breast cancer, the wide indication for post-operative radiotherapy, and an increasing surviving population (estimated to be 1.2 million in the UK by 2030) (31), even a low rate of radiation-induced toxicity can have a significant population effect. Reducing normal tissue dose therefore remains highly topical and at the forefront of any technique development.

From as early at the 1980's, correlations between estimated irradiated lung volume (according to two-dimensionally measured central lung depth) and radiation pneumonitis and fibrosis were being investigated to provide tolerances during breast radiotherapy simulation (32). 2 cm central lung depth was a widely used tolerance parameter. However, cardiac tissue could not be easily visualised on two-dimensional fluoroscopy simulation (figure 1) and so dose could not be estimated, correlations with cardiac toxicity could not be undertaken, and tolerance levels could not be set. The incidental cardiac dose for left-sided breast radiotherapy was therefore largely ignored and remained unreported. This was despite an excess of cardiac deaths highlighted in a number of large, robust studies (3).

Now, with the ability to visualise and delineate the heart and ipsilateral lung tissue on three-dimensional CT data (figure 2), dose estimation may no longer be considered relevant as dose volume histograms can be calculated from the final dosimetric plan. However, there is still a need for virtual simulation surrogates for lung and heart dose, to ensure that the optimised plan does not unexpectedly exceed the tolerance doses.

Central lung depth as a surrogate for ipsilateral lung dose to guide field placement was initially translated from two-dimensional simulation techniques into the three-dimensional CT virtual simulation environment. Despite a positive correlation between increasing central lung depth and ipsilateral lung dose (33), virtually simulating fields to a central lung depth tolerance may result in unnecessary compromise to the target dose, or exceeding the lung tolerance as it is not predictive of the resulting lung dose volume histogram.

In 2013, the seminal publication by Darby *et al* identified mean heart dose (MHD) as an important tolerance indicator in terms of cardiac morbidity and mortality (34). This validated parameter for late major coronary events states that for every 1.0 Gy increase in MHD, risk increases by 7.4%. Prior to identifying MHD as a biomarker for cardiac toxicity, whilst minimising heart dose was acknowledged as an important planning consideration, dose and risk could not be correlated, which made dose constraints difficult to establish. The Royal College of Radiologists have since published guidelines on appropriate MHD constraints depending on the extent of the nodal targets included in the radiation field (26).

However, what is still required is an accurate surrogate for use during virtual simulation to ensure that MHD constraints will be achieved without unnecessary compromise to the target volumes. Without this, the planning process is inefficient, and may require late-stage changes if tolerance doses are exceeded.

There are currently no identified accurate and predictive surrogates for heart or ipsilateral lung dose for clinical use during the virtual simulation of breast radiotherapy. This has the potential to create inefficiencies in the pre-treatment pathway if isocentre placement, field parameters, treatment technique or treatment modality need to be changed at the late stage of plan approval.

1.2.5 Deep inspiration breath hold

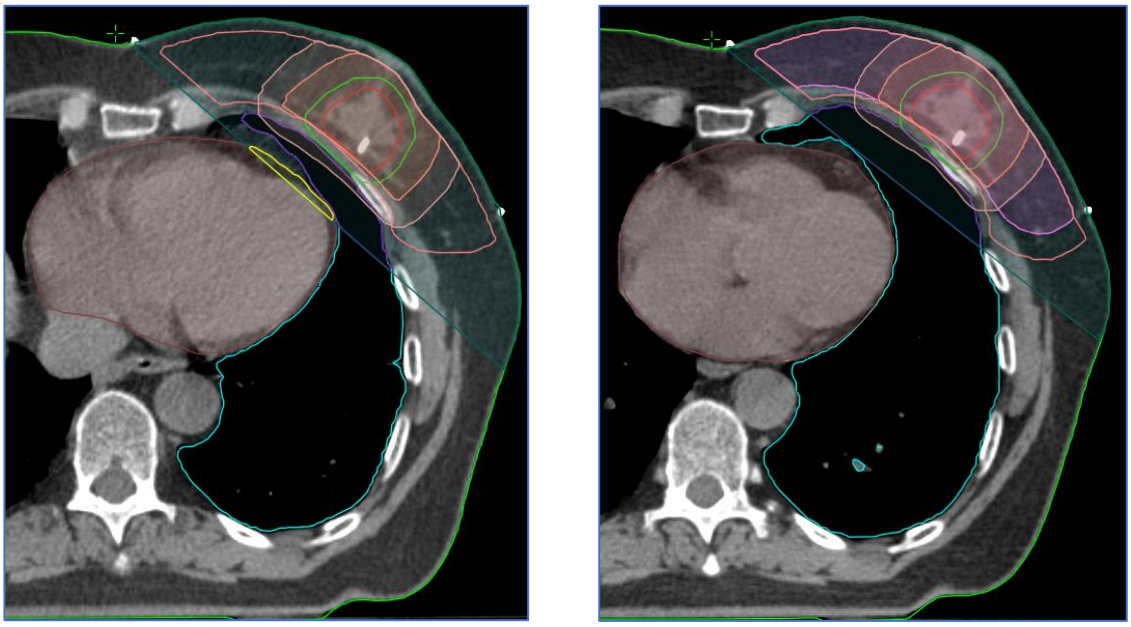
In response to the convincing evidence of excess cardiac morbidity and mortality associated with the incidental irradiation of the heart during left-sided breast radiotherapy, various methods have been employed to reduce cardiac dose.

Physically shielding the heart with multi-leaf collimators, partial breast radiotherapy and prone techniques have all demonstrated some dose reduction in selected cases. However, depending on tumour location, these methods are not universally effective and have limited clinical application (26,35–37).

Deep inspiration breath hold (DIBH) is a technique that exploits the relationship between lung inflation and the displacement of the heart from the target volumes

(38), and has been widely implemented throughout the UK and worldwide. The various methods of delivering treatment in DIBH; be that voluntary or equipment-based DIBH, have demonstrated consistent and effective MHD reductions of around 50% when treating with both conventional tangential, and intensity modulated arc therapy (29,39–44) (figure 6).

Figure 6: Free-Breathing versus DIBH and irradiated heart volume



Left axial CT: Free breathing demonstrating volume of heart (yellow) in radiation field (blue) versus Right axial CT: impact of DIBH eliminating heart from the radiation field.

DIBH has therefore proven very effective in achieving internationally recognised dose constraints for MHD. However, for some patients, the cardiac dose approaches or exceeds tolerance, and a very careful balance between field placement, compromise of target coverage and resulting heart dose must be struck. An accurate surrogate for MHD is therefore required and is currently an unmet need.

1.2.6 Technique selection

For some patients, in particular those with unfavourable anatomy, such as pectus excavatum, and more commonly in those requiring left-sided IMN radiotherapy, a

tangential photon plan cannot achieve organ at risk tolerance levels (ipsilateral lung and heart).

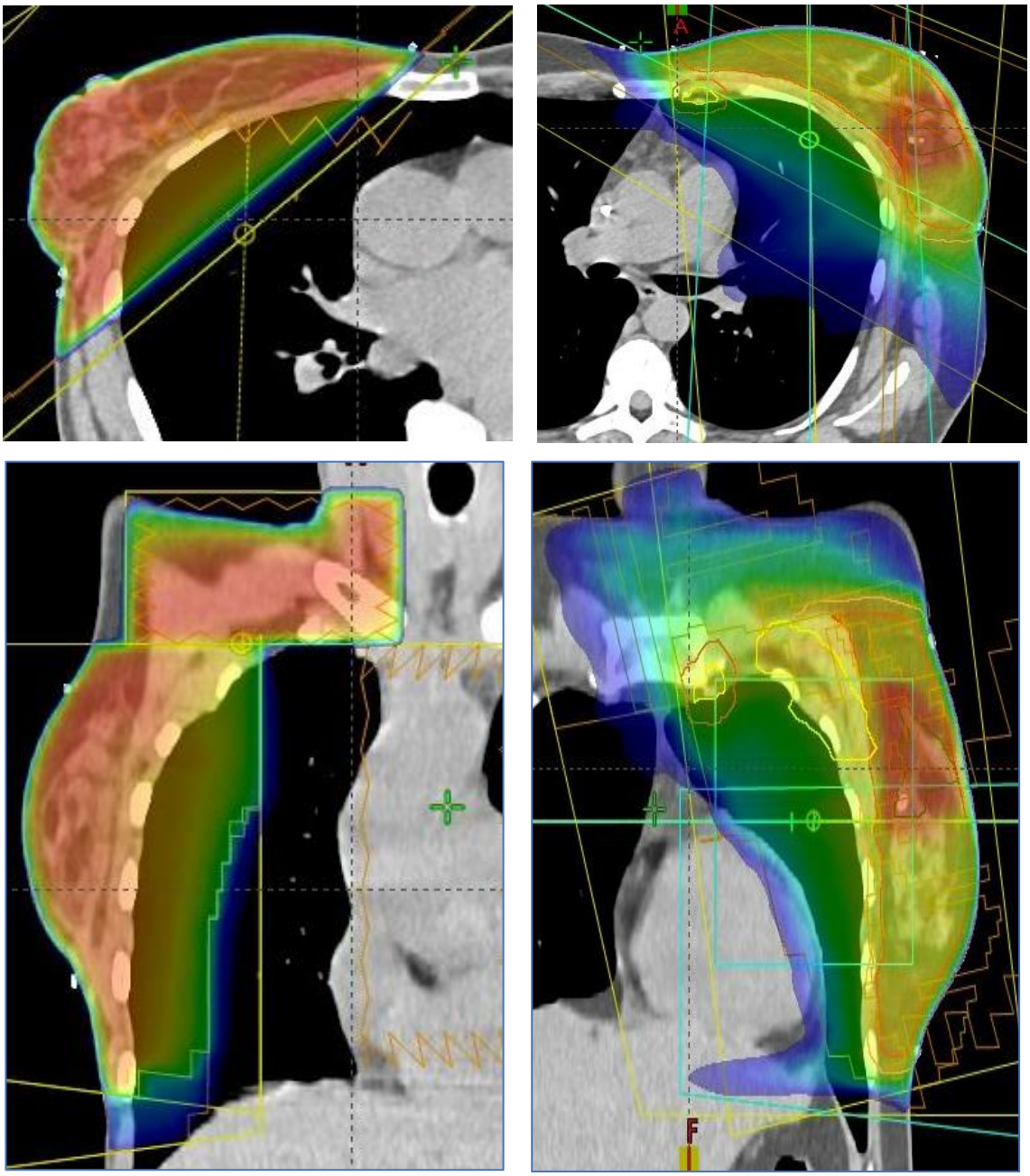
When treating the IMN, a wide tangential photon plan may be considered the primary technique of choice. Firstly, the planning, treatment and verification techniques are similar to the standard breast or chest wall tangential technique; thus, requiring no additional training other than in the delineation of the regional nodal targets. As described above, due to the size of the patient cohort, these are important factors to increase the feasibility of successful implementation of IMN radiotherapy.

Secondly, a wide tangential approach is very successful in minimising the dose to surrounding normal tissues such as the oesophagus, thyroid, contralateral breast and contralateral lung. In cases for whom a wide tangential photon technique is not possible due to either unacceptable organ at risk doses, or inadequate dosing of the targets, intensity modulated arc therapy (IMAT) is usually considered. IMAT is able to deliver radiotherapy more conformally, with a steep dose gradient, sparing tissues and structures in close proximity to the target. This is now the accepted gold standard for many treatment sites, such as cancers of the head and neck where there are multiple dose-limiting structures adjacent to targets with high dose objectives.

However, IMAT does not come without compromise. Unlike in the sites where IMAT is the standard technique, breast and regional nodal RT targets encompass a much longer, and larger volume of the patient. The superior and inferior field extent will commonly extend from the lower cervical spine, down to the diaphragm. It is the exit dose of the rotational beam that gives rise to concern, with a low dose bath to a high volume of normal tissue (figure 7). This may not only increase the incidence of acute and late toxicity of non-target tissue compared to a tangential technique (45), but will also increase the risk second cancers. Hoekestra *et al,* (2018) reported that 75-97% of second malignancies in patients irradiated for breast cancer were of the lung; with a higher excess lifetime risk for IMAT versus 3D conformal accelerated partial breast RT, (3.5% versus 2.5%) (46). It is my opinion therefore, that the importance of giving a wide

tangential technique the best opportunity to achieve the dosimetric requirements must therefore not be overlooked or underestimated before opting for an IMAT technique.

Figure 7: Wide tangential versus intensity modulated arc therapy and volume of incidental irradiation of normal tissues



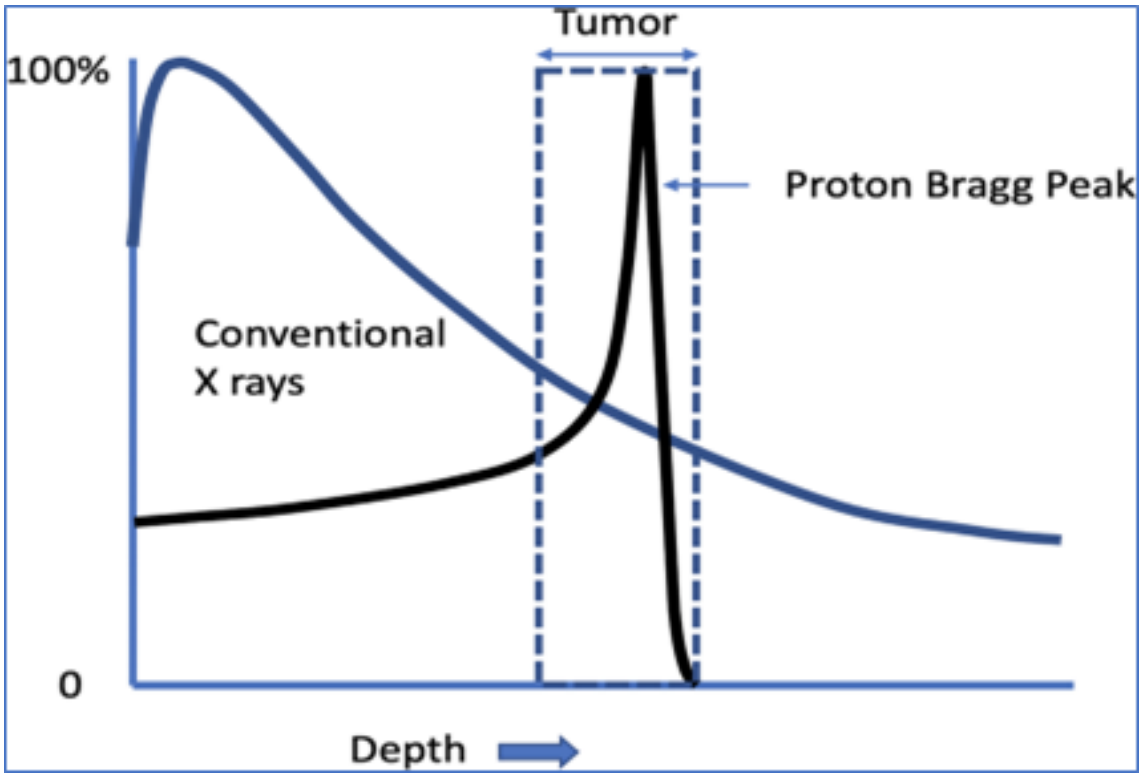
10 Gy low dose bath of wide tangential photons (left) and IMAT photons (right) on axial (upper) and coronal (lower) views.

1.2.7 Proton beam therapy (PBT) and breast cancer

There may be some cases where despite deploying the most modern photon beam dose optimisation in DIBH; a deliverable photon plan is not clinically acceptable in terms of exceeding the normal tissue tolerance doses (lung, heart, contralateral breast) if target objectives are to be met. This is currently subject to international interest; to identify a breast radiotherapy patient cohort that may benefit from proton beam therapy (PBT).

PBT exploits the beam characteristic of low end-of-range doses, affording sharp dose gradients between the target volume and normal tissues beyond the depth of the targeted Bragg peak (figure 8). Various planning studies have demonstrated that PBT results in superior coverage of the planning target volumes, specifically when including the internal mammary nodes, with significantly lower doses to the ipsilateral lung, heart and contralateral breast, therefore likely to reduce the associated risk of acute and long-term side effects.

Figure 8: Proton versus photon dose deposition in tissue (47)



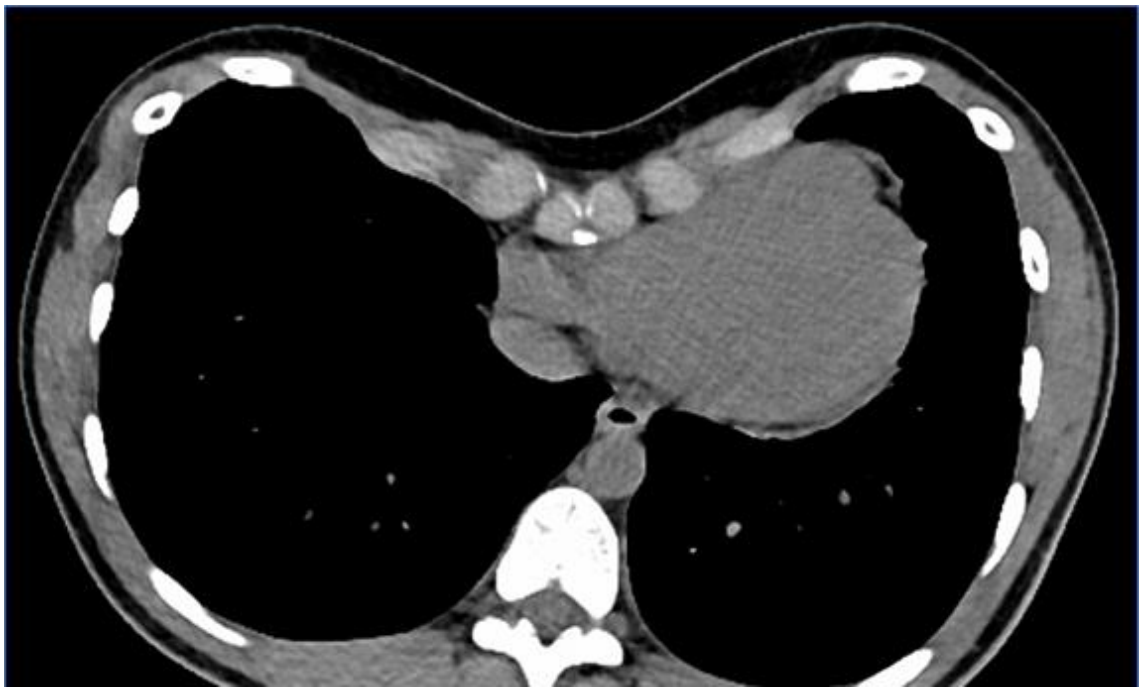
Ares *et al,* (2010), were early investigators of the potential role of proton beam therapy for breast cancer (48). They found that the benefit of PBT was the highest for patients with complex target volumes; namely, the inclusion of the internal mammary nodes. When optimising the IMRT and PBT plans to achieve adequate target coverage, the mean heart dose was reduced from 17 Gy to 4 Gy.

Jiminez *et al* (2013) identified that there may be specific cohorts within the breast cancer population in whom a photon plan is more likely to fail; with potential gains for PBT (49). This was a small planning study of five patients: with target volumes encompassing the regional nodes (including the internal mammary nodes) in patients with bilateral implant-based breast reconstructions. PBT was shown to be superior in terms of heart and ipsilateral lung dose (V20 Gy heart and ipsilateral lung 0.4 and 4.3% for PBT, versus 13.6 and 36.7% for wide tangential photons).

Ranger *et al (*2016) reported reductions in mean heart dose (2.6 versus 0.5 Gy), ipsilateral lung V17 Gy (28.2 versus 16.3 Gy) and contralateral breast mean dose (1.5 versus 0.2 Gy) when comparing DIBH IMAT and PBT for plans that included the internal mammary nodes (29). The IMAT plans in this cohort did not fail planning tolerances in terms of both target volume objectives and organ at risk constraints (albeit OAR doses were significantly lower). Therefore, the much greater cost, resource burden and accessibility issues related to PBT may be difficult to justify, depending on the expected rate of photon plan failure in the entire IMN population. The fourteen patients selected for this study were not necessarily representative of those termed ‘challenging anatomy’, as previously described. However, a larger study (n179) by Stick *et al,* (2019) estimated that 22% of patients will fail dose constraints (mean heart dose tolerance 4 Gy, ipsilateral lung V17 Gy 37%) if meeting internal mammary node dose objectives with DIBH 3DCT or IMAT photon techniques (50).

Settatree *et al* (2021) suggest that the patient cohort most likely to benefit from PBT compared to DIBH IMAT, are those with pectus excavatum (figure 9); with plan comparisons of left-sided treatment that included the regional nodes demonstrating MHD reductions by an average of 3.4 Gy (51).

Figure 9: Axial CT image of patient with pectus excavatum (52)



Proton beam therapy (PBT) has been available as a treatment modality within the UK National Health Service since 2019, following the Department of Health £250 million capital investment to commission two Proton beam centres; the Christie Hospital, Manchester, and University College London Hospital, London (53).

NHS England produced a clinical commissioning policy that lists specific patient cohorts in whom proton beam therapy can be offered as a standard indication (54). Breast cancer is not included on this indication list; the explanation provided for this is that high quality photon beam radiotherapy achieves a low risk of serious side effects, and that there is insufficient evidence to support proton beam therapy in this diagnostic cohort (55). The proton beam therapy indication list is not unchangeable. Therefore, if new evidence emerges to justify a new patient cohort, then this will be appraised and included accordingly.

1.2.8 PARABLE Trial

The PARABLE trial is an Institute of Cancer Research (ICR), National Institute of Health and Care Research (NIHR) [Efficacy and Mechanism Evaluation] (EME) randomised controlled trial that aims to evaluate the role of proton beam therapy

for breast cancer for those patients in whom photon radiotherapy may currently underserve in terms of cardiac dose. This is defined as those patients that have a 2% or greater risk of radiation-induced cardiac toxicity from a photon technique (56).

If the co-primary endpoints of MHD and 2-year patient reported normal tissue toxicity in the breast are demonstrated to be positive outcomes, the PARABLE trial is likely to provide the high-level evidence required for a cohort of breast cancer radiotherapy patients to be included on the proton beam therapy standard indication list. This cohort, if eligible for proton beam therapy, is estimated at approximately 500 of the 30,000 breast radiotherapy patients treated per year in the United Kingdom (57).

The PARABLE trial protocol presents the calculated MHD threshold that would need to be achieved on a photon plan to inflict a 2% or greater risk of radiation-induced cardiac toxicity. The factors affecting the MHD threshold are patient age and the presence of one or more pre-existing cardiac risk factors (56) (figure 10). Eligible patients are therefore most likely to be young (<45 years), with left-sided or bilateral breast cancer, requiring inclusion of the left IMN in the target volume; or patients with anatomy such as pectus excavatum which results in a large volume of the heart being directly located beneath the irradiated breast tissue, and therefore resulting in a significant dose when treated with photons (51) (figure 9).

Figure 10: PARABLE mean heart dose thresholds for 2% cardiac risk (56)

Age	Mean Heart Dose for ≥2% Cardiac Risk			
	No cardiac risk factor		At least one cardiac risk factor	
	No boost	Boost	No boost	Boost
≤44	≥4 Gy	≥3.7 Gy	≥2.4 Gy	≥2.1 Gy
45 - 54	≥6 Gy	≥6 Gy	≥3.6 Gy	≥3.3 Gy
55 - 64	≥6 Gy	≥6 Gy	≥4.3 Gy	≥4 Gy
65+	≥6 Gy	≥6 Gy	≥5.3 Gy	≥5 Gy

For patients to be eligible for PARABLE trial randomisation, the treating photon centre must first estimate the MHD from a photon plan. This requires the patient to complete the entire photon pathway up to the point of final dosimetric plan generation that is usually a just few days before the patient is scheduled to start the treatment course.

The time between the new-patient radiotherapy consultation to confirming trial eligibility is usually around four weeks. Accounting for the time to be seen in the clinical oncology clinic may extend this by a further two to four weeks. Once confirmed as eligible, the patient will provide their trial consent if wishing to participate and will then be randomised. For those patients randomised to proton beam therapy, the patient will be referred via the national proton beam therapy portal and allocated to one of the two proton beam centres (58). The treatment pathway will then restart, with a new-patient clinic at the proton beam centre and replanning from the proton beam CT scanner data. From the point of the new proton beam consultation to starting treatment is approximately three weeks.

Accounting for the time to be seen in the clinical oncology proton beam clinic, this may extend the timeline by a further two weeks. In summary, patients treated with proton beam therapy using the existing trial pathway are likely to have their treatment pathway extended, compared to standard photon beam therapy by approximately six weeks; thirteen weeks from the initial radiotherapy referral.

Once again, this highlights the role of a virtual simulation dose surrogate, in the context of the PARABLE trial, to accurately predict MHD early in the photon patient pathway and identify eligible patients. Prior to my research, there was no such surrogate available. This will be discussed further in Chapter 2.

Chapter 2

Virtual simulation of breast radiotherapy; identifying surrogates for heart and ipsilateral lung dose to guide field placement and modality selection

2.1 Introduction

As described in my introductory chapter, breast radiotherapy continues to utilise virtual simulation for the vast majority of cases. Despite developments in treatment planning and delivery facilitating complex treatment plans, volume delineation has been incorporated into the virtual simulation process rather than moving to pure volume-based planning. This hybrid approach retains many of the benefits of virtual simulation such as keeping field parameters as small as possible to cover the target volume and providing patient set-up instructions for localisation of the isocentre, most commonly from an anterior reference tattoo (most suitably recorded by the pre-treatment radiographers).

Providing a dosimetrist with planning target volumes alone would result in a more extensive radiation field compared to those placed during virtual simulation. This is due to the referring consultant and/or the experienced specialist pre-treatment radiographers applying their knowledge and interpretation of each patient-specific breast cancer (pathology, surgery, excision margins, tumour and nodal stage) in relation to the 50% isodose field borders. For example, for many decades in the context of two-dimensional fluoroscopy simulation, the medial field border of a standard whole breast tangential field did not extend over midline (unless there was an inner quadrant tumour). With the breast clinical target volume and subsequent planning target volume often approaching or crossing the midline, a volume-based plan, even if employing a tangential beam arrangement, would result in a field that breeches the midline; increasing heart, lung and contralateral breast dose. We know from the decades of simulation-based planning experience, that this ‘compromise’ to the whole breast planning target volume does not result in loss of local control, and therefore treating over midline to achieve 95% coverage of the medial whole breast planning target volume is not necessary.

The requirement of dose surrogates for the heart and ipsilateral lung during virtual simulation is required to ensure an efficient pre-treatment pathway and use of resources, as well as identifying early in the radiotherapy pathway when an alternative treatment technique (e.g. IMAT) or modality (e.g. PBT) should be

considered. Having worked as a pre-treatment therapeutic radiographer from early in my career, I identified the value of three-dimensional dose surrogates during the implementation of 3D breast planning. It was clear that using the two-dimensional lung tolerance parameter of central lung depth had little or no bearing on the volume of lung and resulting dose to the ipsilateral lung (V18 Gy). Having first identified a role for accurate dose surrogate for lung, and subsequently heart dose almost a decade ago, I had not envisioned that such dose surrogates may eventually have a role in the streamlining of a future PBT referral pathway. This treatment modality was still several years into the future of the UK radiotherapy service, with many significant photon developments to first navigate.

2.2 Study aim

The aim of this study was to identify surrogates predictive of heart and ipsilateral lung tolerance parameters (based on a 40 Gy in 15 fraction schedule) during the virtual simulation of tangential breast radiotherapy, to aid optimal field placement and treatment modality selection.

2.3 Materials and methods

2.3.1 Model-building cohort

50 patient datasets were retrospectively selected for analysis. To ensure a wide range of heart and ipsilateral lung doses, the eligibility for selection was patients referred for left breast or chest wall RT prior to 2017, when all patients were scanned and treated in free-breathing (FB). From 2017, radiotherapy practice evolved and all patients at our institution were scanned in DIBH, which reduces both heart and ipsilateral lung dose (29). This cohort did not include any elective nodal radiotherapy.

Patients were positioned supine on a 15-degree inclined breast board with both arms raised and supported in a wing-board cradle. The CT scans were acquired in 2.5 mm slice thickness, extending from mid neck to the bottom of the lungs (to facilitate calculation of lung dose volume histograms).

The clinical target volumes (tumour bed, whole breast or chest wall) and organs at risk (heart, ipsilateral lung) were manually contoured and fields virtually simulated by advanced breast therapeutic radiographers. All volumes and fields were peer-reviewed according to standard departmental practice. Plans were generated using the Varian Eclipse treatment planning system (TPS) and calculated with AAA algorithm v13.7. The prescribed dose was 40.05 Gy in 15 fractions delivered with 6 or 10 MV tangential photon fields and a non-divergent posterior field border. Fields were optimised to meet ICRU 52/60 planning criteria using a combination of wedges and segment fields.

Following the virtual simulation of the tangential fields, a field contour was manually delineated on the axial slice at the superior and inferior field extent and interpolated to create a 3D volume. This was modified to exclude any areas where multi-leaf collimators (MLC) were present. The heart and ipsilateral lung contours were automatically duplicated and cropped to remove any part of the volume outside of the virtually simulated fields according to the field contour (figure 11). This added approximately 2 minutes per case to the virtual simulation process. These structures were re-labelled HIF (heart-in-field) and ILF (ipsilateral lung-in-field).

Percentage of heart-in-field (%HIF) and percentage of ipsilateral lung-in-field (%ILF) were calculated and recorded for each patient. Mean heart dose (MHD) and ipsilateral lung $V18_{Gy}$ (percentage of the ipsilateral lung receiving 18 Gy) were recorded from the optimised treatment plan, as reported by the treatment planning system.

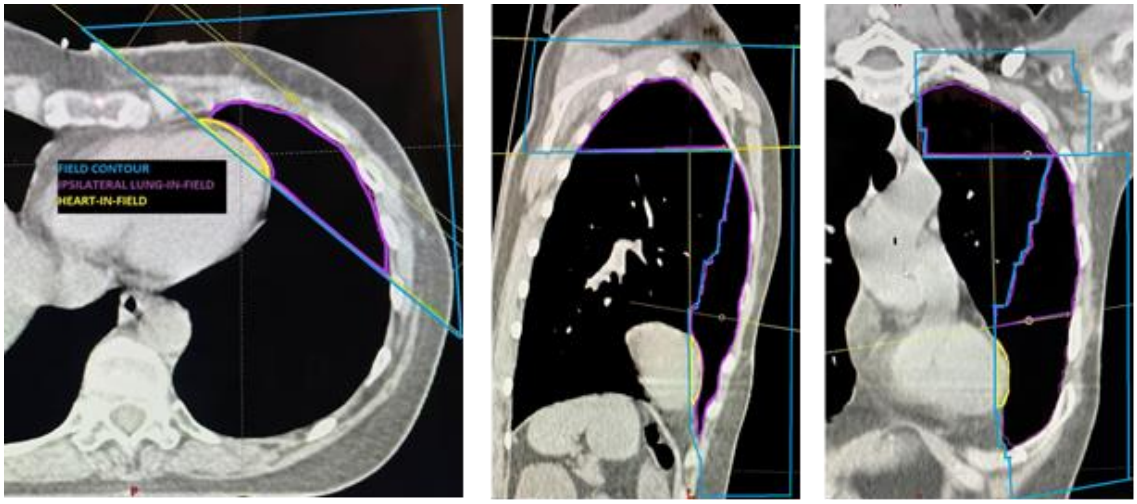
Pearson's correlation coefficients and linear regressions (Microsoft Excel) were performed between; %HIF and MHD, and between %ILF and ipsilateral lung $V18_{Gy}$. Two-tailed statistical significance was set at $p \leq 0.05$. A strong correlation is defined when R is greater than 0.5 (59). The shared variance is reported using R squared (R^2) (60).

2.3.2 Validation cohort

Ten left and ten right-sided cases which included an additional anterior supraclavicular fossa field; and ten left and ten right-sided cases including the internal mammary nodes using a wide tangential technique and anterior SCF field, were selected from patients referred between August 2019 to August 2020 (post-DIBH implementation).

The method described above was repeated and the validation data was plotted against the linear regressions of the corresponding model-based cohort.

Figure 11: Axial, sagittal and coronal views of ILF & HIF contours



2.3.3 Virtual simulation threshold values

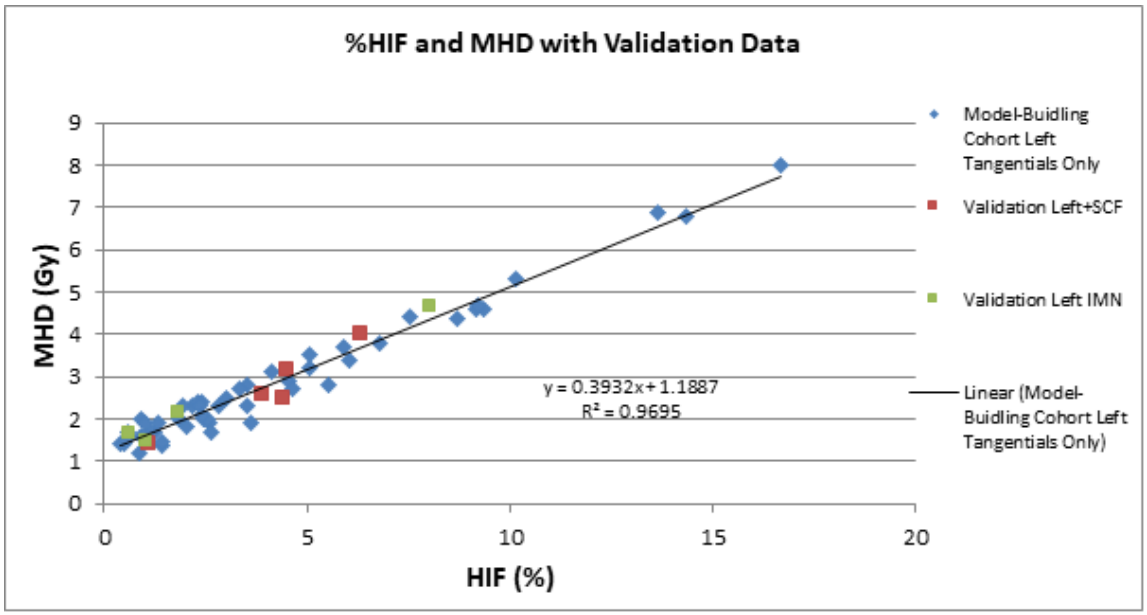
The upper 95% confidence intervals (CI) for the gradient and offset of the corresponding model-building linear regression, were used to calculate maximum point values for %HIF and %ILF to be used during virtual simulation to ensure that MHD and ipsilateral lung $V18_{Gy}$ do not exceed commonly used tolerance doses.

2.4 Results

2.4.1 Model-building cohort (n50)

The median %HIF was 2.6 (0.4 – 16.7). Median MHD was 2.3 (1.2 - 8.0) Gy. A statistically significant strong positive relationship was found between %HIF and MHD, with R^2 = 0.97, *p*<.0001. For MHD, the gradient was an increase of 0.4 Gy (95% CI 0.37 - 0.41) per 1%HIF with an offset of 1.2 Gy (95% CI 1.08 - 1.3) (figure 12).

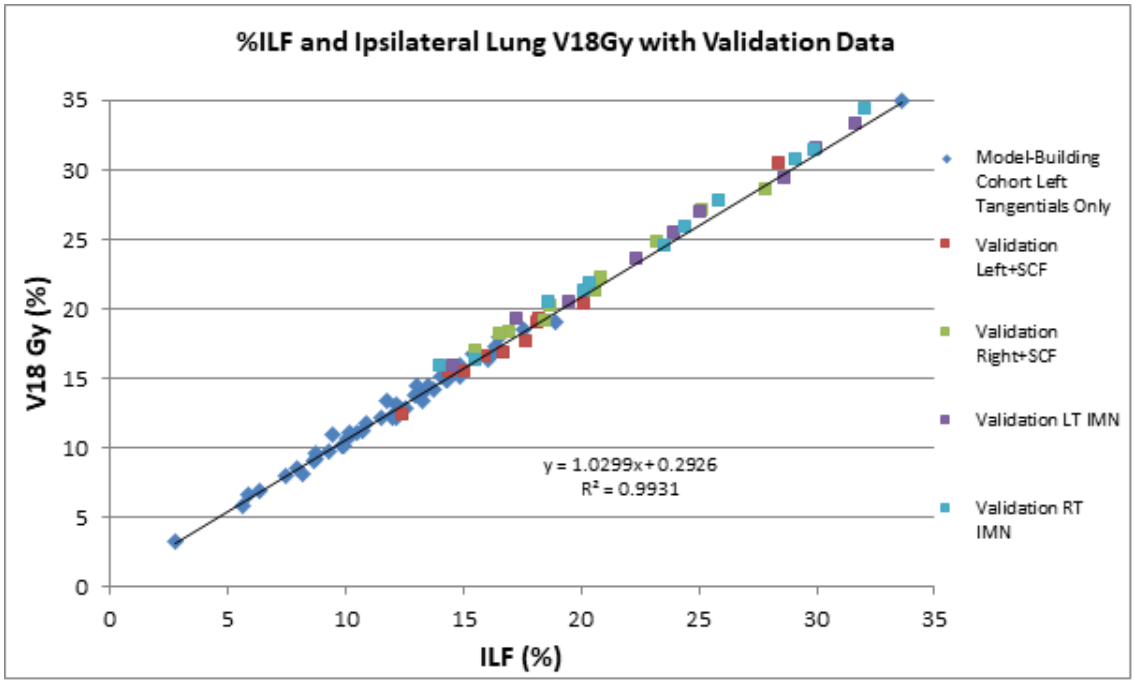
Figure 12: Correlation between mean MHD and percentage of heart in the virtually simulated fields (%HIF)



The median %ILF was 12.1 (2.8 – 33.6). Median IL $V18_{Gy}$ was 12.6 % (3.3 to 35).

A statistically significant strong positive relationship was found between %ILF and ipsilateral lung $V18_{Gy}$ with R^2 = 0.99, *p*<.0001. For ipsilateral lung $V18_{Gy}$, the gradient was an increase of 1.03% (95% CI 1.01 - 1.05) per 1%ILF with an offset of 0.3% (95% CI -0.03 - 0.62) (figure 13).

Figure 13: Correlation between ipsilateral lung $V18_{Gy}$ and percentage of lung in the virtually simulated fields (%ILF)



2.4.2 Validation cohort (n40)

As predicted, due to the implementation of a DIBH technique in 2018 for all left-sided cases, the number of patients with heart-in-field was lower than for the model-building cohort where all patients were scanned and treated in free-breathing.

Five of the ten left-sided cases with an anterior nodal field had heart-in-field, with a median %HIF and MHD of 4.4 (1.1 - 6.3) and 2.6 (1.4 - 4.0) Gy.

Four of the ten left-sided cases including the IMN within a wide tangential technique and an anterior nodal field, had heart-in-field, with a median %HIF and MHD of 1.4 (0.6 - 8.0) and 2.0 (1.5 - 4.7) Gy.

The median %ILF and ipsilateral lung $V18_{Gy}$ was 20.1 (12.4 - 32.0) and 20.9 (12.4 - 34.4) %. Plotted along the linear regression of the corresponding model-building cohort, the validation cohort was consistent. This confirms that %HIF and %ILF are predictive surrogates for MHD and ipsilateral lung $V18_{Gy}$ during the virtual

simulation of left and right-sided cases when treating with; tangential fields alone; tangential fields with an anterior nodal field and wide tangential fields including the IMN and an anterior nodal field.

2.4.3 Virtual simulation threshold values

To provide maximum point values for %HIF and %ILF during virtual simulation to ensure that tolerance doses for heart and ipsilateral lung are not exceeded, the upper 95% CI for the gradient and offset for each linear regression was used for a number of clinically relevant dose levels (figure 14).

Figure 14: Virtual simulation maximum threshold values for %HIF and %ILF for clinically relevant mean heart dose and ipsilateral lung V18$_{Gy}$

Clinical example of common application	**MHD Tolerance (Gy)**	**Maximum %HIF during VSim**
Breast / chest wall only	2.0	1.7
Breast / chest wall + IMN (optimal)	4.0	6.5
Breast / chest wall + IMN (mandatory)	6.0	11.4
	IL V18Gy Tolerance (%)	**Maximum %ILF during VSim**
Breast / chest wall only	15	13.5
Breast / chest wall + SCF +/- axillary nodes (optimal)	25	23.0
Breast / chest wall + SCF +/- axillary nodes (mandated)	30	28.0
Breast / chest wall + SCF +/- axillary nodes + IMN (mandated)	35	32.5

2.4.4 Estimating heart and ipsilateral lung dose

For some cases where further compromise to target volumes is not acceptable, and %HIF and / or %ILF threshold levels need to be exceeded, a simple formula can be used to estimate MHD and IL $V18_{Gy.}$ (figure 15).

Figure 15: Formulae for estimating MHD and ipsilateral lung $V18_{Gy}$ based on virtual simulation dose surrogates %HIF and %ILF

MHD (Gy) = (0.4 x %HIF) + 1.2

IL $V18_{Gy}$ % = (1.03 x %ILF) + 0.3

2.5 Discussion

Radiotherapy has a significant role in the management of early breast cancer, with a large proportion of radiotherapy resources required to treat this patient cohort. Testament to improvements in early diagnosis, surgery, systemic therapy and radiotherapy; is the ever-growing surviving breast cancer population (61), however this has raised the significance of treatment-related toxicity. Advances in radiotherapy technology have responded accordingly, with the ability to manipulate lung and heart position with DIBH management systems, accurately delineate target volumes and organs at risk on high resolution 3D anatomical data, optimise dose calculation using multi-field forward and inverse planning, produce highly conformal plans, and verify and deliver radiotherapy with millimetre precision.

However, whilst national guidelines have been developed in response to the evidence from high quality randomised controlled trials, there remains a wide variation in the clinical implementation in terms of the radiotherapy target volumes and treatment techniques. This was quantified by a national survey of UK breast radiotherapy practice in 2019, representing 81% of UK centres (30). Despite the NICE and RCR guidelines being published 1 and 3 years prior to this data capture (26,62), 46% of left-sided cases were not treated in DIBH as recommended, even though 98% of centres had the technique available. More than 85% of patients did not have their IMN irradiated despite meeting the indicated criteria. The impact on forward and inverse planning pre-treatment resources was suggested as a contributing factor to this lack of compliance.

Optimising the radiotherapy pre-treatment pathway by streamlining processes and utilising the skill mix of the multidisciplinary team, will not only reduce treatment delays, but can release radiographer, dosimetry, physics and clinician resources for those cases requiring more complex technique development, implementation and delivery. This was recognised by the Department of Health's Cancer Reform Strategy 2007) (13), which supported the UK-wide implementation of advanced practice therapeutic radiographers, with similar strategies emerging globally (63). Tsang *et al* (2021) identify the role of consultant

therapeutic radiographers to innovate new ways of providing services and implementing change that will benefit patient outcomes. The unity of their site-specific clinical knowledge and technical expertise can enable consultant radiographers to identify inefficiencies that can have a negative impact on workload and best-practice implementation; particularly when associated with a large patient cohort (14). Identifying and addressing barriers to evidence-based best-practice related to resource impact, should help support its implementation, and reduce the variation in the quality of radiotherapy provision.

Since the publication by Darby *et* al in 2013, MHD has emerged as an important consideration when planning breast radiotherapy (34). This has been a catalyst for the wide implementation of DIBH for left-sided radiotherapy, which is highly successful in keeping MHD to under 2 Gy when treating the breast or chest wall alone (as recommended by the RCR (26)). However, as highlighted by Locke & Drinkwater (2021) (30), the use of DIBH is not universal, and with recent changes in the indication to treat the ipsilateral IMN in a subset of high-risk patients, the heart (and ipsilateral lung) has once again become the dose limiting organ, and the cause of a more widespread, unmet need of including these nodal target volumes in the radiotherapy plan.

The ability for tangential breast radiotherapy to achieve optimum target coverage whilst meeting heart and ipsilateral lung dose constraints can be challenging, particularly (but not exclusively) for left-sided patients requiring irradiation of the IMN, a medial tumour bed, unfavourable anatomy, (pectus excavatum, small lung volume, anterior/lateral heart position), for those patients unable to perform DIBH, or for centres with limited DIBH provision.

Various methods are employed during virtual simulation to reduce the amount of heart and ipsilateral lung in the fields such as reducing the medial and/or lateral tangential field borders, multileaf collimation to shield the organs at risk, or moving the isocentre more superiorly to reduce the volume of lung irradiated in the exit path of the anterior supraclavicular fossa field. However, making beam modifications resulting in target coverage compromise without an accurate virtual simulation surrogate for heart and ipsilateral lung dose may result in unnecessary undertreatment of the target volumes, or organ at risk doses exceeding tolerance

in the final optimised plan. The latter requires detailed discussion between the dosimetrist and clinical oncologist at the late stage of plan approval; only days from when the radiotherapy course is due to commence. Amending isocentre placement, field borders, accepting higher heart and lung doses, changing to an IMAT technique, or deciding to omit nodal targets, are all possible outcomes which can delay commencement of the radiotherapy course. This will also impose short-notice resource demands on the clinical oncologist, dosimetrists and physicists. Therefore, having accurate, predictive heart and ipsilateral lung dose surrogates during virtual simulation is highly desirable.

Lorenzen *et al,* (2016) identified a correlation between maximum heart distance and MHD (64). Despite the linear relationship and R^2 of 0.85, the study did not provide a method for translating this clinically into virtual simulation practice. It is also not as accurate at predicting MHD compared to %HIF as identified in my study (R^2 0.97).

Kong *et al,* (2002) aimed to define a maximum heart distance threshold for field placement of breast radiotherapy (65). Twenty-two left-sided cases were evaluated and demonstrated a positive correlation between maximum heart distance and MHD (R^2 0.76). They provided a method to translate these findings during virtual simulation; suggesting that MHD could be approximated as 3 times the maximum heart distance. However, with a smaller R^2 value, this 2-D surrogate is not an accurate predictor of MHD. Whilst the gradient of MHD appears fairly consistent between similar studies (2.4 - 2.8 Gy and per 1 cm maximum heart distance), the offset appears to be wide (0.4 to 4.1 Gy) (64), suggesting that planning to a maximum heart distance tolerance may result in either unnecessary compromise to target coverage by the virtually simulated fields, or the optimised plan exceeding MHD tolerance.

My study has identified %HIF and %ILF as predictive surrogates for heart and ipsilateral lung dose during virtual simulation. With the high R^2 values and narrow confidence intervals for calculating threshold values for %HIF and %ILF, these virtual simulation surrogates will ensure that target coverage compromises will not be made unnecessarily, and that heart and ipsilateral lung tolerances doses will not be unexpectedly exceeded on the final treatment plan. As acknowledged

in the RCR guidelines (26), tolerance levels for the organs at risk are dependent on the extent of the nodal target volumes (+/- SCF, +/- IMN) to be irradiated. I have provided maximum %HIF to achieve a MHD tolerance of 2, 4 and 6 Gy (1.7, 6.5 and 11.4%), and maximum %ILF to achieve ipsilateral lung $V18_{Gy}$ of 15%, 25%, 30% and 35% (13.5, 23, 28 and 32.5%). This efficiency-improving addition to the virtual simulation process is easy to implement, adding only 2-minutes per case, which as described above is an important factor to support the implementation to the large patient cohort. This has been fully implemented within our breast radiotherapy pre-treatment pathway. Since implementing this at my centre, no patient of the 1000+ planned has required isocentre or field border modifications based on unacceptable lung or mean dose at the point of plan optimisation.

Although my validation cohort has a smaller incidence of HIF compared to the model-building cohort (free-breathing tangential fields only) due to implementation of DIBH, not only did this provide additional data at the higher range of ipsilateral lung volume, but also demonstrated that these surrogates can be employed when nodal targets are included; be that with fields including the supraclavicular nodes, or wide tangential fields that include the IMN.

It is important to acknowledge that in some cases, a modest increase to heart and ipsilateral lung dose will be accepted before considering target compromise or an IMAT technique.

Firstly, compromising target coverage may reduce the chance of tumour control, and potentially reduce the therapeutic ratio of radiotherapy. Secondly, the improved target dose conformity of IMAT must be balanced against the increased low-dose bath to normal tissues, and in many cases, higher MHD.

Whilst Hoekestra *et al,* (2018) reported a 1% increase in excess lifetime risk of second cancers for partial breast VMAT versus tangential radiotherapy (46), this may be considered an underestimation when considering the more extensive field length when nodal targets are included, such as the supraclavicular or IMNs. The exit dose of a pan-nodal IMAT plan includes the thyroid, oesophagus,

contralateral breast and contralateral lung (of between 10-20 Gy); all of which receive minimal internal scatter dose only with a tangential technique (<1 Gy).

Hall *et al* (2003) estimated that intensity modulated radiotherapy may double the rate of second cancers (66). If considering the conclusion of Grantzau & Overgaard (2014) following their meta-analysis of second cancer studies; that any reduction in dose to the organs adjacent to the radiation fields will reduce the rate of second cancer induction; the inverse may also be considered true; that any increase in dose will increase the second cancer rate (67). In their analysis of the data of Morton *et al* (2012) (68), they estimated that risk of second cancer increases by 9% per 1 Gy increase in oesophageal dose. This rate is likely to vary when considering the other organs within the exit dose bath of IMAT. For example, we know that the breast tissue of a young woman (under 40 years), is much more sensitive to radiation-induced second cancer, with this risk increasing as the volume of breast irradiated increases (69).

In cases where the tangential field placement cannot be compromised further, and the virtual simulation tolerance of %HIF or %ILF is exceeded, I have provided simple formulae, which due to the narrow confidence intervals, can accurately estimate the heart and ipsilateral lung doses. In the clinical setting, these dose estimations support the referring consultant and pre-treatment team in deciding whether to proceed to tangential photon dosimetric plan production, or if an alternative technique (IMAT) or modality (PBT in highly exceptional cases) should be considered.

Ranger *et al,* (2016) reported a MHD of 2.5 Gy (± 1.0 SD) when using a DIBH wide tangential technique in a planning study of fourteen patients (29). The mean $V36_{Gy}$ (90% prescribed dose) for the IMN planning target volume was 77.8% (±7.1 SD), with a dose objective of 90%. This may suggest that the wide tangential fields could have been widened further to improve the dose to the IMN, whilst still keeping mean heart dose to under 6 Gy (as recommended by the RCR (26)). Using %HIF as a predictive surrogate for MHD would facilitate this during the virtual simulation of the wide tangential fields, and may avoid unnecessary use of alternative techniques such as IMAT; which, as well as being resource-heavy to deliver, may be associated with greater normal tissue toxicity (45).

As described above, almost all UK centres have DIBH equipment and techniques available, although only half of left-sided cases receive their treatment using this technique (30). Although many patients will have a MHD of under 2 Gy in free breathing (commonly accepted tolerance dose level); there is no safe dose threshold. Therefore, I consider the 50% dose reduction afforded by DIBH should be realised for every patient. However, resources may need to be rationalised, and for those centres with limited DIBH provision, it is reserved for those patients with the greatest actual dose reduction. In such centres, all patients may be scanned in free breathing in the first instance. If a treatment plan can be produced meeting the MHD constraint; patients will continue to a free breathing treatment course which is less resource-heavy in terms of treatment machine time. For those patients exceeding MHD tolerance on the final dosimetric plan, typically identified at a late-stage in the pre-treatment pathway, the free-breathing technique will be rejected. The inefficiencies to the pre-treatment pathway of this approach are significant. Not only will the patient experience a delay of up to two weeks to commencing radiotherapy, but they will also require an additional radiotherapy CT scan, this time in DIBH; doubling their planning CT dose exposure. The volume delineation, virtual simulation and plan production will double the workload of the radiographers, dosimetrists and clinicians involved in that patient's plan. Using %ILF and %HIF during the virtual simulation of the free breathing scan, will avoid all of the superfluous work, other than the double CT dose exposure (for those identified as exceeding MHD tolerance with %HIF calculation from the free breathing CT); justifiable in terms of the 50% MHD reduction that the DIBH technique will facilitate.

2.6 Conclusion

My study has identified accurate dose surrogates for MHD and ipsilateral lung that can be easily and quickly calculated during the virtual simulation of breast radiotherapy (+/- locoregional nodes). This removes the inefficiencies associated with producing a dosimetric plan that exceeds tolerance doses, requiring late-stage changes, and also avoids unnecessary compromise to target coverage, therefore optimising the therapeutic ratio of treatment.

A limitation of my study may be considered with regard to the limited MHD validation data. This was due to the implementation of DIBH at the time of this data capture, which is highly effective at reducing the amount of heart-in-field. However, the validation data conforms tightly to that of the model-building cohort, supporting the confidence that %HIF is an accurate surrogate for MHD. Also, the extensive %ILF validation data gives reassurance that both %HIF and %ILF are reliable dose surrogates as they both rely on the same in-field dose relationship.

The %HIF and %ILF threshold levels that I have presented have been clinically implemented at my institution for all breast and chest wall radiotherapy, including those requiring supraclavicular or IMN irradiation. This optimises tangential field placement and identifies early in the pre-treatment pathway which patients should be considered for IMAT. A limitation in terms of implementation at other centres, is that the parameters of the equations have been generated from local data, which will differ between treatment planning systems, techniques and technology. Therefore, I advise those centres wanting to implement this virtual simulation aid, to perform linear regressions from their own patient data, in order to establish their centre-specific formulae.

2.6.1 Future and on-going project: The challenges of a breast cancer proton beam therapy pathway

As described previously, even though breast cancer radiotherapy is not currently on the proton beam indication list for standard commissioning, this may change if the PARABLE trial reports favourable outcomes at 2 years.

As MHD will be the primary parameter by which defines a patient eligible for PBT or not, I suggest that the use of a photon plan dose surrogate will be essential in terms of streamlining the PBT breast referral pathway. Currently, the most significant delay (four to eight weeks) to the current trial PBT pathway, is the requirement for patients to effectively 'fail' photon planning, whereby the MHD from the photon plan meets the threshold for significant risk of radiation-induced cardiac toxicity. Only then is the PBT pathway initiated. If this method of identifying patients for PBT were to continue post-trial, this would be different to many of the other PBT patient cohorts on the standard indication list, which are automatically eligible based on the location of the target site, and/or due to being a paediatric, teenage or young adult patient.

There is evidence that the benefit of adjuvant breast cancer radiotherapy in terms of local control rates start to reduce if delivered more than twelve weeks after surgery (in those patients who have not had adjuvant chemotherapy) (70). This must be acknowledged when offering a treatment pathway that significantly extends the time between the last definitive treatment and commencing radiotherapy. Balancing the benefits of radiotherapy in terms of local control and overall survival, with the risk of serious late cardiac toxicity may be justifiable when considering some delay to the PBT pathway for those patients meeting the cardiac risk threshold. However, it is not only disease control that should be considered as important when considering delays to treatment; this can also have a psychologically detrimental effect on patients and can also delay the commencement of other adjuvant systemic therapies such as immunotherapy that are indicated after completing radiotherapy in high-risk patients. It is therefore important to streamline the breast PBT pathway where possible.

I am a collaborator, local Principal Investigator and working party member of the PARABLE trial, as well as serving on the Trial Management Group. The initial proposal during protocol development was for a full dosimetric photon plan to be produced for all screened patients to confirm MHD and therefore trial eligibility. I presented my MHD surrogate work and the associated publication in *Clinical Oncology* (71) to the protocol development and Radiotherapy Quality Assurance (RTTQA) groups. I suggested that centres should be encouraged to use dose surrogates or MHD estimation rather than a final optimised plans to quantify MHD

and subsequent trial eligibility. I explained my opinion that this this would support trial activity in terms of screening and recruitment, by reducing wasted resource allocation and the associated delays to the pathway. Consideration by the protocol development group and trial statisticians commenced regarding whether an estimated MHD would suffice when confirming trial eligibility, and how to validate different methods across several recruiting centres with different treatment techniques, planning systems and treatment machines.

The conclusion was that recruiting centres were recommended to establish a trial eligibility assessment pathway that omits the requirement to produce a final dosimetric plan to calculate MHD and confirm whether the dose threshold is achieved or not. This avoided the inefficient use of dosimetric resources for those patients found to be eligible for the trial, who may not ultimately receive the treatment according to the photon plan.

I oversaw the section of the PARABLE RTTQA planning pack (currently unpublished, see appendix 1) that provides a number of examples of how MHD can be estimated from the planning CT scan without the requirement of a dosimetric plan. My centre, amongst others, was granted permission to use the %HIF method (71). I presented this efficiency-saving solution at the national PARABLE trial launch meeting and London Cancer Network PARABLE study day (appendix 2).

Despite saving dosimetry resources which was hoped to improve trial activity by participating centres, using MHD surrogates during virtual simulation on the radiotherapy planning CT scan reduces the pre-eligibility pathway by a modest two to five days. For a meaningful reduction in the breast PBT pathway if a standard indication, I raised the possibility of a project with the Trial Management Group, with the ultimate aim of being able to estimate, within an acceptable confidence interval, the MHD of a tangential photon plan from a diagnostic CT scan. I suggested that members of the trial team would be well-placed to investigate where pathway length could be streamlined; and a working party was allocated to focus on this area.

The majority of patients meeting the cardiac risk threshold of 2% from their photon tangential plan will require irradiation to the regional lymph nodes, including the internal mammary chain. This cohort of patients will have undergone staging investigations as part of their diagnostic work-up, many months before a radiotherapy referral is made. These staging investigations will generally include a CT scan of the thorax (be that conventional CT or Positron Emission CT). The ability to identify PBT-eligible patients from the diagnostic imaging acquired at the very start of their breast cancer pathway, would facilitate the direct referral to PBT centres, avoiding the need to waste the time and resources of having to demonstrate 'failure' of photon planning, and reduce the treatment pathway by several weeks.

A project team has been initiated and an abstract accepted for ESTRO 2025 on the preliminary work of exploring how scripting and machine-learning can support the rapid estimation of MHD using maximum lung distance. Whilst not the primary author on this work, I have provided advice and guidance and have written the conclusion of the abstract to ensure that the findings were described with relevance to the clinical setting (appendix 3). The aim is to use the model-building and learning from radiotherapy data sets to test, validate and translate feasible solutions from diagnostic data.

Whist this work will not mature in time to assist with the recruitment to the PARABLE trial, which is projected to reach the target accrual of 192 patients by August 2025, the ability to identify patients who will be eligible for PBT early in their diagnostic pathway, will be highly valuable if the 2-year co-primary outcome data of PARABLE is positive.

2.7 Related publications

Clinical Oncology xxx (xxxx) xxx

[redacted]

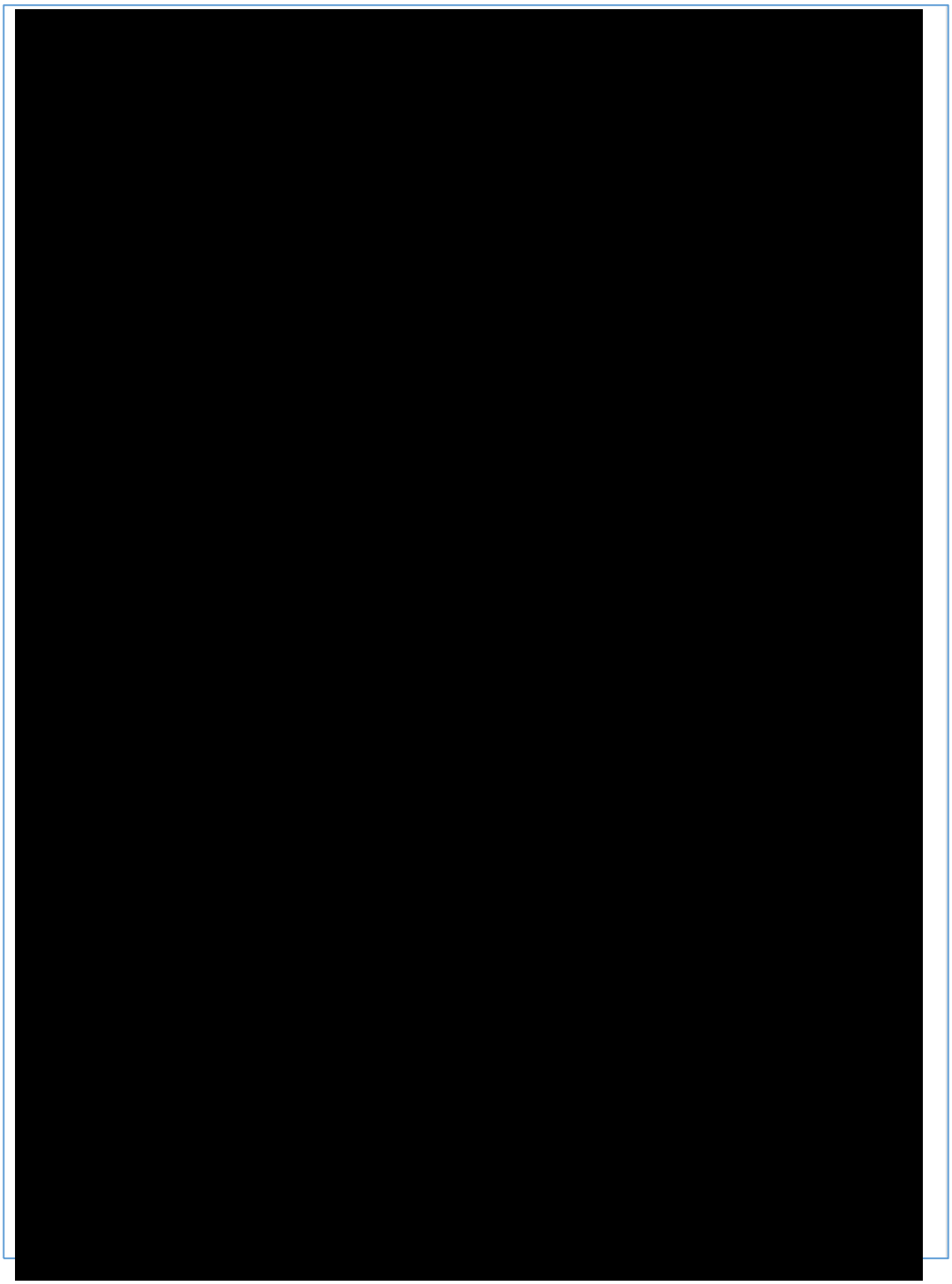
Identifying Surrogates for Heart and Ipsilateral Lung Dose to Guide Field Placement and Treatment Modality Selection during Virtual Simulation of Breast Radiotherapy

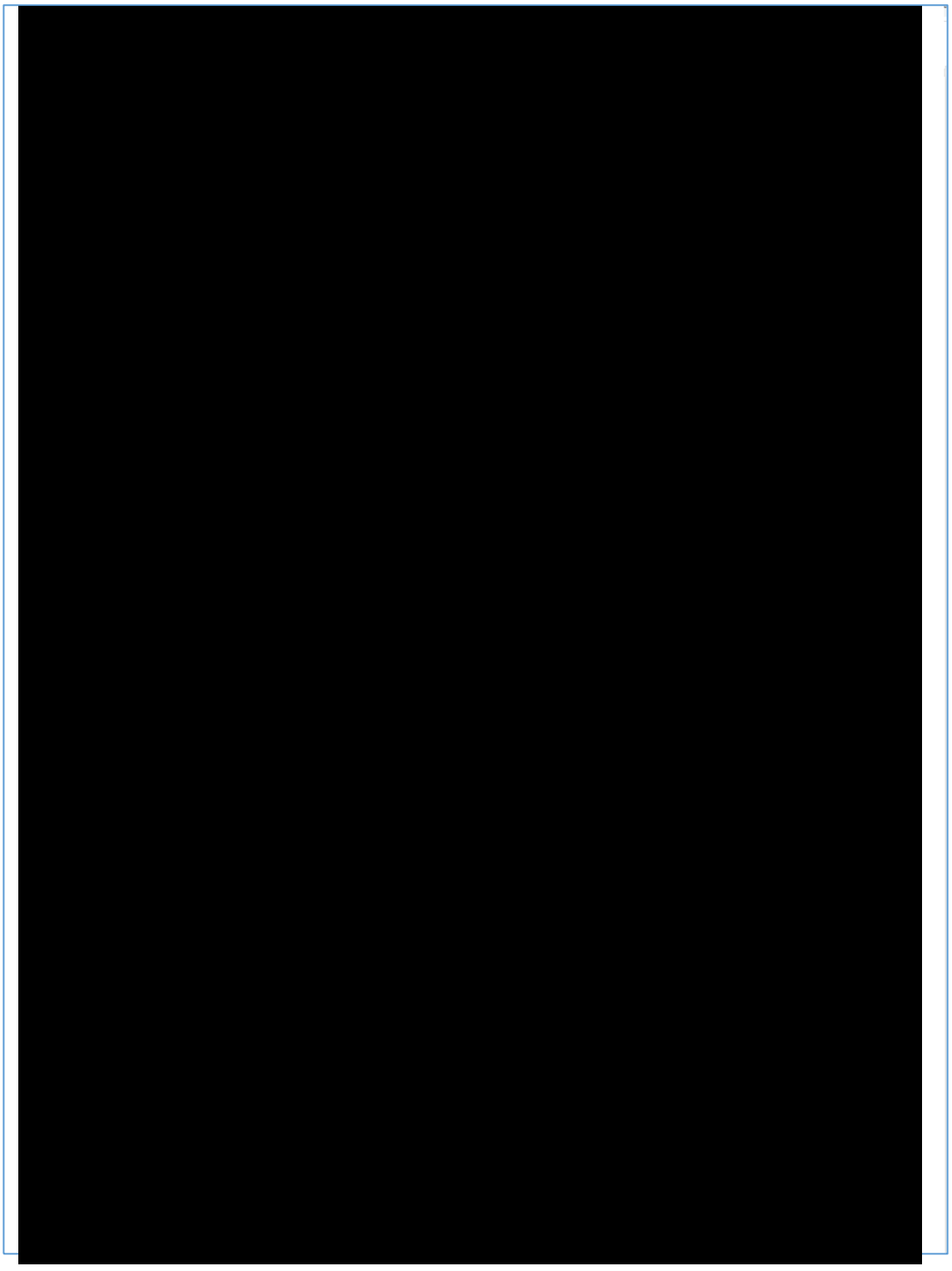
S. Wickers [*], C. Thould [*], J. Keeble [*], R. Bodey [†], C. Harsanyi [†], G. Royle [‡], M.N. Gaze [*]

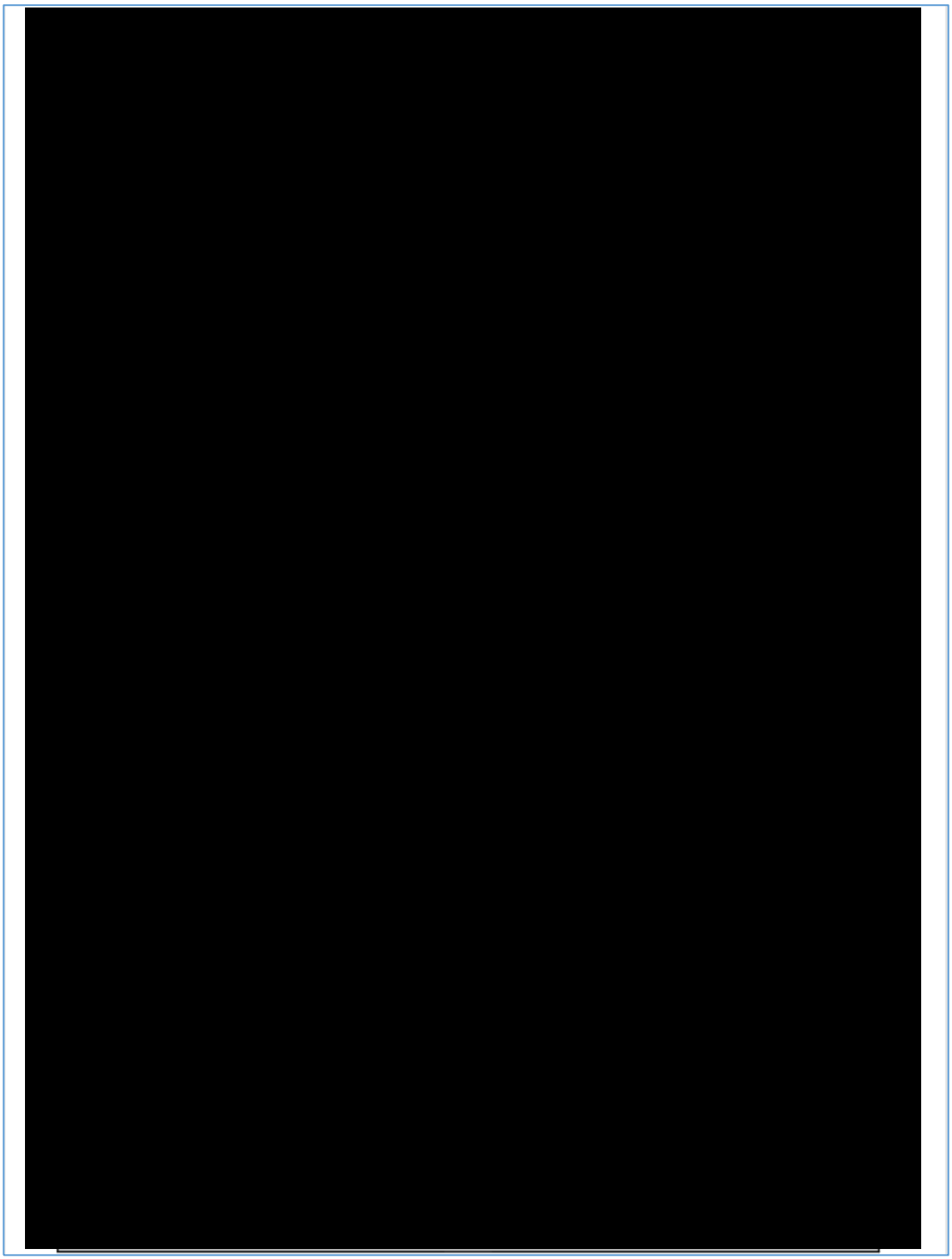
[*] *Radiotherapy Department, University College London Hospital NHS Foundation Trust, London, UK*
[†] *Radiotherapy Physics, University College London Hospital NHS Foundation Trust, London, UK*
[‡] *Department of Medical Physics and Bioengineering, University College London, London, UK*

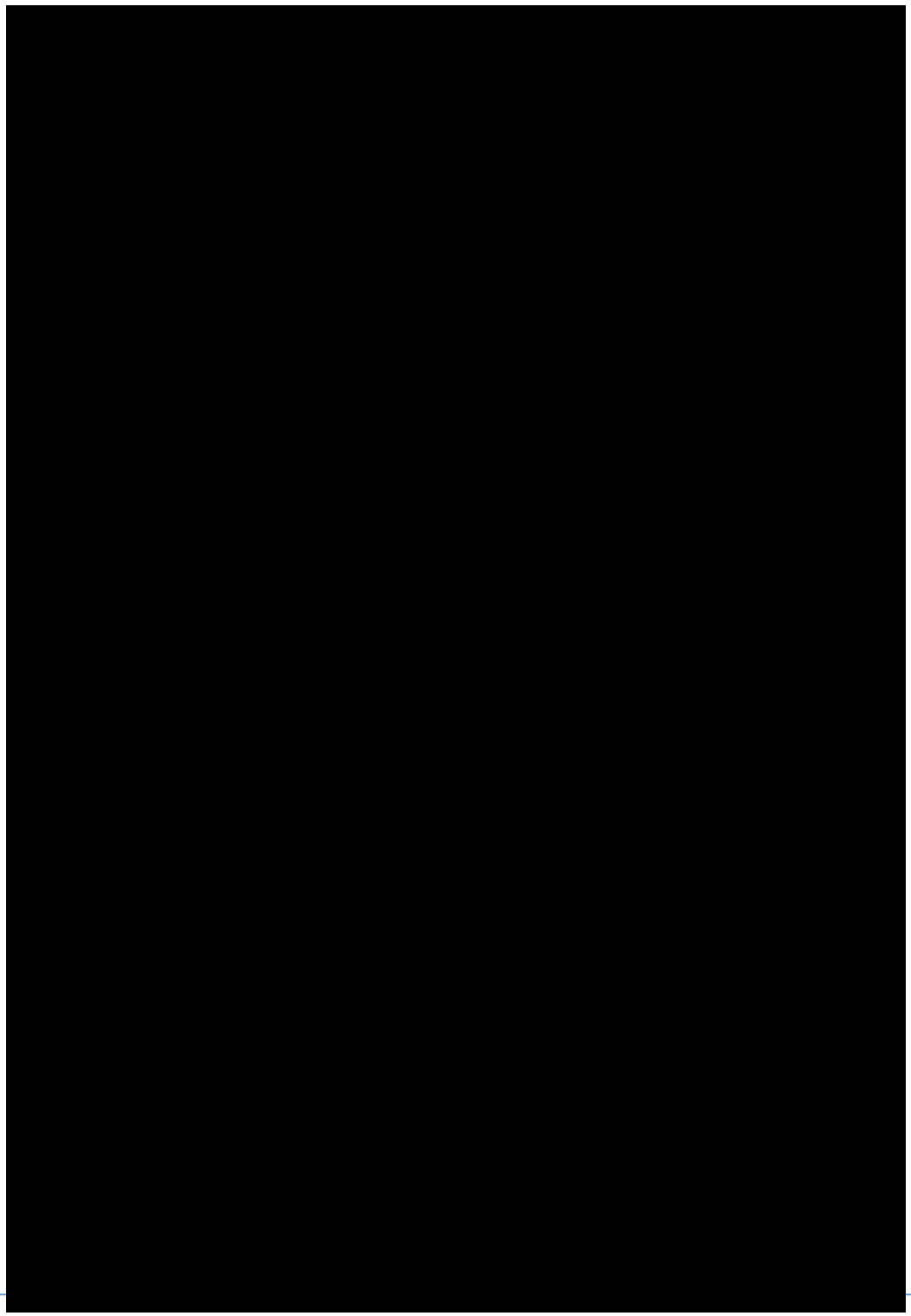
[redacted]

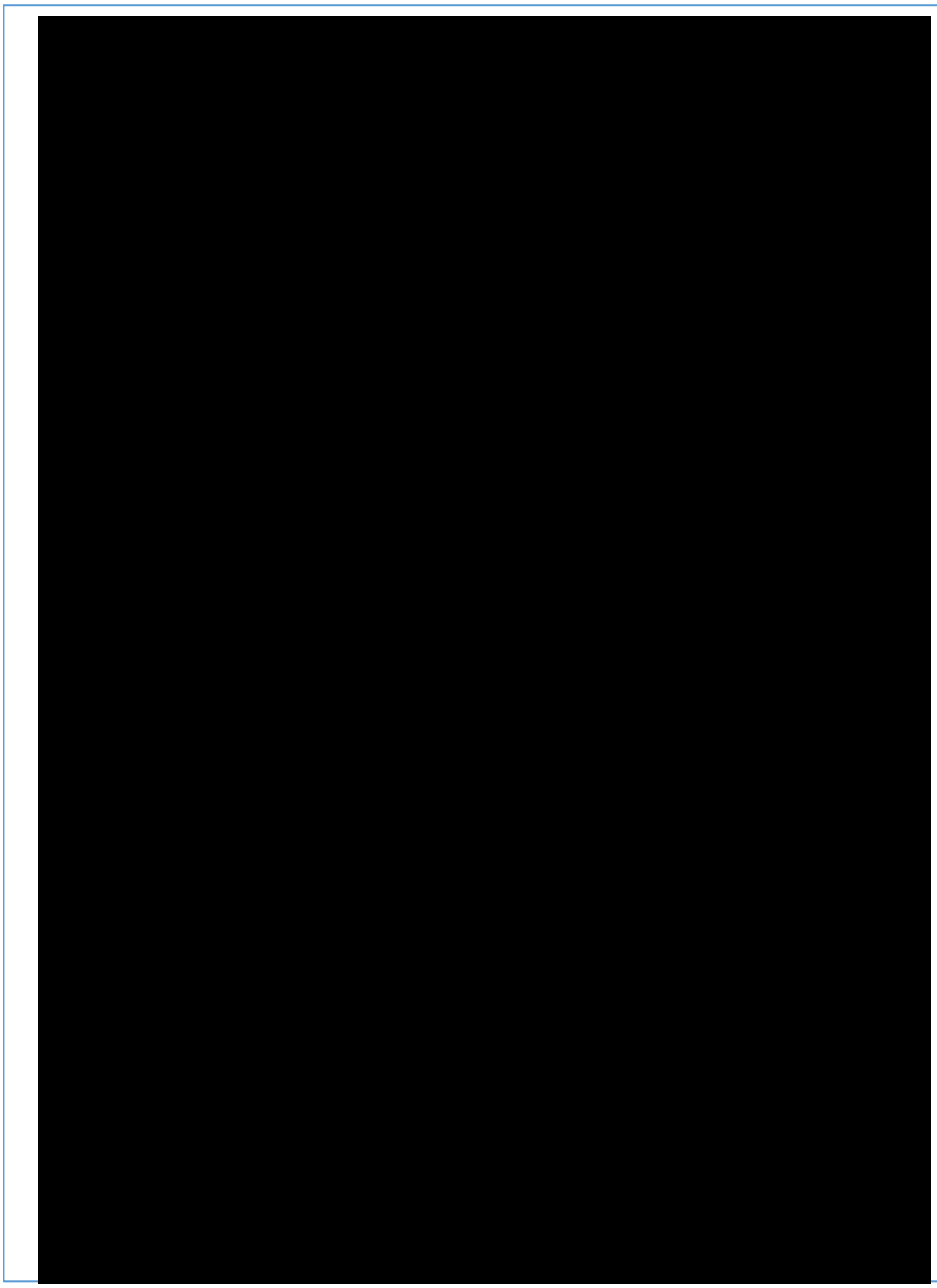
Please cite this article as: Wickers S et al., Identifying Surrogates for Heart and Ipsilateral Lung Dose to Guide Field Placement and Treatment Modality Selection during Virtual Simulation of Breast Radiotherapy, Clinical Oncology, https://doi.org/10.1016/j.clon.2020.12.005











Chapter 3

Responding to dose fractionation changes for adjuvant breast radiotherapy in terms of heart and ipsilateral lung dose surrogates during virtual simulation

3.1 Introduction

3.1.1 Therapeutic ratio

The different characteristics of cancer cells and normal tissues in terms of the effect of radiation and cell survival form the basis of the linear quadratic model (72). This can be used to estimate the effects on both cell kill and acute and late morbidity of different radiotherapy dose and fractionation schedules. The aim of radiotherapy is for maximum tumour control probability, with the least normal tissue effects (73). The therapeutic ratio is an index of how well this is achieved. The separation between the cell survival curves of tumours and normal tissues exists due to variations in the rate and ability of the cells to repair, repopulate, redistribute and reoxygenate; which all contribute to tumour cells being more radiosensitive than normal tissues (74).

3.1.2 Hypofractionation & breast radiotherapy

Normofractionation refers to a radiotherapy prescription delivered in 2 Gy daily fractions, five days a week until the total dose is delivered. Depending on the treatment intent (curative versus palliative, primary versus adjuvant), tumour histology, stage and the dose-limiting surrounding normal tissues, the total dose prescribed will vary.

The effect of therapeutic radiation on the cell survival of tumour cells and normal tissues have historically been calculated, tested and clinically implemented according to normofractionation. The total dose prescribed and organ at risk tolerance doses to optimise the therapeutic ratio for each tumour type and site, result largely from the knowledge, and to some degree assumptions, based on a 2 Gy per fraction treatment schedule.

Hypofractionation refers to a radiotherapy course with fraction sizes greater than 2 Gy, delivered over fewer treatments, often to a reduced total dose.

A fundamental component of any hypofractionated regimen is to maintain or even improve the therapeutic ratio compared to normofractionation. It is therefore

necessary to calculate the effective total dose and organ at risk constraints according to the new dose per fraction (75).

Breast cancer radiotherapy has been subject to much research and subsequent implementation of hypofractionated regimens; delivering greater than 2 Gy per fraction, with a lower total dose, and fewer treatment fractions. This is highly beneficial in terms of reducing the impact of outpatient attendance on both the patient and the healthcare service (21). The national standard for adjuvant breast radiotherapy is currently 40.05 Gy delivered in 15 x 2.67 Gy fractions. The normofractionated regimen for breast cancer prior to this was 50 Gy in 25 x 2 Gy fractions. It was the UK—run START trials that first tested the theory of hypofractionation for breast cancer. These trials concluded that 40 Gy delivered in 15 x 2.67 Gy fractions was at least as safe and effective as 50 Gy delivered in 25 x 2 Gy fractions at 10-years (76); which was subsequently written into national guidelines to become the accepted standard (62).

3.1.3 Alpha-beta ratio

The alpha-beta ratio of a specific cell or tissue type are derived from the linear quadratic model (estimates cell survival in response to radiation dose) and quantify the estimated sensitivity to fraction size in terms of a specific clinical endpoint and are expressed in the unit Gy. The alpha-beta value may, for example, relate to pneumonitis or fibrosis regarding lung tissue, or cardiac toxicity in terms of the heart. The alpha-beta ratio for tumour control probability will vary for different tumour phenotypes.

The ability to deliver adjuvant breast radiotherapy with a hypofractionated schedule has been possible due to the favourable fraction sensitivity of breast cancer; demonstrated by the low alpha-beta ratio of approximately 4 Gy (77). This is in contrast to tumours of the bladder, head and neck, and cervix, which are much less sensitive to a higher dose per fraction, with an alpha-beta ratio of around 10 Gy (78).

Alpha-beta ratios are therefore an important parameter when establishing hypofractionation regimens and the corresponding normal tissue tolerance

doses, in terms of calculating the biologically effective dose (of each clinical endpoint) compared to 2 Gy fractions (75,79).

3.1.4 Biologically effective dose calculation

Biologically effective dose (BED) calculation (figure 16) estimates the true biological dose depending on the dose per fraction, total dose, and the alpha-beta ratio of the clinical endpoint of the specific cells or tissue of interest. This may be a normal tissue endpoint such as pneumonitis, or the tumour control probability of a specific tumour type.

BED calculations can be particularly useful when assessing the biological effect of a proposed hypofractionation regimen compared to normofractionation. An example may be to compare the clinical endpoint, pneumonitis (assuming an alpha-beta ratio of 3 Gy (80), for the current standard hypofractionated regimen (40 Gy in 15 x 2.67 Gy fractions) to normofractionation for breast cancer (50 Gy in 25 x 2 Gy fractions).

Figure 16: Biologically effective dose calculation

$$BED = D\left[1+\frac{d}{a/\beta}\right]$$

***d*: dose per fraction**

D: total dose

For normofractionation (50 Gy in 25 fractions), the BED for pneumonitis is 83.3 Gy. The BED for 40 Gy in 15 fractions is 75.6 Gy, from which one may conclude that the clinical endpoint pneumonitis favours the hypofractionated regimen.

3.1.5 EQD_{2Gy} calculation

More widely used is an extension of the BED calculation; the EQD_{2Gy} Withers formula (81). This provides the equivalent total dose of a hypofractionated

schedule if converted to 2 Gy fractions for each specific clinical endpoint (figure 17).

Figure 17: EQD_{2Gy} calculation (Withers formula (81)***)***

$$EQD_{2Gy} = \frac{D(d + a/\beta)}{2 + a/\beta}$$

With reference to the clinical endpoint pneumonitis (assuming an alpha beta ratio of 3 Gy), the EQD_{2Gy} for 40 Gy in 15 x 2.67 Gy fractions is 45.4 Gy. As this is less than the normofractionation total dose (50 Gy), this supports the theory that for reduced risk of pneumonitis, the hypofractionated schedule is preferable.

EQD_{2Gy} can also be used to calculate equivalent tolerance dose parameters to translate those from normofractionation into hypofractionated clinical practice.

A widely used ipsilateral lung parameter and tolerance for normofractionation for breast radiotherapy, is the volume of lung receiving 20 Gy ($V20_{Gy}$) of 15% (82), which is associated with a low incidence of lung toxicity (83). The equivalent parameter for 40 Gy in 15 fractions (assuming an alpha-beta ratio of 3 Gy) according to EQD_{2Gy} is $V18_{Gy}$. An ipsilateral lung tolerance of $V18_{Gy}$ of 15% was the parameter used in the IMPORT High trial protocol which used 40 Gy in 15 fractions for the control arm (15). This was also the lung tolerance parameter selected at UCLH for 40 Gy in 15 fractions when we first commenced using %ILF dose surrogate (when not including the nodal targets), which pre-dated this trial.

3.2 Global pandemic COVID-19

COVID-19 is the name given to coronavirus (SARS-Cov-2), first detected in Wuhan, People's Republic of China, towards the latter part of 2019. COVID-19 is most commonly a mild or moderate respiratory illness but can have a greater risk of severe illness and mortality in those with pre-existing medical conditions such as diabetes, heart disease, respiratory disease and cancer; and for people over the age of 60, or defined as obese (84).

3.2.1 COVID-19 and the impact on the NHS

The first detected case of COVID-19 in the UK was confirmed on 30th January 2020 (85). The number of positive cases, the rate of transmission and the number of people requiring supportive care quickly escalated. By February 2020, the impact of this global pandemic on the UK National Health Service was becoming increasingly evident. The demand on in-patient admissions, including those requiring intensive care beds; in addition to staff sickness and redeployment to critical care, pushed the workforce and resource capacity of the NHS to such a critical point that a national lockdown was imposed in mid-March 2020.

The wider impact was the reduced access and delivery of non-COVID related healthcare. Many areas of healthcare had to rationalise their service provision, demonstrated by a reduction in outpatient services, operations, and health screening for much of 2020 (86).

Radiotherapy was not exempt from the pressures on workforce and service delivery during this exceptional time, with radiotherapy capacity reduced. There were also two additional concerns to consider. Firstly, that people attending for daily radiotherapy may be at increased of contracting COVID-19 due to their environmental exposure of travelling to and attending the hospital daily for the duration of a fractionated course for up to 7 weeks. As described above, people with cancer were also identified as an 'at-risk' group for developing a more severe illness, with a greater chance of requiring hospitalisation, and a higher mortality rate. The second concern, was the impact on the efficacy of a radiotherapy

course, should it be interrupted or stopped if a patient contracts COVID-19. The risk of this occurring is higher for protracted fractionations.

Fractionation, and more specifically hypofractionation, was therefore an important consideration during this time. Fewer fractions would release radiotherapy capacity, limit the footfall (and therefore transmission risk) within the department, and reduce the chance of treatment interruption, thus protecting treatment efficacy.

3.2.2 FAST Forward clinical trial

The UK FAST-Forward trial was a phase 3, multi-centre, randomised, non-inferiority trial comparing the current 40 Gy in 15 fraction schedule, to a 5 fraction (26 Gy or 27 Gy delivered in 5 x 5.2 Gy or 5 x 5.4 Gy) regimen for breast cancer (87).

The primary endpoint was ipsilateral breast cancer recurrence, with clinician and patient reported outcomes for normal tissue toxicity identified as important secondary outcomes. The trial opened to recruitment in November 2011, and closed, having met the accrual target of just under 4100 women, in June 2014.
In 2016, the trial reported the acute skin toxicity of the 5 fraction schedules in a sub-study of 352 patients, concluding that both resulted in mild acute skin toxicity (87).

FAST-Forward was anticipated by the oncology community to present the 5-year ipsilateral breast cancer recurrence and normal tissue toxicity data at the Summer 2020 international conferences. However, due to the impact that COVID-19 was having on international travel, social gatherings and the clinical demands of the workforce, all national and international conferences were cancelled.

3.2.3 Royal College of Radiologists Guidance

FAST-Forward was a UK trial, and the clinicians amongst the trials' team had first-hand experience of the impact that COVID-19 was having on the NHS and more specifically, the radiotherapy service. Professor Coles, a Consultant Clinical

Oncologist based at Addenbrookes Hospital, with the support of international experts, authored a document published online via the Royal College of Radiologists website on 24th March 2020, and in May 2020 as an international guideline (88,89). This identified a group of patients for whom a 5-fraction dose schedule may be considered and discussed with patients, in response to and in advance of the imminent publication of the FAST-Forward 5-year data. The guideline included the recommendation to use the FAST-Forward planning pack with regard to planning dose objectives and constraints (90).

An international COVID-19 guideline was published a couple of months later (Coles et al, 2020b) which formalised and improved accessibility of the RCR online guidelines.

The 5-year FAST-Forward outcome data was subsequently published in May 2020, and reported that 26 Gy in 5 fractions is non-inferior compared to 40 Gy in 15 fractions in terms of normal tissue toxicity and ipsilateral breast recurrence at 5 years (21). This was applicable only when treating the breast or chest wall as the inclusion of nodal targets are subject to an on-going nodal sub-study. The dosimetric data in terms of the delivered target, lung and heart doses have not as yet been published.

3.2.4 Rapid implementation of a new fractionation

As a result of the RCR COVID-19 guideline (88), many UK centres started to offer and deliver 26 Gy in 5 fractions when treating the breast or chest wall in the identified patient cohort. Following appraisal of the 5-year publication (21), my consultant clinical oncology colleagues and I made the decision to broaden the patients eligible for 26 Gy in 5 fraction consideration, to include patients requiring a tumour bed boost. The total patient cohort eligible for 26 Gy in 5 fractions represented approximately two thirds of our breast radiotherapy referrals.

At my institution, I managed this rapid change of fractionation to a high number of patients from a clinical governance point of view, by producing an over-arching, locally agreed (between the breast clinical oncologists and myself as consultant radiographer) COVID-19 pandemic concessionary document. This outlined the

eligible patients and prescription with reference to the RCR COVID-19 guideline (88).

In mid-October 2020, the RCR hosted a virtual national consensus meeting with an aim to compose new national guidelines with regard to the standardisation of the 26 Gy in 5 fraction schedule post COVID-19. Despite some modest disagreement amongst the clinical oncology community in terms of which patients the 5-fraction regimen should be 'recommended' versus 'considered' (the strength of the recommendation), it was clear that this fractionation was going to be adopted into standard care for a substantial proportion of patients.

3.2.5 Translation of virtual simulation surrogates for ipsilateral lung & MHD

In preparation for the implementation of 26 Gy in 5 fractions from the departmental COVID-19 pandemic concession document into our standard clinical protocols, the translation of parameters for ipsilateral lung and MHD for the well-established 40 Gy in 15 fraction regimen was required. It was noted that our 26 Gy in 5 fraction breast plans were frequently exceeding the ipsilateral lung dose parameter according to the FAST-Forward trial planning pack (90); volume of ipsilateral lung receiving 8 Gy of 15%. Adherence to this parameter would result in less generous field placement compared to the well-established 40 Gy in 15-fraction parameter of V18Gy 15%. I proposed that interchanging between two dose-matched fractionations, should not result in greater compromise to target coverage for one compared to the other. There was also no MHD tolerance provided in the FAST-Forward protocol for us to refer. The trial publication did not include any heart or lung dose volume histogram data, from which to appraise what was clinically achievable versus what the RTTQA planning pack defined as optimum in the study population.

Our virtual simulation thresholds for %ILF and %HIF were no longer predictive or appropriate with the new dose schedule for ipsilateral lung and MHD. We did not know what the equivalent threshold parameters (to ipsilateral lung V18 Gy and MHD) were when acknowledging the lower total dose and fewer treatment fractions.

3.3 Study aim

The aim of this study was to identify maximum virtual simulation threshold values for %ILF and %HIF, for equivalent ipsilateral lung and heart tolerance doses for 26 Gy in 5 fractions compared to the current standard, 40 Gy in 15 fraction schedule.

3.4 Materials & methods

3.4.1 Alpha-Beta ratio assumptions

For the acute and late-responding clinical endpoints pneumonitis and lung fibrosis, an alpha-beta ratio of 3 Gy was assumed for the calculations. Although the true value for these clinical endpoints is unknown (likely to be between 1 and 6 Gy), 3 Gy is widely regarded as an appropriate estimation (91–93). In response to the uncertainty regarding the true alpha-beta ratio, the calculations were repeated assuming a value of 2 Gy.

An alpha-beta ratio of 2 Gy will be assumed for the clinical endpoint cardiac toxicity, as this was the value assumed by Darby *et al* (2013), from which MHD emerged as an important predictor for risk of major coronary event (34).

The alpha-beta value will be explored to define the level whereby 26 Gy in 5-fractions is unfavourable in terms of lung and heart toxicity, compared to the current hypofractionation regimen (40 Gy in 15-fractions), and normofractionation (50 Gy in 25-fractions). This has been suggested as an important step when evaluating dose parameters for new hypofractionation regimens (79,94).

3.4.2 EQD_{2Gy} for 26 Gy in 5-fractions

The EQD_{2Gy} for ipsilateral lung and heart toxicity was calculated for 26 Gy in 5-fractions and compared to 40 Gy in 15-fractions using the Withers formula (81) (figure 17).

An equivalent ipsilateral lung VxGy parameter when expressed as a percentage of total dose (V45%) was proposed for 26 Gy in 5-fractions compared to the current 40 Gy in 15-fraction parameter ipsilateral lung V18Gy, which will achieve equivalent virtual simulation field placement. The EQD_{2Gy} for the proposed 26 Gy in 5-fraction ipsilateral lung VxGy was calculated and compared to the dose parameter ipsilateral lung V18Gy for 40 Gy in 15-fractions and ipsilateral lung V20Gy for 50 Gy in 25-fractions. *D* in the Withers formula is defined according to the total dose parameter, in this case, ipsilateral lung VxGy and *d* as the dose to the lung per fraction.

The EQD_{2Gy} for the widely accepted MHD constraint of 2 Gy (for a prescription of 40 Gy in 15-fractions) was calculated and an equivalent MHD constraint for 26 Gy in 5-fractions was proposed.

3.4.3 Patient cohort data for %ILF & %HIF for 26 Gy in 5-fractions

50 consecutive patient datasets treated with 26 Gy in 5-fractions during the COVID-19 pandemic were retrospectively selected. Patients were positioned, scanned, and target volumes delineated as described previously.

Pearson's correlation coefficients and linear regressions were conducted between %ILF and VxGy, and between %HIF and MHD. Two-tailed statistical significance was set at $P \leq 0.05$. A strong correlation was defined as $r > 0.5$.

The number of patients exceeding the FAST-Forward ipsilateral lung V8Gy constraint of 15% was recorded. The number of patients exceeding the proposed VxGy for 26 Gy in 5-fractions was also recorded.

For the proposed ipsilateral lung VxGy and MHD for 26 Gy in 5-fractions, maximum threshold values for %ILF and %HIF were determined using the upper 95% confidence intervals for the gradient and offset of the relevant linear regression as described previously.

3.5 Results

3.5.1 Patient demographics

Of the 50 consecutive patients retrospectively selected for analysis, all were female, 33 left-sided and 17 right-sided. Reconstruction and nodal irradiation were locally agreed exclusion criteria for the 26 Gy in 5 fraction prescription. 47/50 cases were referred for radiotherapy to their conserved breast, and 3/50 to the non-reconstructed chest wall. A deep inspiration breath hold (DIBH) technique was used in 32/33 left-sided cases. The one left-sided free-breathing case was due to poor patient compliance with the DIBH technique.

3.5.2 Consideration of prescription for late-responding normal tissues

Assuming an alpha-beta ratio of 3 Gy for late responding normal tissues, the EQD_{2Gy}, is 42.6 Gy for 26 Gy in 5-fractions, and 45.4 Gy for 40 Gy in 15-fractions, favouring the 5-fraction regimen.

If the true alpha-beta value is 2 Gy, the EQD_{2Gy} for 26 Gy in 5 fractions is the same as for 40 Gy in 15 fractions at 46.8 Gy.

26 Gy in 5-fractions is unfavourable to normofractionation if the true alpha-beta value is ≤1.4 Gy.

3.5.3 Ipsilateral lung EQD_{2Gy}

The tolerance parameter ipsilateral lung V18Gy for a total dose of 40 Gy, may be expressed as V45% (the volume of ipsilateral lung receiving 45% of the total dose). To facilitate virtual simulation with no impact on field placement, the equivalent ipsilateral lung V45% for 26 Gy is ipsilateral lung V11.7Gy.

Assuming an alpha-beta ratio of 3 Gy, the EQD_{2Gy} for ipsilateral lung V18Gy delivered in 15-fractions is V15.1Gy, almost equal to the EQD_{2Gy} of V15.2Gy for the 50 Gy in 25-fraction dose parameter ipsilateral lung V20Gy if a radiobiological

correction is considered. The EQD_{2Gy} for ipsilateral lung V11.7Gy for 26 Gy in 5-fractions is V12.5Gy, thus lower than for both other dose schedule ipsilateral lung tolerance parameters.

The EQD_{2Gy} for ipsilateral lung V11.7Gy for 26 Gy in 5-fractions remains lower than ipsilateral lung V18Gy for the 15-fraction regimen, even if the true alpha-beta ratio is as low as 1 Gy (V13Gy versus V13.2Gy). This supports the use of ipsilateral lung V11.7Gy as an appropriate dose parameter for 26 Gy in 5-fractions in terms of equivalent field placement and EQD_{2Gy} compared to the current ipsilateral lung parameter for the 40 Gy in 15-fraction regimen.

3.5.4 MHD for 26 Gy in 5 fractions

Assuming an alpha-beta ratio of 2 Gy, the EQD_{2Gy} for a MHD of 2 Gy delivered in 15-fractions is 1.07 Gy. A MHD constraint of 1.8 Gy delivered in 5-fractions gives an equivalent EQD_{2Gy} of 1.06 Gy.

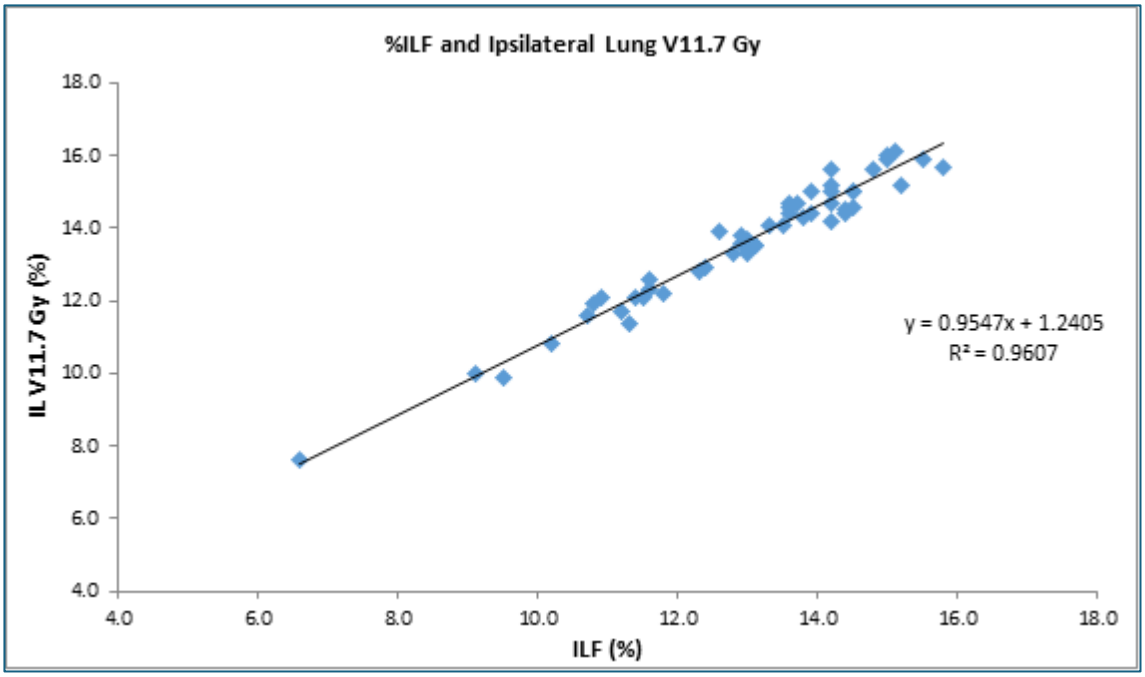
3.5.5 %ILF & ipsilateral lung V11.7Gy

The median %ILF for the entire cohort was 13.4 (6.6 – 15.8). The median ipsilateral lung V11.7Gy was 14.1 (7.6 to 16.1) %.

A statistically significant strong positive relationship was found between %ILF and ipsilateral lung V11.7Gy with $R^2 = 0.96$, $p<.0001$. For ipsilateral lung V11.7Gy, the gradient was an increase of 0.96% (95% CI 0.90 – 1.01) per 1% ILF with an offset of 1.24% (95% CI 0.51 – 1.97) (figure 18).

31/50 patients exceeded the FAST-Forward trial ipsilateral lung dose constraint of V8Gy 15%, with a median V8Gy of 16.4% (15.4 - 18.3%). 6/50 patients exceeded ipsilateral lung V11.7Gy of 15%, with a median V11.7Gy of 15.7% (15.2 - 16.1%) (when using V18 Gy 15% threshold in the absence of a 26 Gy dose-corrected dose surrogate).

Figure 18: Correlation between ipsilateral lung V11.7$_{Gy}$ and %ILF



The upper 95% confidence interval for gradient and offset from the linear regression was used to provide a maximum threshold value for %ILF of 13% during virtual simulation, to ensure ipsilateral lung V11.7Gy of 15% is met (figure 19).

Figure 19: Formula to calculate maximum %ILF to meet V11.7 Gy tolerance

$$\%ILF_{Max} = \frac{\text{IL V11.7Gy tolerance (\%) – upper 95\% CI for offset}}{\text{Upper 95\% CI for gradient}}$$

If during virtual simulation, the field placement requires the %ILF to exceed the tolerance of 13%, the resulting ipsilateral lung V11.7Gy can be estimated according to the formula given in figure 20.

Figure 20: Formula to estimate V11.7 Gy % using %ILF (26 Gy in 5 fractions)

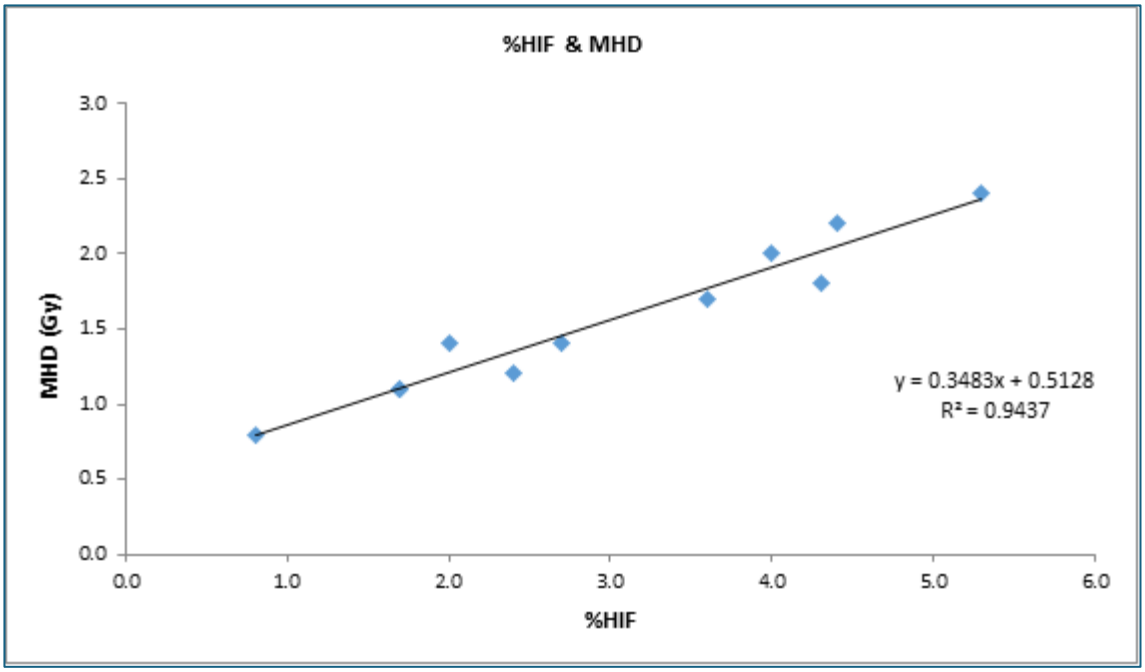
$$\text{IL V11.7Gy (\%)} = (0.96 \times \%ILF) + 1.24.$$

3.5.6 %HIF and MHD

11/33 left-sided patients had heart in-field. The median %HIF was 2.7 (0.8 - 5.3). The median MHD was 1.4 (0.8 - 2.4) Gy.

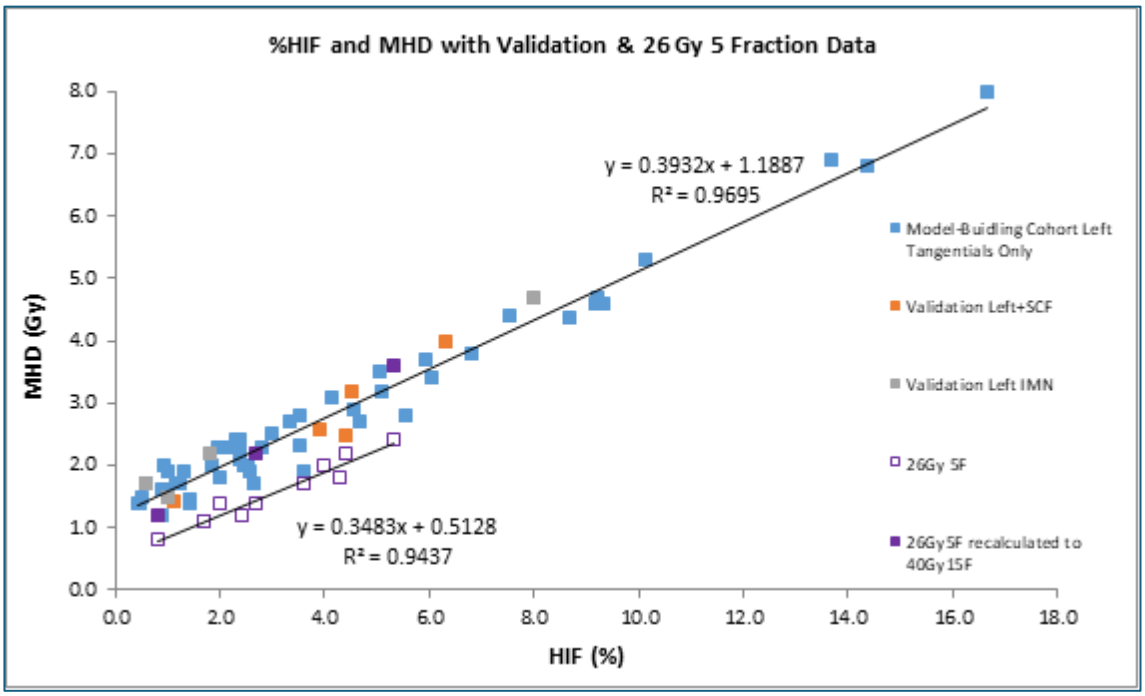
A statistically significant strong positive relationship was found between %HIF and MHD, with $R^2 = 0.94$, $p<.0001$. For MHD the gradient increased by 0.35 Gy (95% confidence interval 0.28 - 0.40) per 1% HIF with an offset of 0.51 Gy (95% confidence interval 0.30 - 0.73) (figure 21).

Figure 21: Correlation between MHD and %HIF



When displayed on the linear regression of %HIF and MHD for 40 Gy in 15 fractions, the gradients are parallel, confirming the strong predictive ability of %HIF. As a further step to validate the data, the plans for 3 patients were selected (lowest, highest and mid-range %HIF) and recalculated using a prescription of 40 Gy in 15-fractions and plotted on the 40 Gy in 15-fraction linear regression (figure 22).

Figure 22: Correlation between MHD and %HIF – 40 Gy in 15 fractions and 26 Gy in 5 fraction data



The upper 95% confidence interval for gradient and offset from the linear regression was used to provide a maximum threshold value for %HIF of 2.7% during virtual simulation, to ensure a MHD of 1.8 Gy is met (figure 23).

Figure 23: Formula to calculate maximum %HIF to meet MHD tolerance

$$\%HIF_{Max} = \frac{\text{MHD tolerance (1.8 Gy)} - \text{upper 95\% CI for offset}}{\text{Upper 95\% CI for gradient}}$$

If during virtual simulation, the field placement requires the %HIF to exceed the tolerance of 2.7%, the resulting MHD can be estimated according to the formula in figure 24.

Figure 24: Formula to estimate MHD using %HIF (26 Gy in 5 fractions)

$$\text{MHD (Gy)} = (0.35 \times \%HIF) + 0.51$$

3.6 Discussion

Adjuvant radiotherapy for those patients in whom breast conserving surgery is feasible was first investigated in the early 1970's, as an alternative to radical mastectomy (95). The normofractionation schedule used was 50 Gy in 25 x 2 Gy fractions. As the study reported equivalent disease-free and overall survival between the treatment groups, this fractionation became the standard regimen for adjuvant breast radiotherapy for many decades (79).

The UK has demonstrated a leading role in the development of hypofractionation regimens for treating early breast cancer. This began with the START trials which recruited 4451 patients between 1999 and 2002 (76,96,97). These two highly influential trials paved the way for the standard delivery of greater than 2 Gy-fractions, over a shorter treatment course, and a reduced total dose. The update to the NICE guidelines in 2018 (62) empowered NHS commissioners to insist that adjuvant breast radiotherapy is delivered in no greater than 15-fractions and has resulted in all UK centres adopting evidence-based hypofractionation for early breast cancer.

Scientific interest for the extent to which hypofractionation can be exploited for breast cancer continues. The main drivers are to; increase the access to radiotherapy; improve the efficiency of the healthcare system; reduce the impact on quality of life (fatigue, convenience); and to improve the therapeutic ratio (21,98).

The low rates of disease recurrence and patient and clinician reported acute and late normal-tissue toxicity for hypofractionation schedules using between 2.66 and 3.3 Gy fraction sizes delivered in 13 to 15 fractions, has provided confidence that the fraction sensitivity of breast cancer is similar to that of late reacting normal tissues (99). Yarnold & Haviland (2010) suggest that the linear quadratic model is reliable for doses of up to 6 Gy per fraction, and with the appropriate reduction of the total dose, this theory formed the basis of the FAST-Forward trials (21,99). The same dose schedule of 26 Gy in 5 x 5.2 Gy fractions, is also being tested in

India with the HYPORT-Adjuvant trial, aiming to randomise 2100 patients by 2024 (98).

Radiobiological calculations are fundamental when establishing new hypofractionation regimens. As dose per fraction increases, the total dose must be reduced appropriately for equivalent late normal tissue effects. However, the efficacy of these dose calculations is heavily reliant on the accuracy of the assigned alpha-beta ratios for the clinical endpoints of interest.

The FAST-Forward trial group acknowledge the difficulty in assigning accurate alpha-beta values for late tissue effects, highlighting inconsistency in the estimated values for clinician, patient and photographic-reported late normal tissue toxicity, with over-lapping confidence intervals between the START and FAST-Forward trials. Their suggestion is that caution may be applied by calculating normal tissue effects using alpha-beta ratios of 1 and 2 Gy; lower than those suggested by either trial. These would result in EQD_{2Gy} of 53.7 and 46.8 Gy for 26 Gy in 5-fractions. Whilst 53.7 Gy is higher than normofractionation (50 Gy), it is suggested that as this dose level is well within the tolerance of all adjacent normal tissues and structures, confirming the safety of the 26 Gy schedule 5. My calculations suggest that 26 Gy in 5-fractions is favourable to 40Gy in 15-fractions and 50 Gy in 25-fractions in terms of late toxicities if the true alpha-beta ratio is ≤1.5 Gy.

Adjusting OAR dose constraints for radiotherapy planning is an important part of the clinical implementation of a new hypofractionation regimen. This was investigated in terms of heart dose by Appelt *et al* (2013) (79), which evaluated five hypofractionation regimens, including 40 Gy in 15-fractions. They found that the hypofractionation schedules resulted in reduced EQD_{2Gy} mean and V40Gy doses to the heart if the alpha-beta ratio is ≤1.5 Gy. 26 Gy in 5-fractions was not included in their analysis, and they also did not provide equivalent OAR dose parameters for the individual dose schedules as was the aim in my study.

Ipsilateral lung V18Gy (EQD_{2Gy} V15.1Gy) for 40 Gy in 15-fractions is the equivalent tolerance parameter to ipsilateral lung V20Gy for 50 Gy in 25-fractions (EQD_{2Gy} V15.2Gy), with regard to pneumonitis and lung fibrosis (assuming an alpha-beta ratio of 3 Gy). Ipsilateral lung V18Gy of 15% was provided as the

tolerance parameter for the IMPORT High trial , which led to the subsequent wide adoption of this dose constraint into standard practice (100).
The 26 Gy in 5-fractions fractionation has been widely adopted throughout the UK for a significant proportion of the early breast cancer radiotherapy cohort (currently only excluding those patients with implant-based reconstructions and the inclusion of nodal targets, as per the FAST-Forward trial population). However, the conservative dose parameters provided by the Fast-Forward trial create some difficulty when implementing into the most commonly utilised clinical practice of hybrid volume-field-based planning.

Firstly, the FAST-Forward constraint V8Gy of 15% gives an EQD_{2Gy} of V7.1Gy; significantly lower than the 40 Gy in 15-fractions parameter ipsilateral lung V18Gy EQD_{2Gy} of V15.1Gy (assuming an alpha-beta ratio of 3 Gy). Ipsilateral lung V18Gy can also be expressed as V45%, with ipsilateral lung V8Gy much lower at V31%. A lower ipsilateral lung constraint will require more compromise to target coverage, directly impacting tangential field placement. This may be difficult to justify in terms of the low incidence of lung toxicity and high level of local control with the established 40 Gy in 15-fraction regimen. The dosimetric data in terms of compliance to the FAST-Forward OAR constraints have not been reported. It may be that the optimal lung tolerance as defined by the trial protocol RTTQA planning pack, and that which was achieved are not concordant.

To ensure field placement is not affected by the hypofractionation schedule selected, I propose that the ipsilateral lung constraint for 26 Gy in 5-fractions should be V11.7Gy, which is ipsilateral lung V45%. Ipsilateral lung V11.7Gy is favourable in terms of the EQD_{2Gy} (V13Gy) compared to ipsilateral lung V18Gy delivered in 15-fractions (V13.2Gy), even if the true alpha-beta value is as low as 1 Gy.

Due to the rapid implementation of the 26 Gy in 5-fraction schedule in response to the COVID-19 pandemic, a maximum threshold for our institution's virtual simulation ipsilateral dose surrogate (%ILF) was not initially available. As a result, 12% of the cohort exceeded the proposed ipsilateral lung constraint V11.7Gy of 15%. The FAST-Forward ipsilateral constraint V8Gy of 15% was exceeded in 62% of patients; demonstrating the potential impact on field placement for more

than half of patients if the lower constraint is used, and the value of an accurate dose surrogate during virtual simulation.

A second issue identified when translating the FAST-Forward trial planning pack into standard clinical practice, is that MHD was not provided as a tolerance dose parameter. Subsequent to the trial development, MHD emerged as an important parameter with regard to cardiac toxicity; that for every 1 Gy increase in MHD, the risk of serious cardiac events increases by 7.4%. A widely accepted MHD tolerance is 2 Gy when treating with 40 Gy in 15-fractions and is largely achievable with breath holding techniques. However, with there being no safe dose threshold, minimising the heart dose as much as possible is advised (26,34).

Using a MHD constraint of 2 Gy for 50 Gy in 25-fractions and 40 Gy in 15-fractions results in similar EQD_{2Gy} of 1.04 and 1.07 Gy (alpha-beta ratio of 2 Gy) but is higher at 1.2 Gy if delivered in 5-fractions. Darby *et al* (2013) reported an 8.4 % increase in the risk of major coronary event for every 1 Gy increase in EQD_{2Gy} MHD (34). Despite this apparently small increase in EQD_{2Gy}, this equates to an additional 1.3% risk of major coronary event for a MHD constraint of 2 Gy delivered with the 5-fraction regimen. It is therefore important to apply radiobiological corrections to establish an equivalent constraint when reducing the fraction number, which for 26 Gy in 5-fractions is a MHD of 1.8 Gy (EQD_{2Gy} 1.06 Gy).

The HYPORT-Adjuvant trial supports recommendation that the MHD constraint should be modified in acknowledgement of reducing fraction number (98). They stipulate a MHD constraint of 1.6 Gy for the 5-fraction regimen, and 2.5 Gy for the 15-fraction control arm. This results in a lower EQD_{2Gy} for the test arm versus the control arm (0.93 Gy versus 1.35 Gy, alpha-beta ratio 2 Gy), the reason for which is not stated in the trial protocol.

For some patients during virtual simulation, the predicted MHD will exceed the dose constraint, and the clinical decision of whether to accept further target compromise versus a higher MHD is a common scenario in breast radiotherapy

planning. I suggest that EQD_{2Gy} calculation to estimate the additional risk per 1 Gy increase in EQD_{2Gy} MHD can support decision-making.

With new tolerance parameters proposed for ipsilateral lung and MHD for 26 Gy in 5-fractions, the linear regressions between ipsilateral lung V11.7Gy and %ILF; and between MHD and %HIF could be performed. This demonstrated the continued strong and predictive relationship of these virtual simulation dose surrogates. The maximum threshold values for %ILF aligned to those that I calculated for a prescription of 40 Gy in 15-fractions (13 versus 13.5%) (71). Due to the lower dose prescription, the maximum %HIF to achieve the equivalent MHD constraint of 1.8 Gy was a little higher at 2.7% versus 1.7% for 40 Gy in 15-fractions.

Virtually simulating to these maximum thresholds will ensure that the equivalent OAR constraints for 26 Gy in 5-fractions will not be exceeded on the final dosimetric plan, target coverage will not be unnecessarily compromised, and the risk of normal tissue effects will not be greater compared to 40 Gy in 15-fractions.

3.7 Conclusion

My study has demonstrated that equivalent parameters for ipsilateral lung and MHD can be readily calculated for a new hypofractionation schedule, using EQD_{2Gy} calculation and the appropriate alpha-beta ratios for the clinical endpoints of interest. There is some uncertainty of the model calculations as EQD_{2Gy} for MHD is an approximation and the assumed alpha-beta values are uncertain.

Challenging new OAR dose parameters with a range of alpha-beta values can provide reassurance in acknowledgement of the ambiguity regarding the true value for alpha-beta.

The new tolerance parameters defined for a 26 Gy in 5-fraction schedule facilitate calculation of the maximum threshold values for virtual simulation dose surrogates %ILF and %HIF. This will ensure that tolerance doses are met, and field placement is not compromised as a result of fractionation change.

Chapter 4

The emotional impact of permanent Indian ink alignment tattoos following breast cancer treatment

4.1 Introduction

4.1.1 The history of breast radiotherapy and skin marking

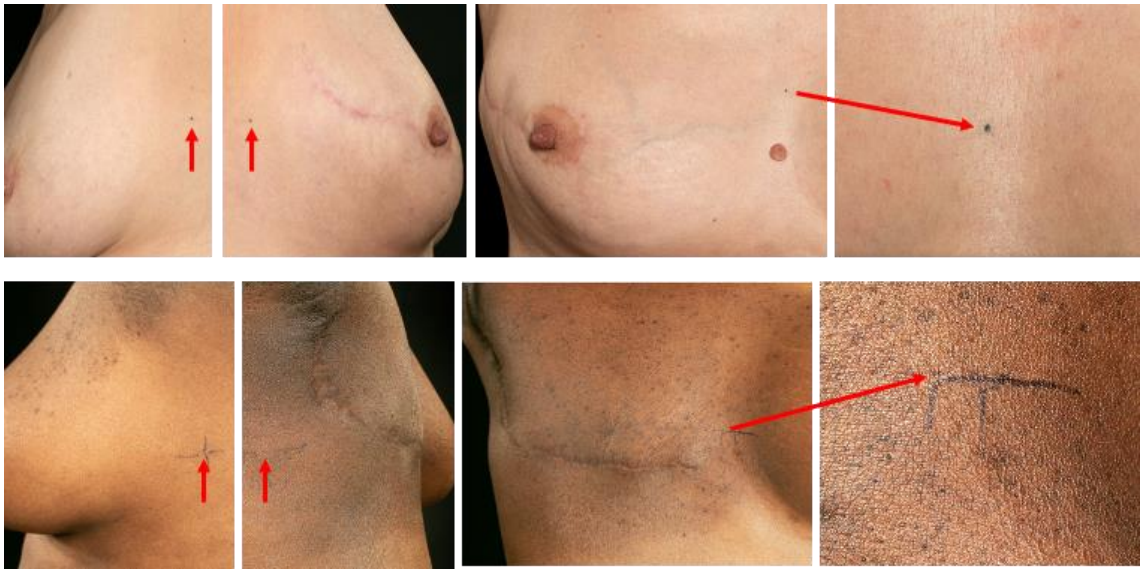
The first recorded use of radiotherapy for breast cancer was in Chicago, 1896, to treat a patient with inoperable, locally advanced breast cancer with low-energy x-rays (101). It wasn't until 1952 that the first patient was treated in London on a linear accelerator. The 1960's saw the introduction of high-energy external beam radiotherapy delivered with 360 degree rotational linear accelerators as we know it today, using the laser technology developed during World War One (102–104). At that time, in terms of treatment for breast cancer, radiotherapy was reserved for high-risk disease post-mastectomy; rarely used and considered highly experimental following breast conserving surgery (105). This is in stark contrast to today's practice which sees over 33,000 people treated with radiotherapy every year in the United Kingdom as part of early breast cancer management; the majority following breast conserving surgery (106).

More than 50 years ago, the role of radiotherapy skin marking was described by Gardner *et al* (1972) during the early implementation of isocentric techniques (107). They refer to the role of three intersecting points marked onto the patient's skin; one anterior and two lateral; to aid reproducible patient set-up and localisation of the treatment isocentre when aligned with wall- and ceiling-mounted lasers. Other than a change in the method of skin marking, [which prior to the mid-1980's was with gentian violet (108), and now most commonly with the application of permanent Indian ink tattoos (109)], this method of patient alignment remains largely unchanged, despite the gradual increased utilisation of surface guidance to aid patient set-up (which can omit the need for skin marking) (110,111).

Radiotherapy alignment tattoos are permanent skin marks applied with Indian ink and a lancing needle. They are black/green/blue in colour and approximately 2 mm in diameter, which may increase to 5 mm in the years following application. Three to six tattoos are typically used for breast cancer radiotherapy. It is standard practice for at least one of the tattoos to be placed in the anterior midline

along the sternum, 5-15 cm inferior to the suprasternal notch, and further tattoos to be located on the lateral chest wall, approximately at the level of the nipple areola. These tattoos can be highly visible during and after treatment on white/lighter skin, and difficult (sometimes impossible) to see on brown and black skin during and after treatment (figure 25).

Figure 25: ***High visibility of Indian ink tattoos on white skin and poor visibility on black skin*** (112)



Radiotherapy tattoos are defunct of purpose once the radiotherapy course is complete, due to the universal adoption of three-dimensional computer tomography (CT) planning. Over twenty years ago when fluoroscopy simulation was used for the localisation and planning of the treatment fields, the tattoos served as a permanent record of the irradiated field borders, ensuring no overlap with previously irradiated tissue if the patient required further radiotherapy simulation and treatment. However, CT planning facilitates the co-registration of a previous dosimetric treatment plan to the new CT scan acquired at the time of subsequent-course radiotherapy planning, to enable avoidance of tissue and organ re-irradiation beyond tolerance doses (113). The radiotherapy tattoos serve no purpose in this process and are often problematic in terms of patient set-up as rarely align for a subsequent treatment course due to changes in patient body habitus, patient positioning and the immobilisation equipment used.

Patients are required to provide their written consent to have permanent radiotherapy tattoos, although are rarely offered a choice or alternative. This breeches one of the fundamental elements of what constitutes informed consent, as described by Hall *et al*, and can be influenced by the healthcare practitioners individual beliefs or unconscious bias (114).

An opinion that is commonly shared amongst the radiotherapy multidisciplinary team is that refusal to have radiotherapy tattoos represents patient non-compliance and increased risk of treatment error (115). This view is contradicted in the literature, with several single centre studies reporting non-inferiority of non-permanent alternatives to permanent tattoos in terms of treatment set-up accuracy (116–118). I was invited to by the UK Health Security Agency to submit an editorial to their *Safer Radiotherapy Bulletin* around the institutionalised belief of the radiotherapy team, that permanent tattoos are a requirement for accurate radiotherapy with little consequence to the patient (119). This opinion also appears to be supported by all three radiotherapy professional bodies (the College of Radiographers; the Royal College of Radiologists, and the Institute of Physics and Engineering in Medicine); in their Public Health England guidance (120) :

> *"Non-compliance is described as being when a patient does not comply with the procedure; this may be through their own volition or through an unknown inability to comply; where cultural, religious and social issues affect the ability of a patient to be consistent with pre-conceived expectations – i.e. tattoos……; where a patient has chosen to purposefully ignore advice which has directly led to an incident."* (Page 8).

4.1.2 Impact of radiotherapy tattoos on emotional well-being

Despite the rising incidence of breast cancer, the proportion of people surviving this disease is also increasing due to earlier detection through the National Breast Screening Programme, optimised diagnostic and staging imaging, and advances in surgical techniques, systemic therapy and radiotherapy (121). It is estimated that by 2030, there will be more than 1.2 million people in the United Kingdom living with or beyond a breast cancer diagnosis; double that of today's number

(122). With breast cancer prevalence increasing, survival rates improving, and the surviving population growing, the emotional and physical impact of this diagnosis and the associated treatments that can bring significant survivorship issues in the months, years and decades that follow, has understandably moved up the priority list of what is important to our past, current and future patients.

Focus on outcomes in addition to breast cancer specific and overall survival, such as cosmesis and emotional well-being, have increased and are acknowledged throughout the pre- and post-treatment pathway. Examples of treatments now available to improve emotional well-being of people living with and beyond cancer include oncoplastic surgical techniques, immediate breast reconstruction, nipple areola reconstruction with cosmetic tattooing of natural pigmentation and contralateral breast symmetrisation; the use of cold caps, wig services, scarf-tying workshops and make-up tutorials aimed to reduce the impact of temporary hair-loss due to chemotherapy. Additionally, support services offer survivorship well-being programs and talking therapy. Holistic therapies are also available, for example acupuncture to alleviate side effects such as treatment-induced menopause (123). All such interventions, especially when deployed together throughout and beyond the patient pathway, will contribute to a more positive survivorship for this ever-growing population.

The improvements that have reduced the negative impact on body image that breast cancer and the associated treatment can inflict, may bring into the spotlight other, previously considered minor interventions such as the application of permanent Indian ink tattoos. This practice remains relatively unchallenged and unchanged despite anecdotal and published evidence that indicates that people living beyond a breast cancer diagnosis find these a distressing consequence of their treatment (115).

Some patients referred for radiotherapy decline tattoos at the point of obtaining their consent for the skin marks. Townsend *et al* (109) surveyed UK centres and reported that patients receiving radiotherapy for primary breast cancer represented the largest patient cohort to decline in the 62% of UK centres with experience of patient refusal. Many patients accept them with resignation, as the therapeutic radiographers stress their requirement for treatment accuracy, with

the tattoos often perceived and presented as having minimal consequence in the context of curative cancer treatment (115). However, the evidence-base is starting to grow from both anecdotal observations, online patient forums and a small field of emerging evidence of patient reported negative outcomes regarding this topic. For example, all participants at a Young Survival Coalition meeting were asked about their overall feelings about their radiotherapy tattoos. 70% of respondents reported negative feelings towards their skin marks (124).

4.1.3 Alternatives to permanent Indian ink radiotherapy tattoos

Surface Guidance radiotherapy (SGRT) involves the use of a projector and several cameras that map the three-dimensional contour of the patient's body surface when lying on the CT or treatment couch. The initial clinical purpose of this technology was to support real-time patient positioning, breathing tracking and breath-holding techniques, to increase treatment accuracy and reduce the incidental dose to non-target tissue such as the heart and lungs (125). However, a welcome secondary benefit of this equipment is that it can omit the need for skin marking as uses the entire surface contour of a region of interest within and around the treatment site, as opposed to three intersecting points as is the case for tattoo-based alignment. A number of studies have demonstrated non-inferior set-up accuracy when compared to tattoo-laser based set-up for breast cancer radiotherapy, facilitating tattoo-less radiotherapy (110,126–128). However, the high capital costs and annual service charges associated with surface guidance hardware and software can be substantial; with limited clinical value and the continued need for radiographic verification given as accompanying reasons that many radiotherapy centres would not be pursuing implementation of SGRT in the survey responses of 278 institutions across 62 countries (128). Therefore, tattoo-laser based patient alignment is likely to exist in many centres internationally unless challenged with feasible alternative skin-marking methods (119).

Interest in semi-permanent alternatives has been evident for over twenty years, with several single centre studies investigating skin-marking methods such as henna, semi-permanent pen marks and fluorescent tattoo ink (116–118,129). Wurstbauer *et al* (129) investigated the use of henna as a method of skin marking, suggesting superiority to pen marks as permits patients to wash normally without

the risk of skin marks ‘drifting’ which may reduce treatment accuracy. They employed this technique on 158 patients and a wide range of treatment sites (including breast radiotherapy). Patients required remarking on average twice during a radical treatment course. However, despite the suggestion in the article title; *Skin markings in external radiotherapy by temporary tattooing with henna: Improvement of accuracy and increased patient comfort;* no data was presented in terms of patient set-up or reproducibility.

Probst *et al* (116) conducted a randomised controlled trial to evaluate the use of pen marks compared to permanent tattoos in 342 breast radiotherapy patients, with a primary endpoint of random and systematic error according to central and maximum lung depth. No significant difference was reported between the skin marking methods. Despite the findings of this UK-based study, there are no UK departments that use pen marks in place of permanent tattoos.

In acknowledgement of the possible negative impact of permanent Indian ink tattoo visibility, Landeg *et al* (117) compared treatment reproducibility and body image scores in a study of 46 breast radiotherapy patients randomised to either standard tattoos or UV ink tattoos (invisible in normal light). They reported no significant difference in random or systematic error according to template matching of the lung and external contour of the tangential treatment field electronic portal images between the groups. The UV group had favourable body image scores at 1- and 6-months after completing radiotherapy compared to the permanent Indian ink tattoos group.

A similar study acknowledging the psychosocial impact of permanent dark-ink tattoos, and also demonstrating no significant difference in set-up error with UV-ink tattoos compared to permanent tattoos in 34 breast radiotherapy patients was conducted by Lim *et al* (118). Their shorter time-point of 6-weeks post treatment to assess body image showed that there was no significant difference between the groups.

Despite the improvements in body image and comparative set-up accuracy described above, Indian ink tattoos persist as the international standard to support laser-based set-up in the majority of radiotherapy centres.

Implementation of the simpler methods of skin marking alternatives such as pen marks or henna, may have not been adopted into standard practice following publication of these studies in-part due to the year of their publication in the early 2000's; during the era of two-dimensional planning when the permanence of tattoos was replied upon to localise previous radiotherapy fields. However, as described above, three-dimensional CT planning has removed this requirement.

It may, therefore, be considered that there are other factors at play that are influencing the lack of challenge to change this practice of permanent tattooing by the therapeutic radiographers, such as the entrenched belief that alternatives are inferior in terms of set-up accuracy, despite the contradictory data. Claw and Allen (115) state that women's voices are absent in the small body of available literature that address radiotherapy tattoos for breast cancer; and that research specifically reporting the radiotherapy experiences of patients does not even acknowledge permanent tattoos as a component of their treatment that could have an impact on their emotional well-being.

4.2 Study aim

The aim of this study was to investigate the impact of permanent Indian ink radiotherapy tattoos on people following breast cancer radiotherapy.

4.3 Materials and methods

4.3.1 Population

Breast Cancer Now is a UK charity that offer support for people affected by breast cancer. They promote their role in research via their website, with their mission statement described as being recognised as a resource that is accessed for information and support to drive breast cancer breakthroughs (130). Breast Cancer Now have a number of patient involvement groups that function and communicate through various social media platforms, such as Facebook. I contacted the Breast Cancer Now Patient Involvement Manager and described the study aim. It was agreed that a link to my electronic survey would be shared with their Insight and Experience Panel and Breast Cancer Now Campaign Facebook groups.

4.3.2 Questionnaire development and distribution

I developed a ten-question survey following a review of the literature and reflection on my insight into the impact of radiotherapy tattoos on patients; observed during my clinical follow up of patients up to ten years after radiotherapy. Content was validated after review by experts in survey [redacted], oncology and radiotherapy clinicians and patients. Breast Cancer Now researchers approved the format and content for the relevant target patient involvement groups.

Four questions collected data on respondent demographics and six focussed specifically on radiotherapy tattoos. Of the tattoo questions, two were nominal (one with the option to add free-text comments), three were Likert scale (all with

the option to add free-text comments), and one was an open free-text question (figure 26).

The electronic questionnaire was produced using SurveyMonkey® (SurveyMonkey Inc. San Mateo, California, USA. www.surveymonkey.com). I shared the SurveyMonkey® link to be distributed by the Breast Cancer Now engagement team, to their Insight and Experience Panel, and Breast Cancer Now Campaign Facebook groups. The questionnaire was available for a period of twelve weeks, with no threshold for the number of respondents.

Figure 26: Survey questions

Question	Response Options
Did you have radiotherapy for breast cancer?	Yes / No
Did you have radiotherapy tattoos?	Yes / No
How did you feel when told that permanent skin marks were required?	**Select all that apply** I didn't mind at all I felt concerned that they would be there forever I would have preferred not to have them but understood they were important for the radiotherapy to be accurate I refused to have them Other (please specify)
How long ago did you finish your course of primary breast cancer radiotherapy?	Less than 6 months 6-12 months 1-2 years 2-3 year 3-5 years More than 5 years
How old were you when you had radiotherapy?	Free text
How would you best describe your skin tone?	Type I - Pale skin, burns easily, never tans Type II - Usually burns, hardly tans Type III - Sometimes burns but does tan Type IV - Rarely burns, tans easily Type V - Very rarely burns, tans very easily Type VI - Never burns, deeply pigmented

If you had a tattoo on the front of your chest near the middle of your breastbone, can you still see it?	Yes / No If you responded 'not applicable', please explain your answer in more detail
How did you feel about receiving tattoos as part of your breast cancer radiotherapy treatment at the time, and do you feel any different about them now?	Free text
Do your tattoos bother you in a negative way?	Not at all A little Quite a bit Very Much Please give a reason for your answer
How much do you agree with the following statement: ***If there was an alternative to the permanent tattoos that was just as accurate, but would fade and become invisible over time, I would opt for this semi-permanent alternative.***	Strongly agree Agree Disagree Strongly disagree Please add here any additional comments you wish you make about radiotherapy tattoos

4.3.3 Data analysis

I exported the raw data in the format of a Microsoft Excel spreadsheet that was exported directly from the SurveyMonkey® application and used IBM SPSS Statistics (Version 28) for all data analysis.

I grouped respondent age at the time of radiotherapy and completing the questionnaire as follows; ≤40, 41-50, 51-60, and >60 years.

I familiarised myself with the free-text comments and generated initial codes aiming to identify repeating themes amongst the respondents. A theme was defined as when more than 1 respondent used a specific emotive verb to describe the impact of their radiotherapy tattoos. A second researcher (Researcher 2, [redacted]) (with extensive experience in patient reported outcomes

and thematic analysis) reviewed the themes that I had identified and confirmed the allocation of codes I had assigned to each respondent.

I quantified the impact of radiotherapy tattoos on each respondent on a Likert scale; from 1 (strongly negatively affected) to 5 (strongly positively affected); which was termed *overall impact score*. This was determined according to the themes identified for each respondent, supported with the surrounding context of the raw free text. To reduce the opportunity for researcher-bias, this was independently scored by Researcher 2. Where any score differed, agreement was reached with further discussion and review of the free-text raw data. It was planned that if no agreement could be reached between us, then a third researcher would be consulted to allow a majority decision.

I performed cross tabulation between the overall impact scores and respondent-ranked impact of how 'bothered' they are by the tattoos. I interrogated incongruence between the paired respondent- and researcher-assigned impact scores by returning to the interpretation of the context of the raw data of the full free-text responses as opposed to just the thematic codes.

I conducted one-way Kruskall-Wallis analysis of variance (ANOVA) tests to interrogate the null hypothesis that there was no difference in the distribution of time since completing radiotherapy, age at the time of radiotherapy, age at the time of completing the questionnaire, skin type, and respondent rank for how much the tattoos 'bothered' (caused upset or worry) them, across the overall impact scores. A significance value of $p > 0.05$ would reject the null hypothesis.

The relationship/agreement between the respondent-ranked and researcher-scored impact of tattoos were assessed using Spearman's correlation co-efficient. Two-tailed statistical significance was defined as $p<0.05$. A large correlation was defined as $r=>0.5$ (131).

To deepen the understanding of the positive and negative effect of radiotherapy tattoos, and in acknowledgement of the shortcomings of the current evidence base (115), I selected and presented verbatim quotations from a wide range of respondents according to each theme or sub-theme (132).

4.3.4 Ethical considerations

The study was conducted in accordance with the UK Framework for Health and Social Care Research. NHS ethics approval was not required because the survey was administered through the accounts of a third-party organisation, Breast Cancer Now. Breast Cancer Now reviewed and approved my survey through their internal governance processes. There was nothing included in the survey that could identify participants and submission of responses was implicit of consent.

4.4 Results

4.4.1 Respondent demographics

A total of 204 people responded to the questionnaire within the 12-week period that the SurveyMonkey® link was live. There were no missing fields for any of the questionnaires completed. All (100%) respondents received permanent Indian ink tattoos during radiotherapy for early breast cancer. The respondents age, time since radiotherapy and skin type is presented in figure 27, but in summary, the mean age at the time of radiotherapy was 48 years (range 23 – 73). The time since completing radiotherapy was >5 years for 35% of the respondents, 1-5 years for 40% and <1 year for 25%. According to the Fitzpatrick scale (133), the majority (n = 168; 82%) of the respondents defined their skin as Type I-III (Type I: pale skin, burns easily, never tans; Type 2: usually burns, hardly tans; Type 3: sometimes burns but does tan), and none as Type 6 (never burns, deeply pigmented).

Figure 27: Respondent demographics

Age at time of RT (years)		**Time since RT**		**Fitzpatrick skin type**	
Mean	48	**<6 mths**	21 (11%)	**I**	27 (13%)
Range	23-73	**6-12 mths**	29 (14%)	**II**	41 (20%)
<30	6 (3%)	**1-2 years**	30 (15%)	**III**	99 (49%)
30-39	37 (18%)	**2-3 years**	25 (12%)	**IV**	28 (14%)
40-49	61 (30%)	**3-5 years**	27 (13%)	**V**	9 (4%)
50-59	73 (36%)	**>5 years**	72 (35%)	**VI**	0 (0%)
60-69	21 (10%)				
>70	6 (3%)				

4.4.2 Application of tattoos

Three respondents (1%) stated that they declined the application of the anterior midline tattoo during the radiotherapy planning process due to concerns regarding the visibility of the tattoos after the radiotherapy course was complete. Twenty respondents (10%) felt concerned about the permanence of the tattoos at the time of application. Two respondents (1%) stated that they were not told

that the tattoos would be permanent, and seventy (34%) did not mind having the tattoos at the time of application. The majority of respondents (n=124;61%) would have preferred not to have the tattoos but accepted their application due to the importance for radiotherapy accuracy.

A total of 201 (99%) of the respondents had an anterior midline tattoo applied during the radiotherapy planning process, of whom 191 (95%) said that it was still visible. One respondent stated that they had this tattoo incidentally removed during a subsequent mastectomy and another respondent had previously had the tattoo removed with a laser tattoo removal process.

4.4.3 Post-treatment impact

Researcher 2 ([redacted]) agreed with the 22 subthemes within three overarching themes of positive (n=4), negative (n=14) and neutral (n=4) from the free-text comments that I identified (figure 28). Some free-text comments made by a single respondent crossed more than one of the themes. In such cases, both themes would be counted. This can be identified in some of the quotes provided below; where despite being given as an example under a specific theme, could have easily been assigned under another. In some cases, a comment may be considered sharing both positive and negative themes.

Positive Impact

Of the four positive themes, ten (5%) respondents were proud of their radiotherapy tattoos:

"I didn't mind. It was my very first tattoo and I was excited. I love looking at them now as it reminds me of the journey I have been through."
"The one in my cleavage is my whole world (stolen from a line in Friends) and they are war wounds I wear with pride. They remind me of my strength and resilience".
"When I see the one on my chest, I don't resent it, I can joke it's a "badge of honour."

"I thought it was fun to have a tattoo this way - and I still smile when I see the little dots. I am almost proud of them."

Eight (4%) respondents found them reassuring during the treatment:

"The permanency of them gave me confidence in the radiotherapy being correctly targeted."
"I wanted to make certain the radiotherapy "hit the right spot!"
"They didn't bother me too much at the time as I knew they were helpful for accurate therapy."

They reminded five respondents that they were survivors:

"They don't bother me now, just another reminder of how lucky I am to have survived."
"If anything, I treat it as a bit of a joke – my tattoo – it makes me feel hard! I guess I am a hard nut as I overcame breast cancer!"
"I feel they help me remember that thanks to my wonderful NHS nurses and doctors my cancer is in remission."
"They definitely are a reminder but in a good way - they remind me what I went through and that I'm still around 19 years after!"

Two respondents stated that they motivated them to have further artistic tattoos:

"I took control and got tattoos that I did want, which I absolutely LOVE. I would never have got tattoos before my cancer, the ones I have now, I love."
"I now see them as markers of a difficult time I went through … I have sometimes thought of using them as a starting point for a larger tattoo."

Negative Impact

Of the fourteen negative themes, the most commonly occurring were:
The feeling that they had no choice in 31% of respondents (n=63):

"It was necessary for accurate radiation therapy."

"A necessary evil, would rather not have them but not overly self-conscious of them, part of my battle scars."

"At the time I was so stressed and anxious, and I just wanted it all to go away. I just did whatever they said. How I feel about them (tattoos) now, is I hate them."

"I was indifferent at the time as I needed the treatment and there was no alternative on offer."

"To be honest I knew I had to have them, it's just that now I have a permanent reminder of what happened to me."

"Initially I said I didn't want them, the staff told me they were necessary so I didn't need to be measured each visit. I felt this was yet one more thing that I had to endure and live with after breast cancer."

"At the time it seemed inevitable and was part of the ongoing horror."

It was necessary so I just got on with it."

"The female staff in the radiotherapy department were very cold and brusque about why I had to have the tattoos saying it was so they could line up the equipment exactly each treatment and it was there should I need further radiotherapy. I really had no choice in being able to refuse."

"At the time I just thought they had to be done, it wasn't a choice."

That they serve as a negative reminder of their breast cancer diagnosis and/or treatment in 27% of respondents (n=54):

"Still after all these years I see them as a reminder of that time."

"Still a constant reminder and I would have preferred them not to be permanent."

"Although small, they are a constant reminder of the diagnosis and treatment."

"They are a reminder of the horrible journey I had to endure and leads to anxiety about cancer coming back when I see them."

"When they show in clothes, some people recognise what they are from, so it puts me back to being a cancer patient. My cancer feels like a long time ago now, and I resent wearing the marks of it unnecessarily."

"I wish I could get rid of them as they are a constant negative reminder."

"It would be nice if the tattoos wasn't there as it is a reminder."

I hate them as they are a constant reminder."

"I do not like the look of the one in the centre of my chest. It is a reminder even when dressed and I look at the black mark of my cancer."

"Feel like it's a permanent reminder. Some days it bothers me other days it reminds me that I got through it."

"I have 8 tattoos, as well as my mastectomy they are a permanent reminder of my breast cancer."

"I'm left with a permanent reminder of the horrible year I had, which sometimes adds to anxiety of it coming back."

"Resigned to it at the time, now I hate them. They're a permanent reminder of treatment that disfigured me."

That they affect clothing choices in 15% of respondents (n=31):

"I am still quite aware of them for example when wearing low cut dresses/tops and gym clothing."

"6 years later I had LD reconstruction, but my tattoo mark is still visible and I hide showing any cleavage or have to wear concealer."

"I was very upset when I heard I had to have them. I was slightly less stressed after having them as they are quite small, but I do feel very self-conscious about the one in my cleavage... this will affect future swimwear and party dress choices."

"Now I really dislike them. One is visible when wearing summer tops and I'm worried people think it's a black head spot!"

"Surgery scars you can't see but this (tattoo) I have to think carefully with low neck lines like swimming costumes."

"I still am conscious about the tattoos and have to think about the tops/dresses I wear/buy so my tattoos aren't on show."

"They are a constant reminder to me as they can easily be seen - I can't wear low cut v necked dresses or tops."

"One tattoo is in my upper cleavage area so on display if I wear a lower neckline. I wear different clothing now because it is on display."

Twenty-three (11%) respondents described feelings of "hating" them:

"To me they felt worse than my mastectomy scar."
"I am embarrassed about them now and feel I need to cover them up. I'm very self-conscious when going swimming. I'm currently single and dread the idea of intimacy with any future partner."
"I felt and still feel marked."
"It felt a bit like branding at the time."
"I absolutely hated them! I was extremely upset. I am very happy now they have been lasered off."
"I didn't think anything at the time but really don't like them now particularly the one in the middle. It's strange really as I no longer have a nipple on by affected side and that bothers me far less and even decided I don't want either nipple reconstruction or a nipple tattoo."
"One more procedure I hated having."
"I still have them over 7 years later and I hate seeing them."
"Hate it. And still do."
"I wish I didn't have them and I wish I could afford to have them removed."

The 'negative appearance' of the tattoos, mainly in relation to the unnatural colour of the tattoo ink (black/blue/green), or because it looked like a spot, was referred to by twenty-six (13%) respondents. Many commented that if the tattoos were a more natural brown colour, then they would be less noticeable and bothersome.

"Some days I dislike the one in my breastbone area, because it can be seen when I'm wearing certain clothing and is slightly green in tone."
"Another disfigurement caused by the treatment."
"Reminds me I had cancer. It is visible to others and looks like a blackhead. I feel I have to wear clothing that covers it."
"They look like ugly blue pen marks."
"I prefer my scars to the radiotherapy tattoos."
"I was told they would hardly be able to be seen but this is not the case. I have had four laser treatments to try and get rid of them so far and they're still visible."

"Several times when swimming friends have commented on my "blackhead" and once my beauty therapist offered to squeeze it !!!"

"I have a permanent tattoo of a blackhead in my cleavage."

"They are green and quite prominent".

"I hated the one in the middle and even attempted to scratch it away...would rather they were not there, particularly since they are blue... If they had been brown, they might have looked more like a freckle."

"The one in the middle of my chest looks like a blackhead which I don't like."

"I keep seeing it and thinking it's a spot or dirty mark and sometimes have scrubbed at it a couple of times before I realise what it is."

"The tattoo looks like a giant blackhead."

"I was very upset by them. I didn't ever wish to have a tattoo. They still upset me now, although more so in the summer when they can be easily seen. They look like dirty marks."

"I absolutely hate the blue dot that is often visible depending on what I am wearing".

Other less commonly occurring, but high impact themes included recalling that they were painful when applied (n=3), and concerns associated with the tattoos and their religious beliefs (n=2).

"I disliked the procedure – the sharp prick of the needle. I had been through so much; I hated any pain."

"The tattoos were painful as they are over the breastbone and ribs where there is little soft tissue."

"I was surprised how painful tattoos are to do."

"My religion doesn't approve of tattoos and although I'm not devout it was not something I was comfortable with."

Figure 28: Themes from free-text responses

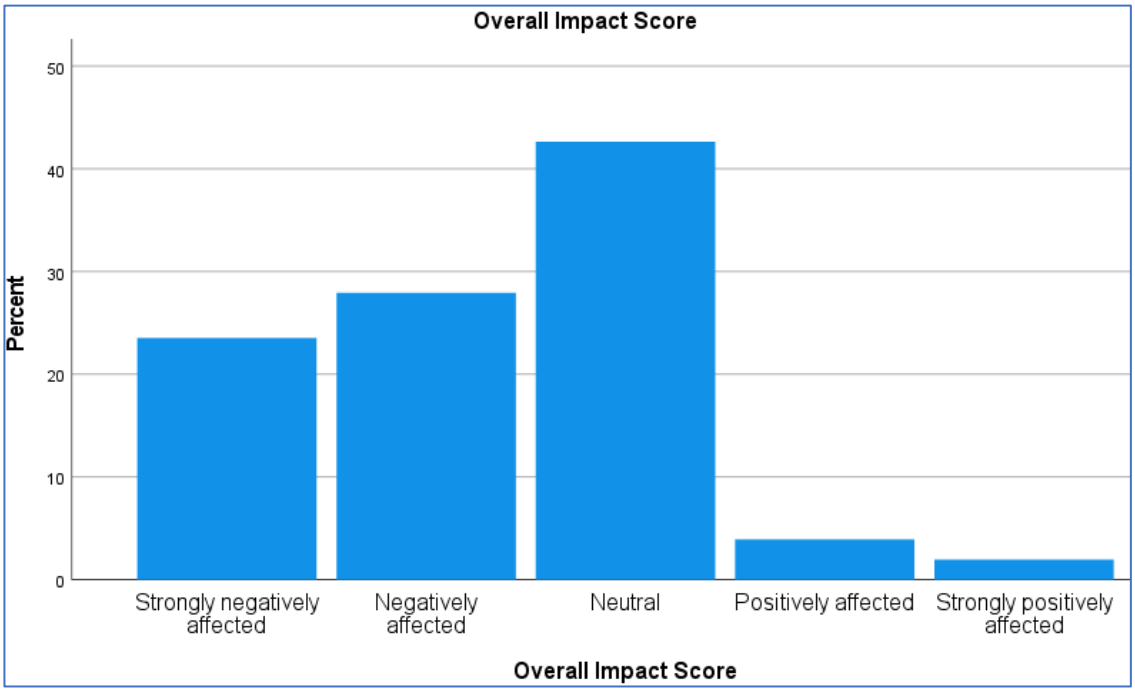
Positive themes	
Feel proud/positive about them	10 (5%)
They were reassuring during treatment	8 (4%)
Reminds me that I am a survivor	5 (3%)
Impetus for further tattoos	3 (1%)
Negative themes	
Felt I had no choice	63 (31%)
Constant negative reminder	54 (27%)
Affects what I can wear	31 (15%)
Negative appearance of tattoos	26 (13%)
Hate them	23 (11%)
Felt ok about them at the time but not now	10 (5%)
Shows you've had cancer	9 (4%)
Bothered at the time and bothered now	8 (4%)
Would like to be offered removal	5 (3%)
I wanted to be someone who has no tattoos	5 (3%)
Other people notice them	5 (3%)
Painful	3 (2%)
Religious concerns	2 (1%)
Has a negative impact on my mental wellbeing	2 (1%)
Neutral themes	
Never bothered me	59 (29%)
I don't notice them	25 (12%)
Minimal in the greater scheme of things	21 (10%)
Bothered at the time but not now	12 (6%)

4.4.4 Overall impact

There was excellent agreement of the overall impact scores that I and Researcher 2 assigned to each participant. No score differed by more than one point, and we reached agreement for all cases without the need for a third researcher.

Eighty-seven (43%) respondents were assessed as having a neutral overall impact score. Twelve (6%) were assigned a positive overall impact score. Of the 105 (51%) respondents with a negative overall impact score, forty-eight were strongly negative (figure 29).

Figure 29: Researcher-assigned overall impact score of permanent Indian ink radiotherapy tattoos (112)



There was no difference in the strength or direction of overall impact scores according to; time since radiotherapy (p=0.771), age group at the time of radiotherapy (p=0.134), age group when completing the questionnaire (p=0.484) or skin type (p=0.439).

The was a large positive correlation (r = 0.82, p< 0.001) between respondent-ranking of how 'bothered' they were by their radiotherapy tattoos and the researcher-assigned overall impact score. All respondents (10%) that stated they were bothered 'very much' (n=9) or 'quite a bit' (n=11) had an overall impact score of 1 (strongly negatively affected). Of the 32% (n=65) of respondents reporting that they were bothered 'a little' by their tattoos, 95% (n=62) had an overall impact score of 1 or 2 [strongly negatively or negatively affected] (n=27 and n=35).

Despite 119 respondents stating that they were 'not bothered at all' by their tattoos, 19% were assigned negative (n=22) or strongly negative (n=1) overall impact scores; 71% (n=84) neutral and 10% strongly positive (n=4) or positive (n=8) overall impact scores. This demonstrates that despite a strong correlation between the respondent and researcher scores, that in some cases, opposing or conflicting scores were given.

4.5 Discussion

Historically, the multidisciplinary radiotherapy team has generally considered radiotherapy tattoos as a low-impact, essential part of treatment delivery, due to their small size and integral role in supporting accurate and efficient patient set-up during each radiotherapy treatment fraction. The permanent skin marks are therefore commonly perceived and communicated as such (directly or indirectly) to the patient by the health care professional, as an inconsequential intervention when considered alongside the assumed, more significant side effects of other curative breast cancer treatments that our patients endure, such as chemotherapy and surgery (115).

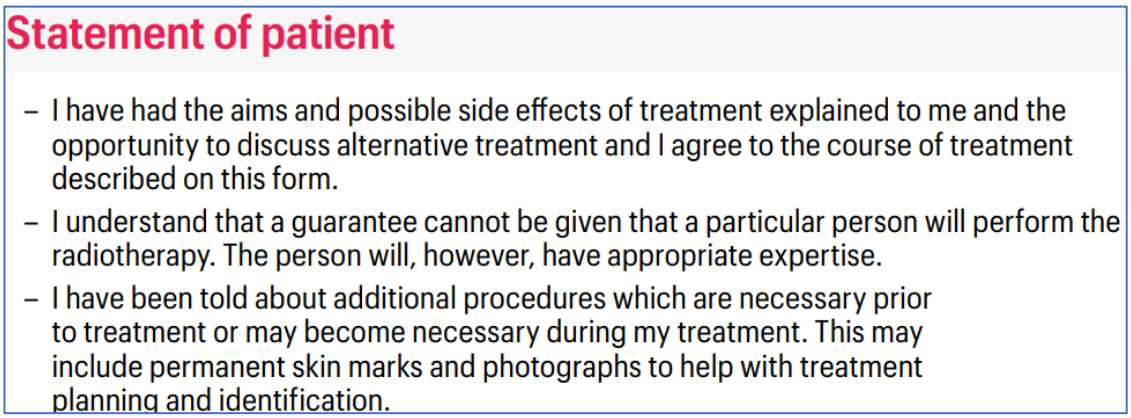
An important part of the radiotherapy consent process is to provide written information about a treatment or procedure that supports that which is given in a consultation, in advance of obtaining a patient's written consent. Below is an excerpt taken from the patient information leaflet at my institution (134). This demonstrates the lack of choice about radiotherapy tattoos that is embedded deeply within the accepted departmental processes, and the strong statement that they are required for accurate treatment, with no acknowledgement of the impact these may have on the patient in the months and years that follow.

> *"When the scan is done, and the radiographers have checked the images they will re-enter the room. The radiographers will then mark several specific points (also called tattoos) on your skin. These are alignment marks to ensure each treatment is accurate. The marks are permanent and are done by placing ink on the skin and then gently scratching the surface of your skin with a fine needle."* (Page 5-6).

The dismissive trend regarding the inconsequential impact and no choice of permanent tattoos is also evident at a national level. Permanent skin marks are not included in the list of common or frequently occurring side effects of radiotherapy on the Royal College of Radiologists site-specific consent form (135). The application of permanent skin marks is instead only mentioned in the patient statement section, alongside the potential use of photographs to aid

identification. This may be considered suggestive that they are of low significance with minimal impact to the recipient during and after radiotherapy, to both the health care provider and the patient (figure 30). Figure 31 demonstrates how this translates on a local level, with only a simple tick-box procedure used at my institution to confirm tattoo consent.

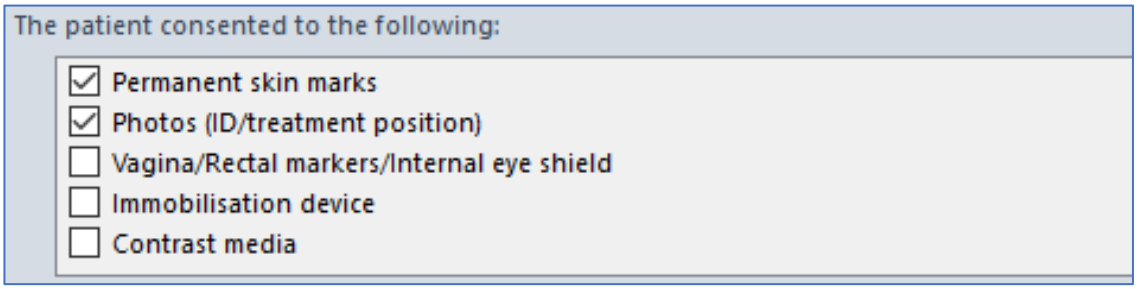
Figure 30: Royal College of Radiologists radiotherapy consent form (135)



Statement of patient

- I have had the aims and possible side effects of treatment explained to me and the opportunity to discuss alternative treatment and I agree to the course of treatment described on this form.
- I understand that a guarantee cannot be given that a particular person will perform the radiotherapy. The person will, however, have appropriate expertise.
- I have been told about additional procedures which are necessary prior to treatment or may become necessary during my treatment. This may include permanent skin marks and photographs to help with treatment planning and identification.

Figure 31: UCLH consent form regarding permanent Indian tattoos



The patient consented to the following:

- [x] Permanent skin marks
- [x] Photos (ID/treatment position)
- [ ] Vagina/Rectal markers/Internal eye shield
- [ ] Immobilisation device
- [ ] Contrast media

The opportunity for the respondents of my questionnaire to provide free text comments has afforded detailed insight beyond what a closed question would have yielded in terms of patients accepting lack of choice at the point of tattoo consent, and the impact that this can have in the future, when the perception and acceptance of side effects of an intervention can change. For example, the verbatim quotes below demonstrate the relationship between a patient's resignation of accepting 'no choice' due to their emotional vulnerability related to their fears associated with a breast cancer diagnosis, and the impact this can have in the future, such as leading to feelings of hate and the constant reminder of treatment, that were probably not considered at the time of consent.

"I was indifferent at the time as I needed the treatment and there was no alternative on offer."

"At the time I just thought they had to be done, it wasn't a choice."

"To be honest I knew I had to have them, it's just that now I have a permanent reminder of what happened to me."

"At the time I was so stressed and anxious, and I just wanted it all to go away. I just did whatever they said. How I feel about them (tattoos) now, is I hate them."

The perception that the tattoos were mandatory and that no alternatives exist is factually incorrect. Challenging this patient belief relies on the therapeutic radiographers being open and honest about possible alternatives, if adhering to the main principals of informed consent (114). However, alternative skin-marking methods are generally considered inferior to permanent tattoos by therapeutic radiographers; whereby the belief that they facilitate less accurate radiotherapy, take longer to apply (e.g. henna), have a risk of replanning if lost (e.g. pen marks, stickers), and have little consequence to patients, are embedded during radiographer training (119). The examples of departmental and national documentation given in figures 30 and 31 further support this ingrained belief; that permanent tattoos are inconsequential and the only suitable method of skin-marking in the absence of surface guidance technology.

My study is the largest to date to investigate how permanent Indian ink tattoos affect people in the months and years following breast cancer radiotherapy. The large sample size and wide range of respondent ages and time since radiotherapy provides confidence that the themes identified are likely to be representative of the surviving breast radiotherapy population, and that failure to detect a statistically significant difference in overall impact according to these variables is a true finding. This has highlighted the significant impact that permanent Indian ink radiotherapy tattoos can have on people treated for early breast cancer; both positive and negative (figure 32).

I have presented the emotional descriptions in the form of verbatim quotes, that have been so generously shared by those with lived experience, giving context and insight into the real-life impact that these small blue/black/green permanent

skin marks can have (132). I suggest that presenting data in this way, and performing detailed thematic analysis, has provided a foundation for an evidence-base that represents the patient voice, that as described by Clow and Allen (115) is largely absent with regard to the impact of radiotherapy tattoos as a part of breast cancer radiotherapy experience and outcomes of our patients.

Figure 32: Word cloud created from respondent quotes about permanent Indian ink radiotherapy tattoos (112)

Moser *et al* (124) reported the results of a single open question that was asked at a Young Survival Coalition annual meeting: "What are your overall feelings about requiring tattoos as part of your cancer treatment". Approximately 70% reported negative or strongly negative feelings about the skin marks, with three phrases; "annoying"; "felt awful"; and "concerned" identified during linguistic analysis (124).

Although going further than many studies by including patient reported outcomes of radiotherapy tattoos, the interpretation of this finding in terms of the impact on quality of life is limited in the absence of respondent demographics or direct quotes, which can provide detailed insight on personal impact and put phrases such as 'concerned' and 'felt awful' into context (132). For example, 'felt awful' could refer to the painful application, or to the lack of choice. 'Concerning' could

relate to thoughts of permanent visibility to others even when dressed, or that tattoos contradict religious expectations.

I propose that it is the current lack of patient voice that has contributed to the continued assumption by the radiotherapy team that Indian ink tattoos do not have any or enough of an impact on people to warrant consideration or investment of time and resources of an alternative. This has led to a lack of impetus and motivation to explore or acknowledge alternatives; some of which have shown promising set-up accuracy in the literature, albeit the low-resource options (pen-marks) published during the now superseded era of two-dimensional planning and verification (116,129), and others such as SGRT with high capital cost (110,136).

From the fourteen negative themes identified amongst the 204 respondents of my questionnaire, the majority may be considered high impact in terms of the effect on quality of life, even if only one of these fourteen is experienced by an individual. High-impact themes identified include the tattoos: serving as a constant negative reminder of breast cancer diagnosis and treatment; directly affecting clothing choices; hating them; painful application, and concerns about religious expectations. The frequency of five of the themes is reported by 10-31% of our study population, suggesting that many of the emotional impacts identified in my study are likely common amongst the ever-growing breast cancer population, and continue to persist many years post-treatment.

Many of the individual respondent comments crossed a number of themes, some within the same sentence:

> ***"Resigned to it at the time, now I hate them. They're a permanent reminder of treatment that disfigured me."***
> [Themes: no choice, hating their appearance, constant reminder].
> ***"I was very upset when I heard I had to have them. I was slightly less stressed after having them as they are quite small, but I do feel very self-conscious about the one in my cleavage... this will affect future swimwear and party dress choices."***
> [Themes: no choice, affects clothing choices].

By providing a detailed insight into the impact of this intervention; albeit in only in one diagnostic cohort (breast cancer), I suggest that this will resonate more with those practitioners obtaining consent and applying the skin marks (and thus well-placed to drive and implement change), compared to reporting purely numerical data. For example, it may be considered both surprising and horrifying to read that two respondents considered their midline tattoo to be “worse” or “more hated” than their mastectomy scar. The real-life impact and distress to these people is less sensitively captured in the quantitative data: 5% of respondents reporting that they are bothered ‘very much’ by their tattoos; and 23% strongly negatively affected according to researcher overall impact scores.

Despite the strong positive relationship between researcher-assessed overall impact scores and respondent-ranking of how much they were bothered by their tattoos, there was some discordance for those respondents reporting being bothered a little or not at all. For example, respondents who ranked their tattoos as not bothering them at all, were assigned overall impact scores of 1 or 2 (strongly negatively affected or negatively affected), if their free-text comments referred to being constantly negatively reminded of their diagnosis and treatment, or that they were not able to wear certain clothes due to the visibility of the tattoos. This demonstrates the value of free-text comments, which was encouraged by the patient representatives when developing the questionnaire. The sensitivity to quantify impact would have been reduced had all the questions been closed, Likert scale questions.

Whilst more than half of the cohort were not negatively affected by their radiotherapy tattoos, 1 in 7 were unable to make clothing choices that were unaffected by the presence of their radiotherapy tattoos. This was irrespective of age group, skin type and time since radiotherapy. Over half of the study population experienced negative thoughts or effects to their body image in the months and years following radiotherapy as a direct result of their visible alignment tattoos. This strongly supports the need to implement less-impactful alternatives to permanent Indian ink tattoos.

Impeding the inclination and ability to implement alternative skin marking methods, may in-part also be related to the Medical Device Directive (137). The

associated licensing requirements to evaluate and implement new medical equipment, whilst crucial for patient safety, is complex and costly, often requiring specialist expertise in this field, which may not be in the multidisciplinary team's experience or competence. There are currently only 3 radiotherapy medical-device certified inks available, manufactured and distributed by produced by one company, Biotic Phocea Laboratories, (Marseille, France) (138). These are available in black, green and red. Many of the questionnaire respondents commented on the negative appearance of their Indian ink tattoos, specifically with regard to their unnatural colour, and that if they were brown, then they would be less impactful.

> ***"They look like ugly blue pen marks."***
> ***"Several times when swimming friends have commented on my "blackhead" and once my beauty therapist offered to squeeze it !!!"***
> ***"I have a permanent tattoo of a blackhead in my cleavage."***
> ***"They are green and quite prominent".***

My research has provided valuable insight into what patients may be willing to accept, if tattoos are to remain standard of care for many centres, and the fundamental importance of collaboration between radiographers, clinicians, manufacturers, researchers, funders and patient representatives for the successful investigation and clinical implementation of alternatives that are fit for purpose, safe, more acceptable to patients, and likely to be adopted by the treatment team as standard of care.

My study has a number of limitations. Firstly, this was a self-selected group of people who were accessing third sector social media. It may have therefore gained representation from a particular demographic and people who felt passionately about this subject. Secondly, there was no representation from people with black skin (Fitzpatrick Type VI). This may be due to the insensitivity of the scale used to define skin colour effectively and may have been better collected using a tool such at the Ho and Robinson skin colour chart (139).

Conversely, this underrepresentation may be a true finding, due to the poor inclusion and representation of black people in mainstream campaigns and

charities (see first limitation above), as described The Leanne Pero Foundation - the Black Women Rising Cancer support project (140). Indian ink radiotherapy tattoos can be invisible on black skin, and therefore the distribution of overall impact may have been different if the population had been inclusive of all skin colours. Townend *et al* (2020) reported that the pen marks and stickers were skin-marking alternatives in 70% of cases when Indian ink tattoos were not adequately visible (for example, due to skin colour) (109). This poses two important questions. Firstly, if we cannot see the standard, permanent, preferred skin-marking method on some skin tones, are we able to demonstrate equity of care?

One member of the Black Women Rising community reported her negative experience of radiotherapy tattoos due to the colour of her skin compared to the ink of the tattoos offering little contrast (141).

> *" ….. radiotherapy was rife with issues with my tattoo markers …. very few radiographers could ever find my tattoo marker. I'm Black, and my skin tone was too dark to be able to see it …. It should have taken five minutes... inevitably it would always take 20 minutes or more.*

Secondly, if non-permanent alternatives such as stickers have been identified and are deemed clinically acceptable for some patients in whom Indian ink tattoos are not adequately visible, could this not be applied to all patients regardless of skin colour?

4.6 Conclusion

The national and international practice of radiotherapy skin marking for laser-based set-up is likely to continue for many decades to come, despite the gradual increase in surface guidance radiotherapy. Indian ink radiotherapy tattoos continue to be considered by health care professionals as inconsequential to patients, with the importance of offering and discussing alternatives omitted from the consent process on a national level. My study has presented the *patient voice* in terms of the negative impact that permanent Indian ink tattoos have on people in the months and years following breast cancer radiotherapy, serving as a constant reminder of cancer diagnosis and treatment, and affecting clothing choices due to their unnatural colour and visibility. This may differ across treatment or tattoo sites, but my findings are unlikely to be unique to the breast cancer population; with children and young people, pelvic and thoracic radiotherapy patients representing an interesting area for further investigation.

Acknowledgement of the significant negative impact of this intervention by the multidisciplinary radiotherapy team is key to challenging current practice and enabling change. This will also require industry, healthcare professionals and patients to work collaboratively if suitable alternatives are to become standard of care. An alternative to Indian ink tattoos must be less-impactful to the recipient, accessible for people of all skin colours, and be fit-for-purpose in terms of radiotherapy set-up throughout the treatment course.

4.7 Related Publication

4.7.1 Journal article

Radiography xxx (xxxx) xxx

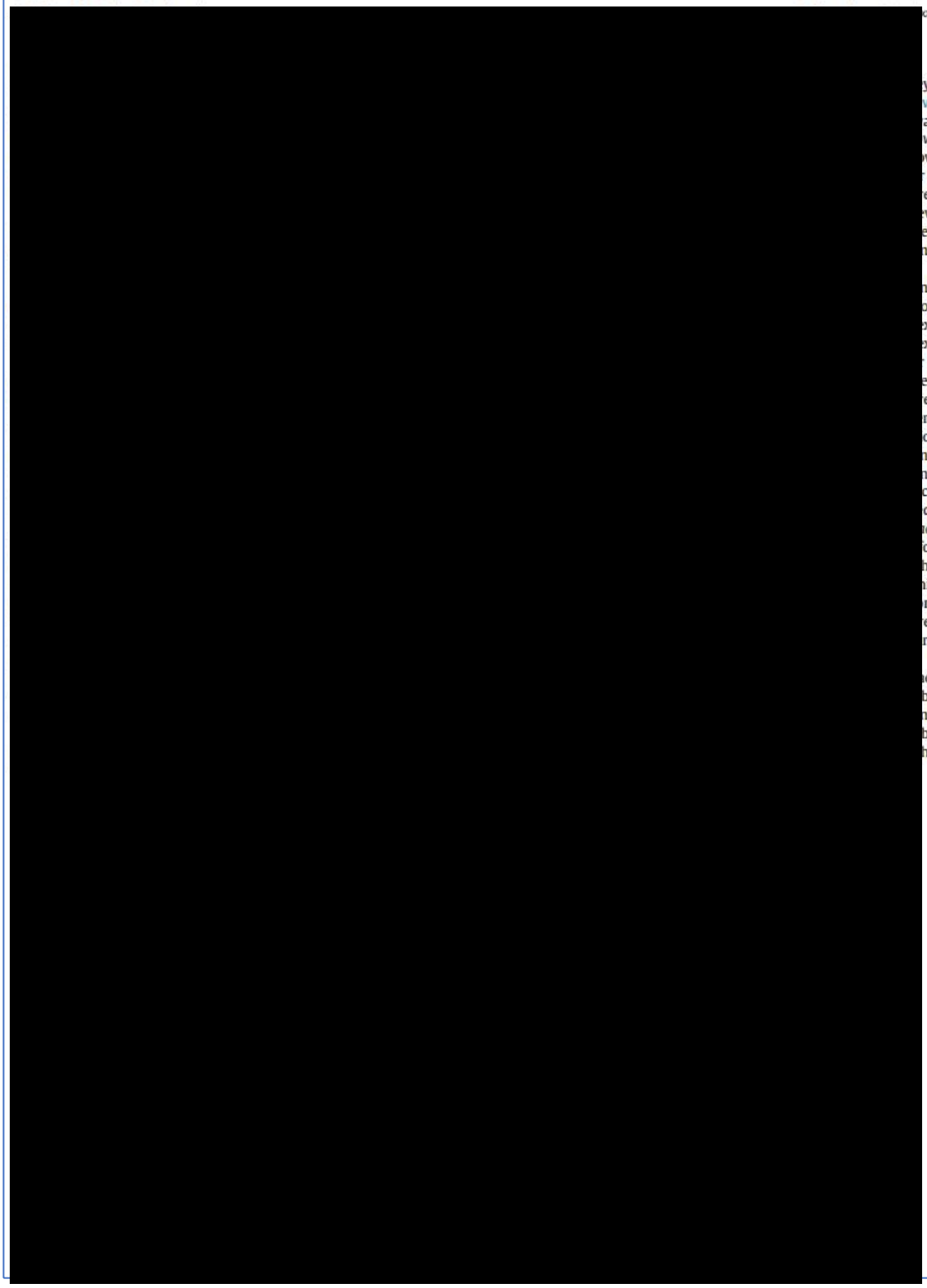
[redacted]

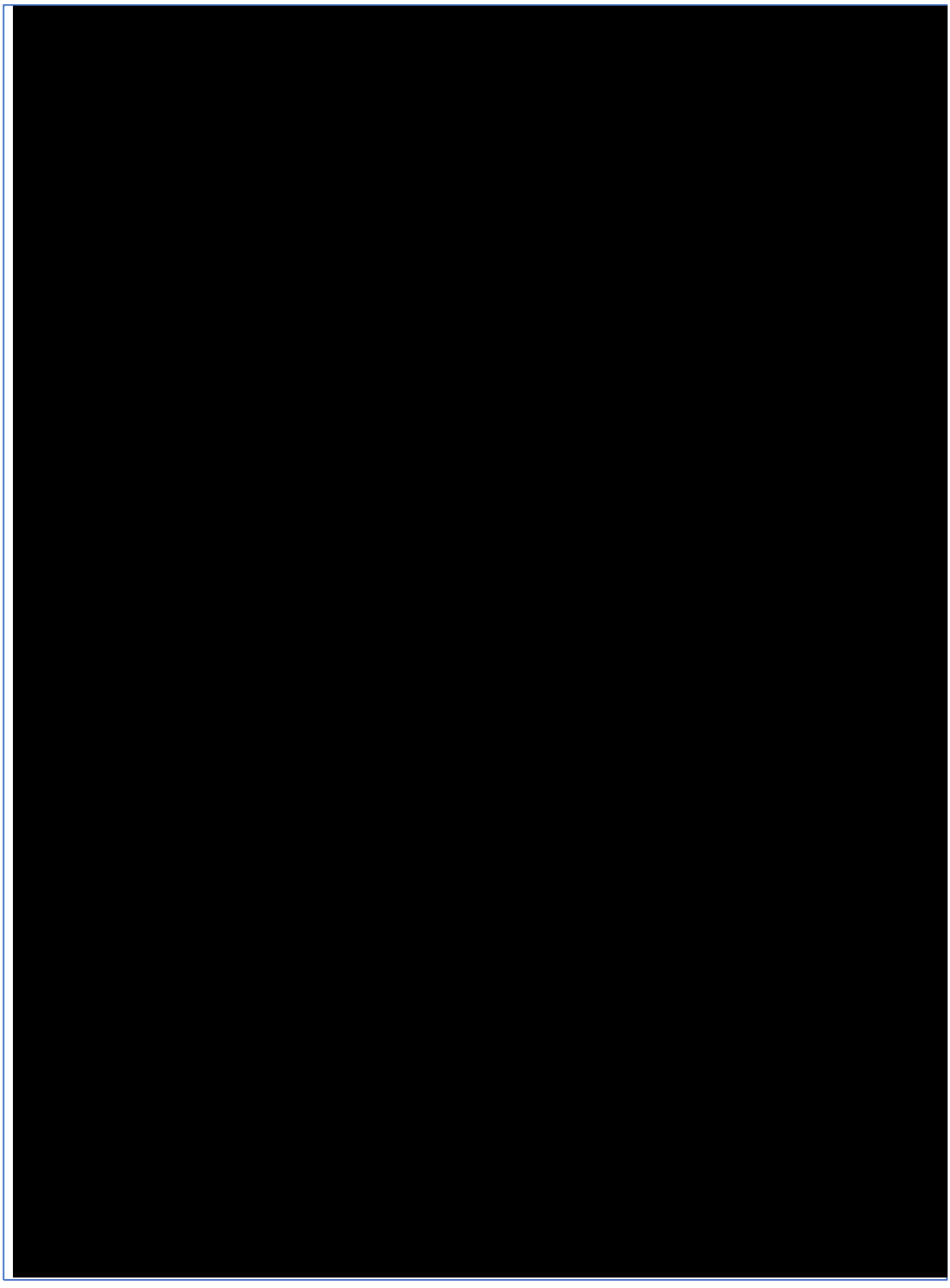
Permanent Indian ink tattoos for breast cancer radiotherapy: A United Kingdom study of the emotional impact on patients following radiotherapy

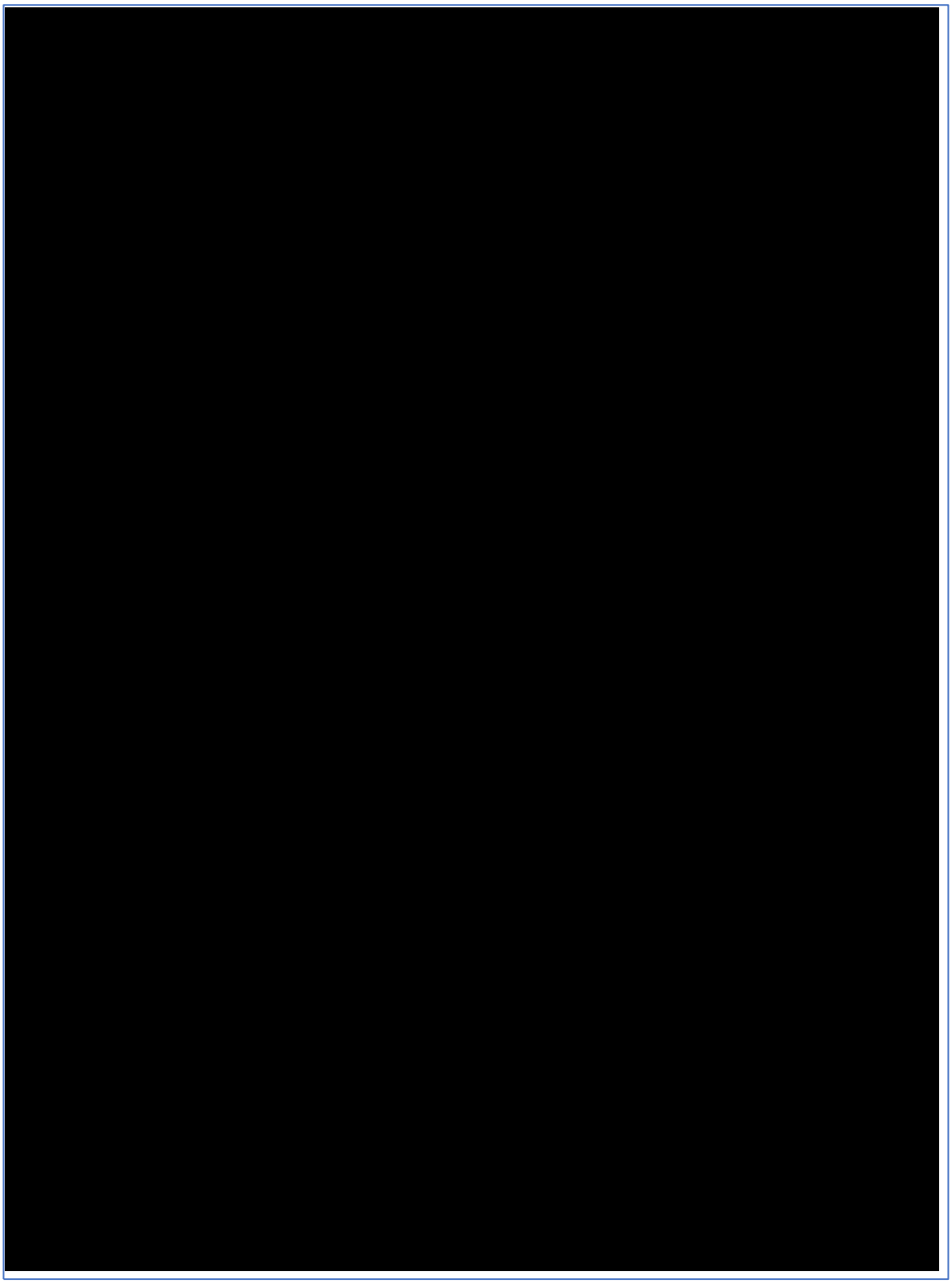
S. Wickers [a, b, *], R.M. Taylor [a, b], G. Royle [b], M.N. Gaze [a, b]

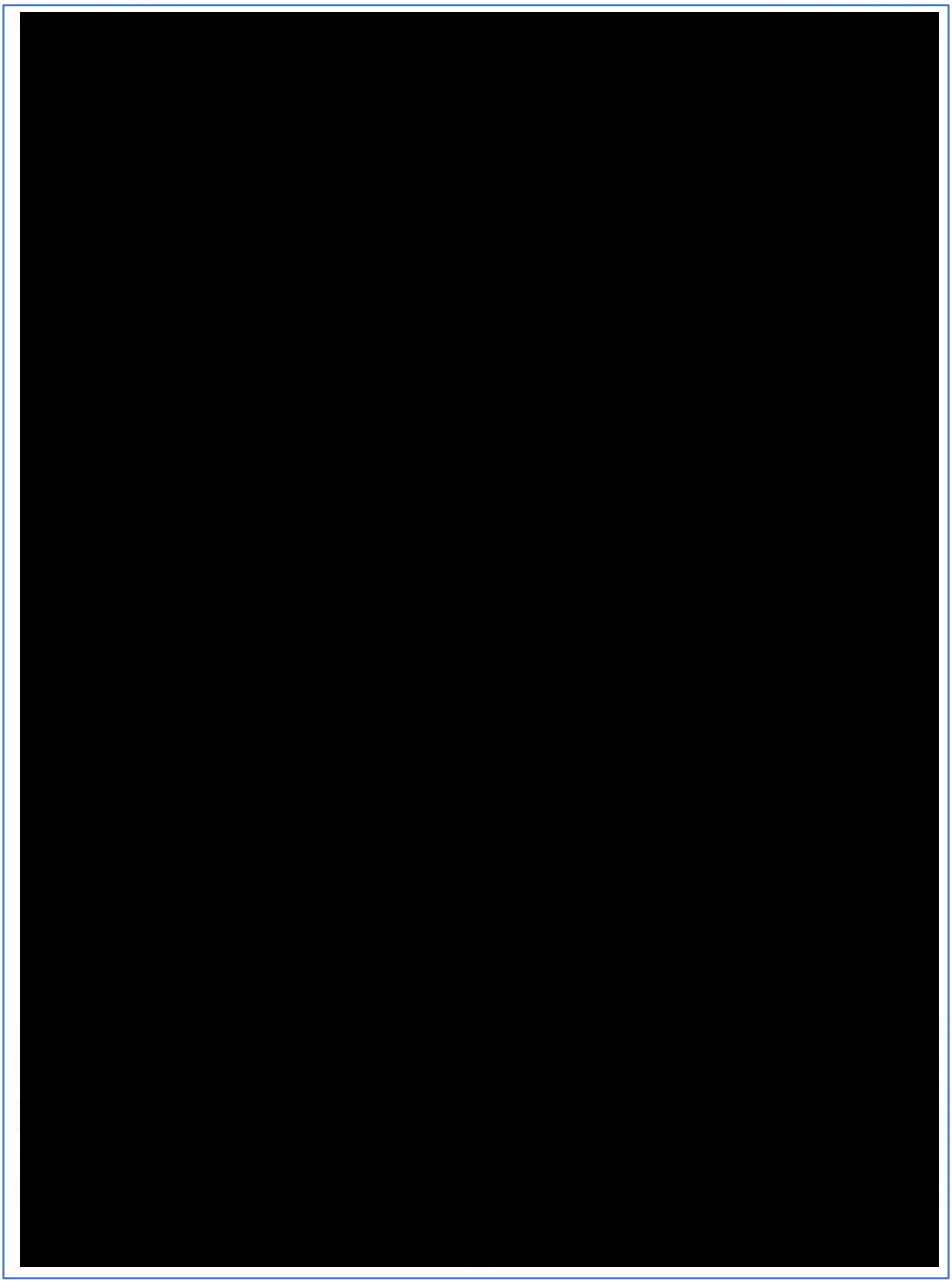
[a] University College London Hospital, UK
[b] University College London, UK

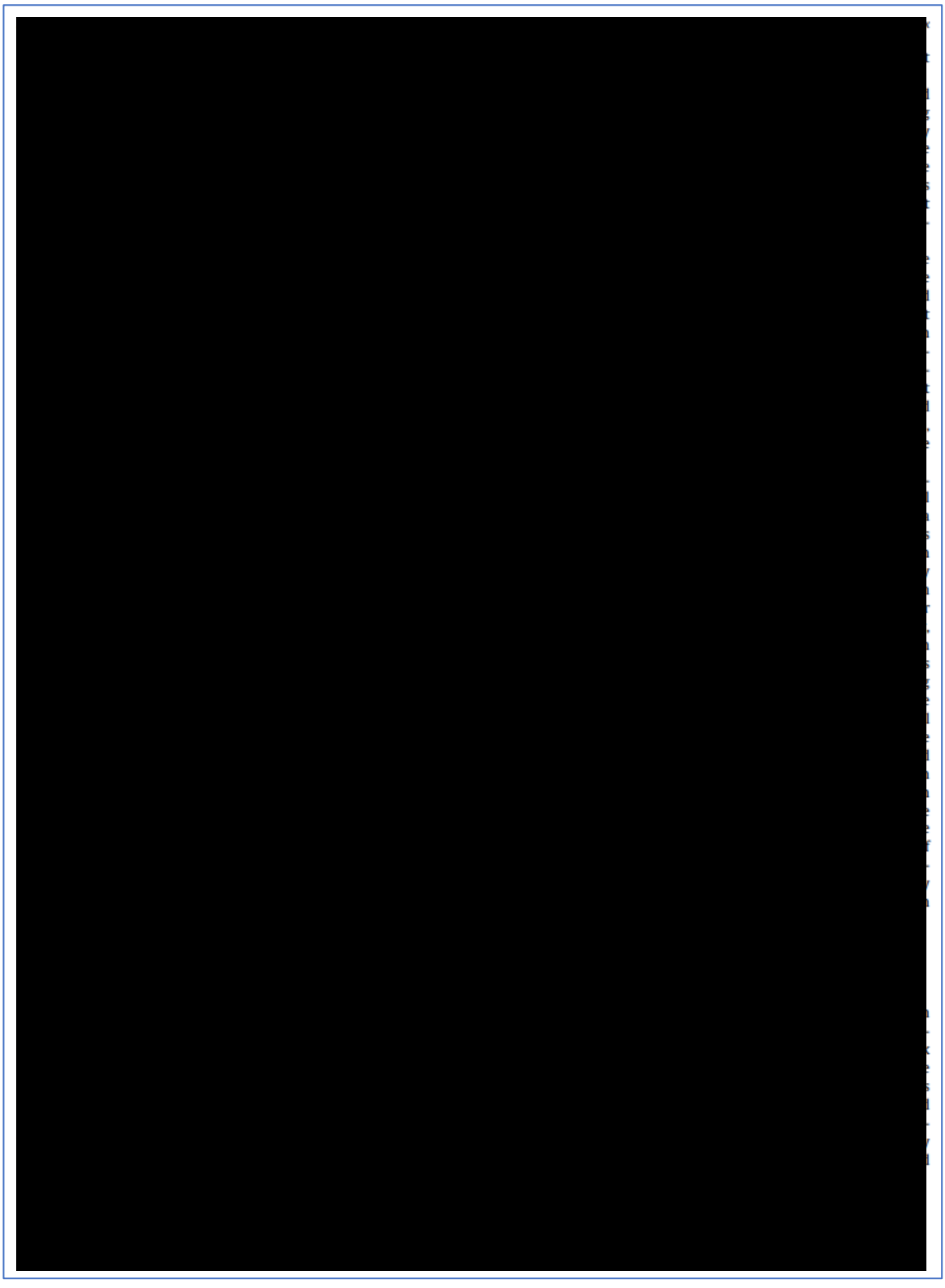
[redacted]

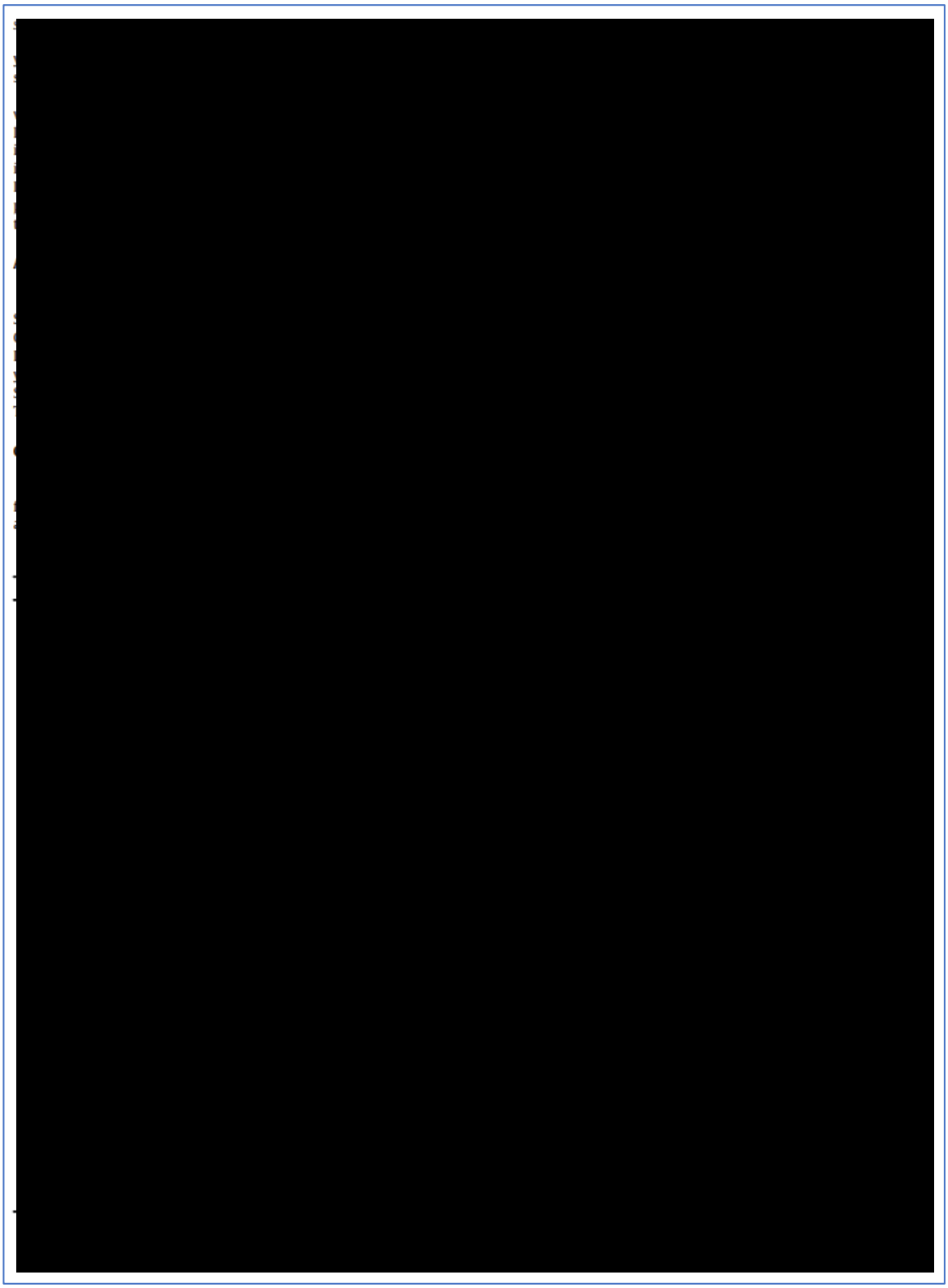












8

4.7.2 **Editorial** (119)

Guest editorial:

Radiotherapy alignment tattoos with Indian tattoo Ink: Time for challenge and change?

Sairanne Wickers, Consultant Therapeutic Radiographer (breast cancer), UCLH NHS Foundation Trust **sairanne.wickers@nhs.net**

With input from Heidi Probst, Sheffield Hallam University, Naman Julka-Anderson, Macmillan Cancer Support and Rachel Harris, Society of Radiographers

Image gifted with consent by UCLH patient undergoing radiotherapy. Image not to be used without permission of the author.

Radiotherapy (RT) utilises a mixture of technology and multidisciplinary working to deliver patient centred care. This area of healthcare continuously advances in the use of technology and the development of new techniques. Although each treatment is unique to the individual patient, there are standard requirements for good patient set up to ensure accuracy of treatment, these include:

- Effective communication with the patient
- Patient comfort and compliance
- Use of effective immobilisation devices
- Clear and accurate set up information
- Use of standard nomenclature
- Clear reference marks (e.g., alignment tattoos)
- Appropriate reference images (e.g., photographs, surface templates, skin rendered imaging)
- Treatment verification – on-set image acquisition and correction

The majority of RT departments apply skin marks to support patient set up and reproducibility. These skin marks are used as a reference point to which beams are localised for each treatment fraction. Technology such as Surface-guided RT has provided some opportunity to consider RT without skin-marking but cannot provide a solution for all patients.

Radiotherapy tattoos:

The most common method of skin-marking is with permanent dark-ink tattoos, applied with a lancing needle, usually between 3 and 6, dark green/blue/black in colour, and approximately 2mm in diameter. They are defunct of purpose after the treatment course has completed, typically 1-2 months after application. They can be difficult to localise on brown and black skin and can remain highly visible on white skin. RT tattoos are associated with a negative impact on body image due to their permanent visibility and unnatural colour. They may increase in size in the years following treatment, sometimes up to 5 mm in diameter.

Patients are asked/expected to provide their consent for RT tattoos, but alternatives are not routinely offered. We must therefore ask ourselves whether this is informed consent. Suggestions of less accurate treatment, the risk of needing to replan and incur a delay if alternatives such as pen marks are lost, are often communicated to those patients not wanting tattoos, which commonly results in reluctant consent.

If a patient has a natural skin mark or mole at the location of a proposed tattoo, this can often be considered a frustration and move the reference position to an area of skin that will not confuse the tattoo visibility – why? Other tools are available such as

photographs and templates to facilitate using a natural skin mark as the reference mark, meaning one less permanent unnatural tattoo for the patient, this may make a difference to the impact on body image.

Tattoos can be difficult to localise on brown and black skin. The picture above shows the poor contrast between tattoo and skin colour. Localising the tattoos commonly requires at least 2 radiographers to closely scrutinise and confirm the tattoo location with the aid of a torch on the exposed patient. Transparent dressings are placed over pen marks which highlight the difficult-to-see tattoo position, to preserve them throughout the treatment course. These interventions can have a negative impact on the dignity of our patients.

Patient experience:

Although small, the permanent tattoos do have a negative impact on the quality-of-life for many following RT. Some patients have stated that 'the tattoos bothered them more than their mastectomy scar'. They matter to patients, and therefore they should matter to us. Tattoos can directly impact patients' choice of clothing, particularly due to the unnatural colour and feeling self-conscious about them, continuing to bother them in a negative way in the months and years following treatment. A common theme is that they serve as a constant reminder of the cancer diagnosis and treatment.
One patient stated they "didn't want to be tattooed but felt they could not refuse as they didn't want to be labelled as a difficult patient. They didn't have the confidence to say no."

Challenging the current standards:

The NEAT (Non- permanent alignment tattoos for breast cancer radiotherapy) trial aims to evaluate to accuracy of using non-permanent ink for patient alignment marks during RT.

The Support4All project (S4A) has tested the feasibility of using a specially designed bra for RT positioning for women diagnosed with breast cancer (following conservative surgery). The randomised feasibility trial tested using a single lower midline permanent tattoo with the remaining set up marks placed on the S4A bra. The lower mid-line tattoo was positioned closer to the xiphisternum to avoid visibility when wearing normal clothes. Reproducibility using this single lower tattoo and the marks on the S4A bra was clinically acceptable but further testing across a larger sample is needed.

Natural skin marks could be used in place of a tattoo. A pen mark and transparent dressing could be considered for some anterior mark (often the most visible and troubling to people post-treatment). This could also be considered for single fraction and short-course radiotherapy, do these patients need a permanent mark when they are having their radiotherapy on the day of, or a few days after planning when the pre-treatment alignment pen marks are still clearly visible?

The first step in driving and implementing change is to challenge practice. Alternatives are worthy of acknowledgement, conversation, and consideration.

Dates for the diary	
RCR, Annual conference 2023	12-13 October, Birmingham
BIR, Annual congress 2023	2-3 November, London

Chapter 5

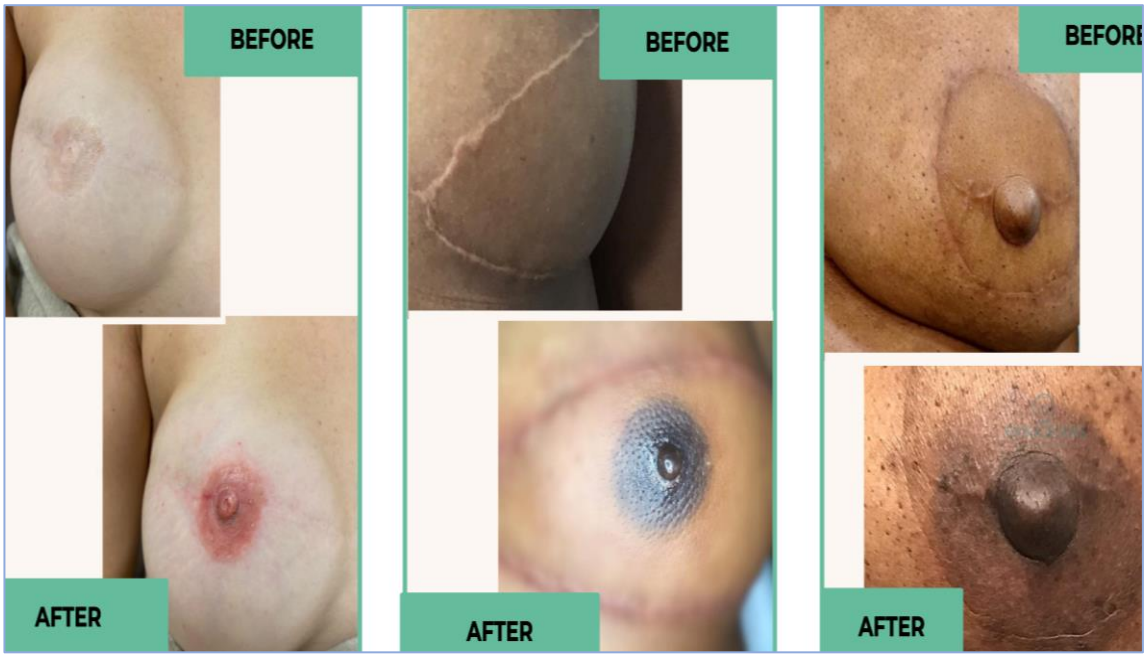
NEAT: A randomised controlled trial investigating the efficacy of using non-permanent ink and micropigmentation technology for radiotherapy alignment marks versus permanent Indian ink tattoos for breast cancer radiotherapy

5.1 Introduction

5.1.1 Medical tattooing in breast cancer

Medical tattooing is a growing field, utilising the knowledge and skills from the permanent make-up industry for medical cosmetic procedures. The natural-coloured ink pigments and micropigmentation technology can be used to disguise surgical scars, give the appearance of hair follicles (where the hair has been permanently lost due to treatment) and create the illusion of a three-dimensional nipple areola following mastectomy and breast reconstruction in the treatment of breast cancer (142). Several companies offer specific training in medical tattooing to health care practitioners (143), with nipple areola tattooing available in many hospital networks. This acknowledges the positive impact on body image of a pigmented nipple areola and can be applied either in conjunction with surgical nipple reconstruction, or instead of surgery in the case of three-dimensional tattooing (144) (figure 33).

Figure 33: Three-dimensional nipple areola tattoos (courtesy of Biotic Phocea Laboratoires)



The ink pigments used for medical tattooing are organic mineral-based pigments and are available in an extensive range of colours suitable for nipple areola

tattooing for a natural look on all skin colours (145). Figure 34 shows examples of the colours available for medical micropigmentation.

Figure 34: Organic pigments for medical tattooing (146)

Despite an absence of any formal reporting of the visibility duration of cosmetic medical tattoos, it is acknowledged in the training and patient information that the colour and visibility of these tattoos can fade and/or disappear in the months and years following application, often necessitating ‘top-ups’. The tattoos are therefore commonly referred to as semi-permanent.(144,147,148).

In contrast, Indian tattoo ink is permanent, with evidence of these carbon-based pigments being used in humans several thousand years ago, still being visible in preserved mummified remains and with life-long visibility in millions of people from all ethnicities (149). Indian tattoo ink is used in the majority of radiotherapy centres both nationally and internationally for radiotherapy skin marking. Due to their permanence and unnatural colour, there is a strong association with a negative impact on body image and emotional well-being in the months and years after radiotherapy (112). It may therefore be reasonable to consider the use of the nipple areola ink pigments in place of Indian tattoo ink for radiotherapy skin marking due to their natural colour and semi-permanence.

5.1.2 Medical device regulations and radiotherapy tattoos

The Medicines and Healthcare Products Regulatory Agency (MHRA) defines a medical device as any item (including software, material, appliance) used for a medical purpose, and requires conformity assessment and certification marking before being commercially available for its intended use (150).

Despite practices such as nipple areola tattooing referred to widely as ‘medical tattooing’; the ink pigments and micropigmentation equipment associated does not require medical device certification due to the purpose being for cosmesis, as opposed to relating to a therapeutic intervention or treatment. There is governance around the ink pigments used, however. Since 2022, all tattoo ink pigments are controlled under the European Union REACH Regulations which restrict the use of chemicals associated with skin irritation, genetic mutations and those that may be toxic to the reproductive system (151).

Conversely, a radiotherapy tattoo is considered an intervention directly related to a medical treatment, and therefore the equipment (including the ink pigment) used to apply radiotherapy tattoos does fall within the medical device regulations.

Even in the case of medically certified areola tattooing ink pigments and machines, these can only be used for the specific purpose specified in the certification. If using a certified medical device for a medical application that is not explicitly listed in the certification, the device is no longer considered a certified medical device, and its use will breech the medical device directive/regulations.

In summary, it is not permissible to simply use the ink pigments routinely used for nipple areola tattooing for radiotherapy skin marks, even if used in a clinical setting within the same hospital site, as the intended purpose has changed from being a cosmetic use to a medical use.

5.1.3 Current limitations of Indian ink radiotherapy tattoos

The Indian tattoo ink that is used widely for radiotherapy skin marking is not certified as a medical device and is therefore in breach of the medical device

directive. Due to the product being used for almost five decades for the purpose of radiotherapy skin marking, in the absence of medical device regulations as we know them today, many centres have taken a pragmatic approach to the historical safety and governance of its use. For example, at my institution, the internal pharmacy team conduct routine quality assurance tests on batch deliveries of the Indian ink pigment and authorise supply from only one specified UK-based manufacturer.

There is one company, Biotic Phocea which manufacture and distribute tattoo ink pigments that can be applied with either a lancing needle or micropigmentation device that is medically certified with the intended purpose of the application of radiotherapy skin marks (152). The colours available are green, red and black; arguably not addressing the negative patient impact of being an unnatural colour (112), but do permit compliance with the Medical Device Directive.

There is a second clinical, psychosocial and equity of care limitation of Indian ink tattoos for radiotherapy skin marking, and that is the poor contrast with brown and black skin (figure 25). This can lead to poor patient experience, due to longer treatment times, reduced dignity with multiple practitioners required to localise and confirm the tattoos, and inequity of washing ability if stickers are utilised to mark the tattoo position during the treatment course (141).

There have been a number of studies identifying alternatives to Indian tattoos for radiotherapy skin marking, such as henna and pen marks (116,129), but these have not been implemented in the majority of centres. Wickers *et al* (119) describe the deep-seated belief of therapeutic radiographers that tattoos are the optimal method of skin marking for the safe, accurate and efficient delivery of radiotherapy. It may be that the implementation of natural-coloured tattoos that fade over time may therefore address both the clinical need and patient impact that has currently remained unchallenged and unchanged over the past five decades with regard to Indian ink radiotherapy tattoos.

5.1.4 Forming a research idea and peer review

Utilising the natural-coloured ink pigments used for medical tattooing for radiotherapy skin marking has not been previously investigated, supporting the development of a feasibility study.

I was the primary author of a research proposal that was submitted and of which I subsequently presented to the National Cancer Research Institute (NCRI) Clinical and Translational Research Working Group (CTRad) in October 2019, and the NCRI UK Breast Intergroup in November 2019 (appendix 4 and 6) for peer review.

The feedback was supportive; acknowledging that this research question is important, with insightful and constructive advice provided (appendix 5 and 7). This resulted in me making some significant amendments to the proposed trial protocol; changing the primary endpoint to reproducibility (used to calculate the sample size), and tattoo visibility changed to a secondary outcome as there was no available data to allow this variable to be used to accurately power the study. Additional important secondary outcomes were highlighted and subsequently included into the protocol, such as patient-reported pain of tattoo application. The most significant change to the proposed protocol following a period of reflection of the presentation discussion and peer review comments, was to conduct a randomised controlled trial (RCT) rather than a single-arm cohort study. An RCT was largely required to answer the primary endpoint, but also to add valuable comparative data of the new skin-marking technique versus standard of care, as there is a significant absence of outcome measures such as pain and tattoo visibility according to skin colour for permanent Indian ink radiotherapy tattoos (115).

From the open discussion with the audience, which included the wider members of the breast multidisciplinary team (surgeons, pathologists, medical oncologists, clinical oncologists, breast care nurses, radiographers, dosimetrists, physicists) and patient representatives, there was a mixed perception of the impact that permanent Indian ink tattoos can have on patients following breast cancer radiotherapy. The discussion at times between audience members became

somewhat heated with polarised opinions. The consensus advice was to *"prove that patients do not like permanent Indian ink radiotherapy tattoos"* before taking the research proposal any further. The suggestion was that this would increase the probability of being successful in grant applications, and to ensure that any study would be investigating a valid problem.

I approached UK charity, Breast Cancer Now, and asked if they would support this work by surveying their members. Chapter four of this thesis presents the results of my survey, which includes over 200 women that had permanent Indian ink tattoos for breast cancer radiotherapy. Sharing the unpublished preliminary results that strongly evidenced that permanent tattoos really do matter to patients (most often in a negative way), was a key component to me securing a successful research grant application from the College of Radiographers.

5.1.5 Funding

The College of Radiographer's Industry Partnership Scheme research grant (CoRIPS) awards small, competitive project grants, of up to £10,000 to Society of Radiographer members (153). There are two grant calls per year, and successful applicants are automatically eligible to apply for National Institute for Health Research (NIHR) Clinical Research Network (CRN) support. This means that the study will eligible for support from the host institutions Cancer Clinical Trials Unit (CCTU), with study related activity such as participant screening, randomisation and data collection.

I submitted a CoRIPS grant application in October 2021 (appendix 8), with funding requested to cover excess patient travel costs, consumables (ink pigment, needles), radiographer training (of the new tattooing system), randomisation software, and protected junior radiographer time reimbursement to support data collection. Following a rigorous review process (appendix 9 and 10), a letter of full award was received in December 2021 for £10,721 (appendix 11).

5.1.6 Trial Steering Group

An important part of trial governance, and to provide reassurance GCP to the sponsor and funding body, is for independent oversight of the study. This is the role of the Trial Steering Group (TSG), which as well as ensuring scientific integrity, also assess patient safety, study timelines, protocol adherence, and advise on protocol amendments and whether a trial should continue or close early. The TSG also have a duty of ensuring that trial results are disseminated appropriately and accurately (154).

In adherence to study guidelines, a TSG was formed for the NEAT trial in July 2021. All members were independent and had experience of clinical trial management. The Chief Investigator invited a Chair, lay-person (who was also a patient representative) and radiotherapy expert to form the TSG. All those approached accepted the invitation. The TSG terms of reference were written and agreed at the first TSG meeting in July 2021 (appendix 12).

The TSG met on a monthly basis between July 2021 and March 2022; and then as required according to trial set-up progress thereafter, up to the first patient being recruited in February 2023. TSG meetings were conducted over MS Teams with supporting documentation in the form of an agenda and minutes for each meeting prepared and circulated by the Chief Investigator and agreed by the TSG members (appendix 13 and 14). The TSG supported and advised me as the Chief Investigator regarding protocol development, trial sponsorship, ethical and regulatory processes, grant application review and reflection. Following the trial opening to recruitment and commencement of the feasibility run-in phase, the TSG met less frequently; ad-hoc as required to discuss agenda items such as recruitment, stop-go criteria, training requirements, and run-in feasibility phase results.

The role of the TSG evolved after the study completed the recruitment phase, advising and supporting the Chief Investigator in terms of possible future projects and dissemination of results.

5.1.7 Sponsorship

As stated by the Health Research Authority (HRA), clinical trials are required to have a named sponsor who are responsible for ensuring that a study has the appropriate arrangements in place to fulfil a studies requirements from set-up to reporting its findings (155). University College London (UCL) is the named sponsor for the NEAT trial and following review of the trial protocol and related study documentation (appendix 15-22), confirmed the sponsorship agreement in February 2022 (appendix 23).

5.1.8 Medical Research Ethical Approval

NEAT is categorised as a medical device study, as involved the use of medical devices outside of their UKCA/CE/CE UKNI marked purpose.

Medical device studies are required to apply to the Medicine and Healthcare products Regulatory Agency (MHRA), via the *Notification of Clinical Trial of Medical Device* pathway. However, there is an exemption clause to this timely and costly process. If the clinical trial is a single centre study with no involvement of the device manufacturer, and with no intention of commercialisation, an in-house exemption can be raised when completing the Integrated Research Application System (IRAS) form to be assessed by a Research Ethics Committee (MREC) (156). This necessitates approval and final sign-off of the IRAS application by the host institutions Head of Clinical Engineering who assumes overall responsibility for the safety and conformance of the medical device being used.

This was the process for the NEAT trial, whereby the nominated Lead Clinical Engineering IRAS signatory reviewed the medical device brochures, data safety sheets and requested a hazard risk assessment (appendix 24 and 25). In summary, NEAT required REC and Health Research Authority (HRA) approval only, as was eligible to for in-house exemption from MHRA approval. The IRAS application form was submitted in March 2022 (appendix 26), and following successful REC review was granted favourable ethical opinion in July 2022 (appendix 27 and 28).

5.2 Study aim

The aim of the NEAT study is to investigate the efficacy of using semi-permanent ink and micropigmentation technology as an alternative to permanent Indian ink radiotherapy alignment tattoos for adjuvant breast cancer radiotherapy, in response to the strong evidence I reported in Chapter four regarding the negative impact to people in the months and years after treatment due to their permanence and unnatural colour.

A PICO-T approach was used to support the development of the clinical research (figure 35) (157).

Figure 35: PICO-T supporting the research question development

P	**Population**	Patients referred for breast cancer radiotherapy
I	**Intervention**	Non-permanent alignment tattoos
C	**Comparison group**	Permanent Indian ink alignment tattoos (standard of care)
O	**Outcomes of interest**	Radiotherapy reproducibility, duration of visibility, impact on CT and treatment times, impact on body image, pain score, equipment acceptance
T	**Time**	18 months

5.2.1 Primary objective

The primary objective of NEAT is to evaluate the inter-fraction reproducibility of non-permanent alignment marks using semi-permanent ink and micropigmentation technology over a course of adjuvant breast cancer radiotherapy, compared to standard of care; permanent Indian ink alignment tattoos.

5.2.2 Secondary objectives

The secondary objectives are to assess patient satisfaction, new technology acceptance (radiographer), pain score of tattoo / alignment mark application, impact on planning CT and treatment session length, and visibility duration of non-permanent ink alignment marks according to radiographer assessment and patient assessment.

In acknowledgement of the volume of data that will be generated from the NEAT trial, and with the constraint of time for some of the secondary outcome data to be available (body image and patient reported tattoo visibility 12- and 18-months post-application will be reported at a later date), not all of the secondary outcomes will be reported in this chapter. It is considered that in the context of a feasibility study of the new tattoo method; i.e. is the new tattoo method fit for the intended clinical purpose, that omitting these outcome measures in this preliminary report is reasonable.

5.3 Materials and Methods

5.3.1 Eligibility criteria

Eligible patients are those that require adjuvant breast or chest wall radiotherapy (+/- reconstruction) to a dose of 26 Gy in 5 fractions or 40Gy in 15 (+/- nodes), +/- tumour bed boost.

Patients are not eligible if they are under 18 years of age, lack capacity to provide informed consent, are unable/not willing to attend the trial follow up schedule, have previous Indian ink radiotherapy tattoos to the thorax, or are unwilling to have standard of care (permanent Indian ink tattoos).

5.3.2 Randomisation

Participant randomisation was undertaken centrally by the coordinating trial team. Following participant confirmation of eligibility and written consent, the trial registration and randomisation procedure will be carried out by a member of the research team.

Participants were allocated a trial specific identification (ID) number and entered onto recruitment log by a member of the research team. An individual electronic case report (eCRF) was initiated to include each participants personal demographics (name, date of birth, hospital ID and preferred email address and phone number). The baseline body image and modified body image questionnaires (appendix 29) was completed by the patient prior to randomisation.

Following randomisation, the allocation of either standard of care (permanent Indian ink tattoos) or test arm (non-permanent tattoos) was recorded on the eCRF. The patient and CT radiographers were informed of the skin-marking allocation (un-blinded) prior to the CT acquisition. The skin-marks were applied immediately following the CT acquisition, according to the randomisation result.

The randomisation list detailing all participants and their allocated arm was held in the electronic site file.

Randomisation was allocated in blocks of 6, with a ratio of 1:1, with no stratification or balancing of factors. This was undertaken using the online randomisation service, Sealed Envelope™ (158).

5.3.3 Sample size calculation

At the study centre, a set-up tolerance (according to image registration of the treatment field parameters) of 5 mm is considered both acceptable and achievable for breast radiotherapy. When using permanent Indian ink tattoos, the mean population set-up error is 2 mm, with a standard deviation of 2 mm. An increase in the population random set-up error of 1 mm when using non-permanent alignment marks would be considered acceptable. Therefore, to rule out an increase in random set up of >1 mm with non-permanent ink alignment marks compared to permanent Indian ink tattoos, and a standard deviation of 2 mm, 57 patients will be required in each group based on a two-sample t-test with 80% power and a one-sided 5% significance level (allowing for a 10% drop-out rate). This method of calculating the sample size was similar to that employed by Landeg *et al* (117).

5.3.4 Primary outcome

In terms of the primary endpoint, the mean, range and standard deviation will be reported for the population systematic and random set-up error for both the groups, as per the Royal College of Radiologists guidelines (159). Depending on an assessment of the normality of the data, parametric t-tests or the non-parametric equivalent will then be performed to look for any trend's observable in the data. For example, an independent sample t-test will be performed to look for statistically significant differences in set-up error between the groups.

5.3.5 Secondary outcomes

The sample size has not been powered to detect statistically significant differences for the secondary outcomes, and therefore this data analysis will be largely descriptive, reporting trends and clinically significant findings. Statistical tests will be undertaken where appropriate on the secondary outcome data. However, failing to prove a statistically significant difference may not be a true finding and may be reflective of an inadequate sample size for the variable being measured.

Skin colour

All patients will be asked to state the colour of their skin on their anterior thorax according to both the Fitzpatrick and the Ho & Robinson scales (160,161) (figures 36 and 37; appendix 30 and 31). This will be recorded by the CT radiographers.

Figure 36: Fitzpatrick skin type scale (161)

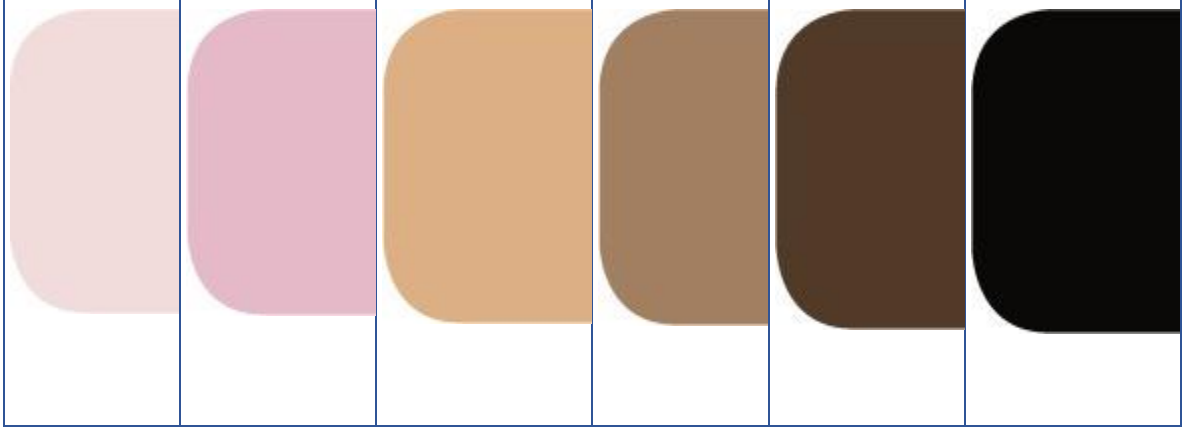
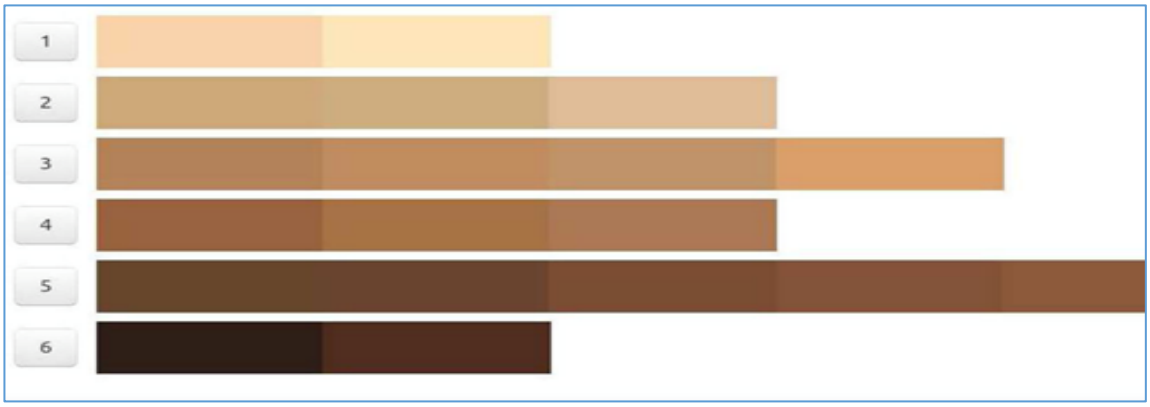
Type I	**Type II**	**Type III**	**Type IV**	**Type V**	**Type VI**
White Always burns, never tans	Fair Always burns, tans with difficulty	Average colour Sometimes mild burn, tan about average	Light brown Rarely burns. Tans easily	Brown Never burns. Tans very easily	Black Heavily pigmented. Never burns, tans very easily
					

Figure 37: Ho & Robinson skin colour scale (162)



Tattoo application time

The time to apply the tattoos will be recorded for both trial arms by the CT radiographers.

Pain scoring

All patients will be asked to score the pain of each tattoo being applied on a 5-point Likert scale, from *not at all* to *very much.* This will be recorded by the CT radiographers.

Tattoo alignment time

The time to align the radiotherapy tattoos for all patients will be recorded for every treatment fraction by the treatment radiographers.

Tattoo visibility assessment

There are several time-points that tattoo visibility will be scored and recorded by the therapeutic radiographers. This will be on a 3-point Likert scale; *easy to localise*, *difficult to localise but adequate* (for treatment alignment), or *not adequate* (for treatment alignment).

- At the time of application – all patients
- 2-weeks post-application – test arm only
- Fraction 1 of treatment – all patients
- All treatment fractions – test arm only
- 3-months post application – test arm only
- 6-months post application – test arm only

Equipment acceptance questionnaire

In the absence of a validated radiotherapy equipment questionnaire, the technology acceptance questionnaire used in the Support4All study (163) [adapted from the Holden & Karsh (2010) technology acceptance model (164)] was selected. The Support4All trial (testing a bra-immobilisation system) closely aligns with the NEAT trial, in terms of being a feasibility study of radiotherapy equipment used for breast cancer radiotherapy, with common outcome measures such as set-up reproducibility and radiographer satisfaction. The Support4All technology acceptance questionnaire was therefore modified (with permission) to relate to the non-permanent tattoo method, and peer reviewed by the Chief Investigator of Support4All study (appendix 32).

The questionnaire will be distributed to the radiographers involved in the application of the new tattoo method, and the treatment of the test arm patients within one month of the final test arm patient completing their radiotherapy treatment course.

The questionnaire will capture radiographer demographics such as; number of years qualified; area of specialty (pre-treatment or treatment); and the number of test arm patients tattooed or treated. There are twenty statements under the subheadings of; perceived usefulness/performance (n = 7); perceived ease of use/effort expectancy (n = 5); facilitating conditions (n = 4); and social influence (n = 4). Each respondent will be asked to select the strength and direction of their agreement with each statement; *strongly agree, agree, disagree* or *strongly disagree*. There is also the option of free-text comments within each of the four sections.

Descriptive statistics will be used to describe the respondent demographics. Cross tabulation will be used to highlight pertinent findings in the data amongst the whole cohort and by radiographer group. Due to the small sample size, no statistical tests will be performed. Thematic analysis of the free-text comments will be conducted to investigate any recurring or frequently mentioned topics or opinions.

5.3.6 Feasibility run-in phase

As part of the main trial, a feasibility run-in phase was conducted to assess several outcomes and logistical components when twelve patients from each group had completed their radiotherapy treatment course. This provided an opportunity to amend the trial protocol if required prior to continuation of recruitment.

The TSG agreed several important *stop-go* criteria (figure 38), covering:

- Rate of non-permanent alignment mark re-application
- Compliance and appointment attendance
- Data quality (radiographer assessments and patient reported outcomes)
- Appropriateness of attendance schedule for radiographer assessment of non-permanent alignment mark visibility.
- Review the screening log in relation to the population demographic of the trial participants.

I prepared and presented a summary report to the TSG upon completion of the feasibility run-in phase. There was no scheduled pause in recruitment, but this could be considered and recommended by the TSG depending upon the data analysis during and on completion of the feasibility run-in phase.

Figure 38: Stop-Go criteria for the feasibility run-in phase

Criteria to be assessed	Proposed action
Loss of skin marks at 2-week visibility assessment for >20% patients	Review patient demographics and tattoo operator across the sample. Investigate confounding variables, e.g. operator, skin colour, ink pigment selected. Re-training of new tattoo method may be appropriate.
Loss of skin marks day 1 of treatment for >20% patients	Review patient demographics and tattoo operator across the sample. Investigate confounding variables, e.g. operator, skin colour, ink pigment selected. Re-training of new tattoo method may be appropriate.

Alerts to issues regarding on-treatment set-up and verification for >10% of the test-arm patients requiring additional imaging.	Investigate confounding variables - review of alignment times, ease of localisation of skin marks, patient demographics. Consider additional training of localisation of skin marks and method of data collection during treatment that may impact treatment session length.
If one patient test arm patient requires replanning due to set-up issues.	Investigate whether cause of replan requirement is due to loss of skin marks or unrelated event, e.g. seroma resolution.
Loss of skin marks during the treatment course for >30% test arm patients requiring re-application	Review skin-mark application and patient demographics across the sample. Investigate for confounding variables, e.g. operator, skin tone, visibility assessment scores, re-application rates. Review training of daily on-treatment visibility assessment.
Recruitment rate of 12 patients in each group exceeds 5 months	Review recruitment process and devise strategy to enhance recruitment for definitive study.
Pain score >4 (very much) for >20% of the test arm patients	Review the operator within the sample population. Review the training of new skin-mark application.

5.3.7 Data analysis

IBM SPSS Statistics (Version 28) was used for all data analysis.

5.3.8 Ethical considerations

This study was conducted in accordance with the UK Framework for Health and Social Care Research. NHS favourable opinion was confirmed (appendix 27 and 28), and no trial related activity involving patients commenced until all internal approvals (managed by the UCL/UCLH Joint Research Office) was received (appendix 33). All participants provided written informed consent to participate (appendix 18), having been given the patient information sheet (appendix 17) and at least 24 hours to consider their participation, in accordance with GCP guidelines (165).

5.4 Results

5.4.1 Feasibility run-in phase

Recruitment and randomisation

NEAT was given formal notification to open to recruitment on 6th December 2022 by the UCL/UCLH Joint Research Office. However, the Cancer Clinical Research team was not in a position to commence screening and approaching eligible patients until the first week of February 2023. This was due to the requirement to complete the radiographer training on the new tattoo method, and for me as Principal Investigator to sign-off the delegation log (appendix 21) to ensure that all trial related activity was appropriately assigned and authorised. The first patient was randomised one week after discussing the trial in the new patient breast radiotherapy clinic and providing the patient information sheet (appendix 17) on 21st February 2023.

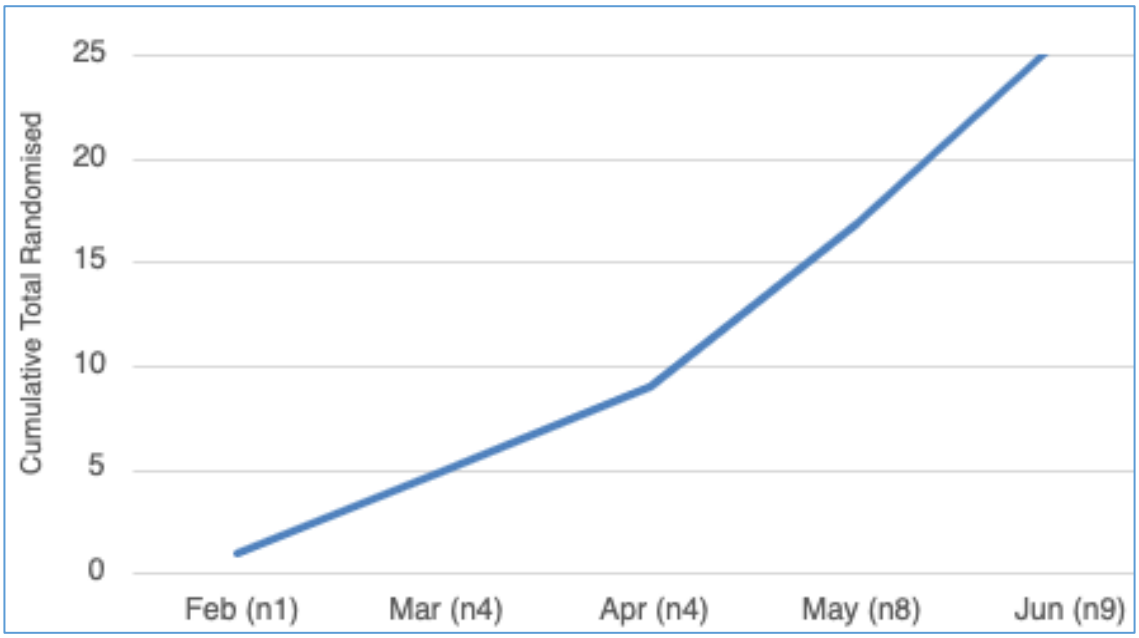
One month into recruitment, I approached the trial team and confirmed that all new adjuvant breast radiotherapy patients were being screened prior to the new patient clinics, and if eligible were given the patient information sheet, with a follow up telephone call to answer any questions.

The feasibility run-in target number was achieved on 28th June 2023; satisfying the *stop-go* criteria that this would not exceed five months. This also provided reassurance that a recruitment period of 12 months was achievable, especially when considering that 9 patients were randomised in June 2023 (figure 39), having observed recruitment increase month-on-month. The number of patients included in the feasibility-phase was twenty-six; thirteen in each arm, which is one more than that specified. This was due to patients 24-26 being randomised on the same day.

Initially, the Cancer Clinical Trials Unit research nurses were consenting and randomising all patients in the radiotherapy planning department via the Sealed Envelope™ website. To improve efficiency, share the workload, and spread the high number of patients throughout the week, the research nurses conducted

training of the pre-treatment radiographers. This ensured that all eligible and consenting patients could be randomised on any CT planning day, thus not incurring any delays to their pathway.

Figure 39: Feasibility phase recruitment: February to June 2023



Skin colour

With skin colour an important variable when discussing radiotherapy tattoo visibility, it was important to ensure that there was a wide demographic within the initial cohort, that was representative of the ethnic diversity of patients referred to the study centre. It was also important to confirm that this data was being captured accurately. Following my review of this data, it was clear that communicating the need to collect this for the control arm patients as well as the test arm patients to the pre-treatment radiographers was required, as it was missing in 31% of standard versus 0% of the test arm patients (figure 40). As this data was not time-sensitive, it was decided that this would be retrospectively collected at a scheduled follow up appointment.

On discussing the recording of skin colour with the pre-treatment radiographers in response to the missing data, it became apparent that the method for doing this was not consistent amongst the team, or always compliant with the trial protocol. For example, some patients were simply asked “what colour is your skin according to this chart?” Additional training was provided to ensure that all

members of the team were asking patients to confirm their skin colour at the location of the medial tattoo; best captured at the time that the patient is undressed on the CT scanner couch.

On review of the distribution of the skin colour recorded, I was satisfied that this was likely representative of the patient cohort, with an appropriate level of diversity amongst the sample that would likely increase with higher patient numbers and consistent data collection methods as per the re-training specification.

Figure 40: Skin colour according to Ho & Robinson scale (162)

Skin colour scale	Standard (n13)	Test arm (n13)
1	6	7
2	3	4
3	0	1
4	0	1
5	0	0
6	0	0
Missing	4	0

Time to apply tattoos

There were nine operators in the application of the test arm tattoos across the thirteen patients. The pre-treatment team reported that whilst taking longer to apply the test arm tattoos, that this was still feasible within a standard scanning slot, and that times were reducing as they became more familiar with the equipment and technique (figure 41).

Figure 41: Time to apply radiotherapy tattoos

Time to apply (mins)	Range	Mean	Median
Standard	2.0-3.5	2.5	2.3
Test arm	2.0-13	6.9	6.8

Pain score

The pain score data collection was relatively compliant. Three patients from the standard arm and two patients from the test arm did not have this recorded. I verbally reminded the pre-treatment team of the importance of recording this secondary outcome. The pain of the test arm tattoo application did not raise any concerns, with none of the thirty-three test arm tattoos being scored as very painful, and no obvious difference observed between the groups (figure 42).

Figure 42: Tattoo application pain scores

Pain Score	Not at all	A little bit	Moderately	Quite a bit	Very much
Standard (n30)					
Medial	1	4	4	1	0
Left lateral	3	5	0	2	0
Right lateral	4	4	1	1	0
Test arm (n33)					
Medial	6	3	3	0	1
Left lateral	9	4	0	0	0
Right lateral	6	7	0	0	0

There were no concerns regarding test arm tattoo visibility at the time of application (figure 43), with only one of the thirty-nine test arm tattoos applied assessed as inadequate and requiring a second application attempt. Data capture was good, with only one standard arm patient where this was not recorded.

Figure 43: Tattoo visibility assessment at application

	Easy	Difficult but adequate	Not adequately visible
Standard	35	1	0
Test arm	27	11	1

Ink pigment selection

All of the test arm ink pigments were used during the feasibility run-in phase, demonstrating that the pre-treatment radiographers were aware of the range

available (figure 44). However, the black pigment was selected in a relatively high percentage of cases which was not expected based on the skin colours recorded. I suspected that the radiographers were selecting the pigment that achieved maximum contrast as opposed to that which provided adequate contrast with the skin colour. I therefore reminded the pre-treatment team that the patients should be involved in selecting the appropriate tattoo pigment, and that maximum contrast is not the requirement as long as the tattoos are adequately visible for localisation and alignment.

Figure 44: Test arm ink pigment selection

Ink pigment	Patient number
Coconut	2
Hazel	6
Black	5

Reapplication of test arm tattoos

Four (17%) of the patients required reapplication of their tattoos at various time points. I noted that three of these patients had their tattoos applied by the same operator and represented 100% of the patients tattooed by this operator (operator C). Two (15%) of these patients required reapplication of the lateral tattoos at the 2-week post-application assessment (18- and 23-days post-application), and one (8%) patient required reapplication of one of the lateral tattoos at the first treatment fraction. The fourth patient (operator T) required reapplication of the lateral tattoos at the 2-week visibility assessment (23 days post-application – reapplied by operator C) and at fraction 1. This identified a training issue with operator C whereby the tattoos were not being applied according to the training specification, resulting in inadequate ink deposition in the skin, and ineffective cleaning of the area post-application to confirm adequate tattoo placement. This operator received additional training in response to this finding.

My review of this data also highlighted that attendance at the 2-week visibility assessment was not being scheduled within the correct timeframe, or at all for some patients. One patient in the standard arm attended a visibility assessment which is not required. Additional training was provided to the radiotherapy administration team in response.

I noted that some of the patients requiring reapplication of their test arm tattoos had the black ink pigment selected for the reapplication, even though the hazel ink was used for the initial application. I communicated the importance of using the same ink colour in the case of reapplication, unless the reason for inadequate visibility was due to poor contrast with skin colour. There was no indication that the ink pigment colour specifically was the cause for inadequate visibility, as three of the patient's requiring reapplication had the hazel pigment, and one patient had the black pigment tattoos at initial application, all of which provided adequate contrast with their skin colour.

None of the patients required reapplication of their tattoos during their treatment course, and no patients required any additional verification imaging or replanning during the feasibility phase.

The reapplication of the test arm tattoos was therefore deemed compliant with the *stop-go* criteria and anticipated to improve for the subsequent patients following the interventions such as re-training and communication with the radiotherapy teams.

Treatment set-up

No alerts were raised regarding test arm patients having set-up issues during their treatment course that was related to their skin marks. All image verification was within the acceptable tolerance levels, with no patients requiring replanning.

Continuation of recruitment

I presented the feasibility run-in phase results to the TSG, and all proposed or completed remedial action was agreed. There was no indication from the results to pause or stop recruitment, or to propose a trial protocol amendment. The TSG therefore gave confirmation for continuous recruitment until the total accrual of 114 patients was reached.

5.4.2 Full study: Patient demographics

A total of 114 patients referred for adjuvant breast cancer radiotherapy were randomised between February 2023 and April 2024. 68% (n=78) received 26 Gy

in 5-fractions to the breast or chest wall, and 32% (n=36) 40 Gy in 15 fractions (breast or chest wall +/- regional lymph nodes). Age was normally distributed, with a mean of 59 years (range 31 - 82).

Skin Colour

Patients defined the colour of their anterior chest according to the Ho and Robinson skin colour scale; 62% (n=71) as 1; 17% (n=19) as 2; 14% (n=16) as 3; 3.5% (n=4) as 4; 2.5% (n=3) as 5; and 1% (n=1) as 6. 112 patients also described their skin colour according to the Fitzpatrick scale; 7% (n=8) as 1; 35% (n=39) as 2; 32% (n=36) as 3; 18% (n=20) as 4; 6% (n=7) as 5; and 2% (n=2) as 6 (figure 45).

According to Spearman's Rho correlation, there was a strong, positive correlation between the two skin colour scales, $r = 0.62$, $n = 112$, $p = <0.01$.

Agreement of the paired skin colour values from the two theoretically equivalent scales was not consistent throughout the cohort, with only 38% of shared variance according to the coefficient of determination. This is also demonstrated according to crosstabulation of the percentage describing their skin colour as 1,3 and 4 for Ho and Robinson versus Fitzpatrick (63% vs 7%; 14% vs 32% and 4% vs 18%) (figure 45).

Tattoo groups

56 patients were randomised to standard permanent Indian ink tattoos and 58 to test arm tattoos.

A Mann-Whitney U test revealed that there was no statistically significant difference in the distribution across the tattoo groups according to: skin colour (Ho & Robinson and Fitzpatrick scales) [$U = 1758$ and 1453, $z = 0.870$ and -0.698, $p = 0.384$ and 0.485; $r = 0.08$ and -0.07]; age [$U = 1432$, $z = 1.089$, $p = 0.276$, $r = -0.10$], or number of treatment fractions [$U = 1548$, $z = -0.528$, $p = 0.598$, $r = -0.05$].

Of the three ink pigments available for the test arm tattoos, the most commonly selected was Truly Hazel (n=40; 69%), followed by Black Tourmaline (n=15; 26%). Three patients (5%) had tattoos applied with the Coconut pigment.

Figure 45: Crosstabulation Fitzpatrick and Ho & Robinson skin colour scales

		Skin type Ho & Robinson						
		1	**2**	**3**	**4**	**5**	**6**	**Total**
Skin type Fitzpatrick	**1**	8	0	0	0	0	0	8
	2	35	2	2	0	0	0	39
	3	22	7	7	0	0	0	36
	4	6	7	5	2	0	0	20
	5	0	1	1	2	3	0	7
	6	0	0	1	0	0	1	2
	Total	71	17	16	4	3	1	112

5.4.3 Primary endpoint: Reproducibility

The mean population set-up error in the vertical direction for the standard tattoos was higher than reported at the time of trial development (*actual*: 0.28 cm ± 0.22 cm versus *expected*: 0.2 cm ± 0.2 cm). This is due to a change in the verification technique to 3-dimensional kV orthogonal imaging (just prior to the trial opening to recruitment), which more accurately quantifies this directional error compared to tangential 2-dimensional MV imaging (166).

Population systematic set-up error

Population systematic error (cm) for the standard tattoo group was 0.22, 0.36, 0.22; and 0.21, 0.26 and 0.23 for the test arm group (vertical, longitudinal and lateral directions) (figure 15).

I conducted an independent-samples t-test to compare the vertical, longitudinal and lateral population mean errors according to tattoo group. There was no

significant difference in the vertical (standard tattoos: M = -0.28 cm, SD = 0.22 cm; test arm tattoos: M = 0.22 cm, SD = 0.27 cm; *t* (110) = -1.26, *p* = 0.21, two-tailed) or longitudinal directions (standard tattoos: M = -0.05 cm, SD = 0.36 cm; test arm tattoos: M = 0.08 cm, SD = 0.44 cm; *t* (110) = 0.38, *p* = 0.70, two-tailed). There was a statistically significant difference in the lateral direction (standard tattoos: M = -0.11 cm, SD = 0.22 cm; test arm tattoos: M = 0.01 cm, SD = 0.27 cm; *t* (110) = -2.62, *p* = 0.01, two-tailed).

The magnitude of the differences in the mean set-up error was very small for the vertical and longitudinal directions (vertical; mean difference = -0.06 cm, 95% *CI*: -0.15 to 0.03 cm, eta squared = 0.014; longitudinal; mean difference = 0.03 cm, 95% *CI*: 0.12 to 0.18 cm, eta squared = 0.001). With respect to the lateral set-up error, the effect size, whilst in favour of the test arm tattoo method, was still only moderate (167), with only 6% of the variance explained by tattoo group (lateral; mean difference = -0.13 cm, 95% *CI*: -0.22 to –0.03 cm, eta squared = 0.06).

Random set-up error

I conducted a one-sample t-test to determine whether the random error for the test arm tattoos was <0.1 cm greater than for standard tattoos; defined as <0.3 cm. The mean random error was <0.3 cm in all directions, and did not meet the threshold of a 0.1 cm increase. Mean vertical random error for the test arm tattoos was statistically significantly greater by 0.03 cm (95% CI, 0.005 to 0.05 cm) compared to the standard tattoos (mean 0.18 cm, *t*(56) = 2.450, *p* = 0.017). There was no statistically significant difference in longitudinal and lateral random error for the new tattoos compared to standard tattoos (*p* = 0.0662 and 0.688) (figure 46).

The magnitude of the differences in random set-up error (cm) between the tattoo groups was very small in all directions (vertical; mean difference = -0.03 cm, 95% *CI*: -0.06 to 0.004 cm, eta squared = 0.045 ; longitudinal; mean difference = 0.006 cm, 95% *CI*: -0.05 to 0.04 cm, eta squared = 0.0007 ; lateral mean difference = 0.005 cm, 95% *CI*: -0.04 to 0.05 cm, eta squared = 0.0004). Even though vertical random error was in favour of the standard tattoos, the effect size was small, with only 4.5% of the variance explained by tattoo type.

Figure 46: Summary of population set-up error (cm)

Measurement		Standard tattoos	Test arm tattoos	Significance (two-tailed)
Vertical	Mean error	-0.28	-0.22	
	Mean systematic error	0.22	0.27	0.21
	Mean random error	**0.18**	**0.21**	**0.025**
Longitudinal	Mean error	-0.05	-0.08	
	Mean systematic error	0.36	0.44	0.7
	Mean random error	0.25	0.26	0.79
Lateral	Mean error	-0.11	0.01	
	Mean systematic error	**0.22**	**0.27**	**0.01**
	Mean random error	0.24	0.23	0.84

5.4.4 Secondary outcomes

Tattoo application time

The median time to apply the tattoos for the whole cohort was 4 minutes (interquartile range (IQR): 3 – 6 minutes); 3 minutes for the standard tattoos (IQR: 2.5 - 3 minutes), versus 6 minutes for the test arm tattoos (IQR: 5 - 7 minutes). A Mann-Whitney U test revealed that the difference was statistically significant, with a large effect size, U = 2977, z = 8.019, p = <0.001, r = 0.75. A Spearman rho correlation revealed a small negative correlation (r = -0.26, n = 58, p <0..45) between participant number (a surrogate for experience) and time to apply the tattoos using the new method, i.e. as experience increased with more patients having the new tattoo method, the time to apply the tattoos reduced. The strength of this relationship is likely to have been diluted by the high number of operators (n = 15) and would likely to have been stronger if there had been fewer operators involved of the tattooing of the 58 patients.

Tattoo application pain scores

Pain scoring was completed by 112 of the participants. 96% (n=108) reported pain on application of one or more of the skin marks. Of the 335 tattoos applied, no pain was reported for 22% (n = 75), a little pain for 46% (n = 154), moderate pain for 19% (n = 62), quite a bit of pain for 9% (n = 31) and very painful for 4% (n = 13). Of the five patients (4%) reporting no pain for any of the tattoos applied, two were in the standard tattoo arm and three were in the test arm. Of the twenty-six patients (23%) reporting quite or very painful application of one or more of their tattoos, eleven were in the standard tattoo arm and fifteen were in the test arm (figure 47).

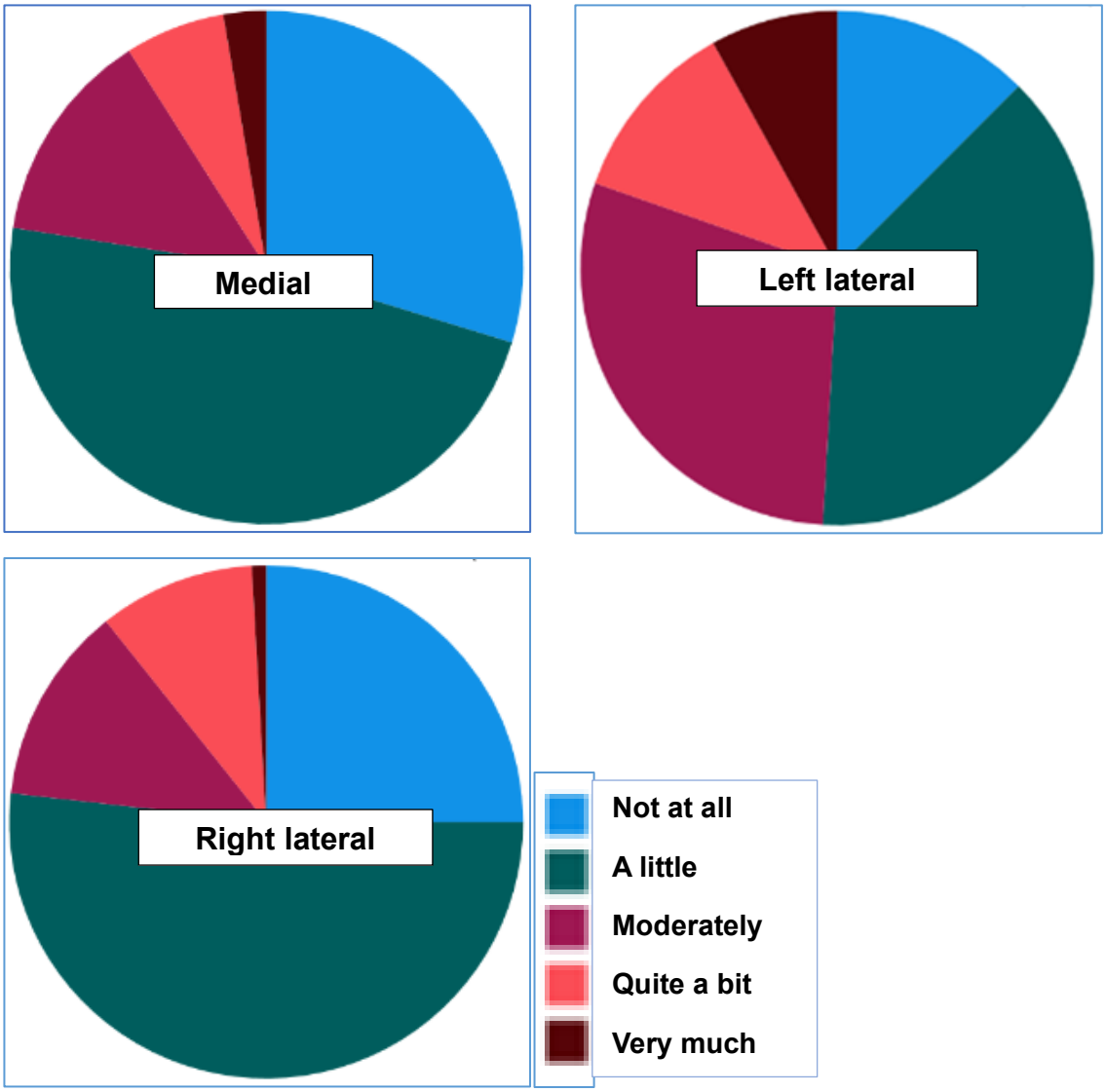
A Kruskal-Wallis test revealed that there was no significant difference in the pain scores of the tattoo application across the standard or test arm groups for the medial, left or right lateral tattoos; X^2 (1, n = 113) = 0.28; 1.76; 1.32, p = 0.867; 0.185 and 0.251. No significant difference between the standard and test arms persisted when combining the pain scores for each of the 3 tattoos applied for each patient (total pain score), X^2 (1, n = 111) = 0.31, p = 0.579.

I investigated the relationship between pain scores at the medial and lateral tattoo locations using Spearman's correlation coefficient. There was a moderately strong positive correlation between the pain scores of the medial tattoo location with the lateral (left and right) tattoo locations, r = 0.33 and 0.43, n = 112 and 111, p = <0.001, with higher levels of medial tattoo pain associated with higher levels of lateral tattoo pain. The medial tattoo application was associated with a higher frequency of pain rated as quite a bit or very much compared to the left and right lateral tattoo application (n = 22 versus n = 12 and n= 10).

Tattoo Alignment Time

The median time to localise and align the tattoos was 2 minutes for standard tattoos (interquartile range (IQR): 2 minutes; range 1-10 minutes) versus 2.5 minutes for the test arm tattoos (IQR: 3 minutes; range 1-10 minutes). A Mann-Whitney U test revealed that this difference was statistically significant, with a small effect size, U = 23126, z = 2.493, p = <0.013, r = 0.12.

Figure 47: Pain on application according to tattoo location



Radiographer-assessed tattoo visibility

<u>At the time of application (both groups)</u>

Standard tattoos:

The standard tattoos were easy to visualise at the time of application for 96% of the medial,100% of the left lateral and 93% of the right lateral tattoos. Six tattoos (two medial and four lateral) amongst five patients were difficult to visualise but adequate. Four patients with difficult to visualise standard tattoos described their skin colour as 1 according to the Ho & Robinson scale, and one patient as skin colour 3.

Test arm tattoos:

The test arm tattoos were easy to visualise at the time of application for 100% of the medial, 81% of the left lateral and 72% of the right lateral tattoos. Twenty-seven tattoos (all lateral) amongst seventeen patients were difficult to visualise but adequate. Seven patients with difficult to visualise test arm tattoos described their skin colour as 1 according to the Ho& Robinson scale, seven as 2 and three as skin colour 3.

2-weeks post application (test arm)

85% (n = 49) of test arm patients attended their 2-week post-application radiographer visibility assessment. Of the 147 tattoos assessed, 136 (93%) were easy to visualise (n = 116) or difficult to visualise but adequate (n = 20). Eleven (7%) tattoos (two medial and nine laterals) were considered not adequately visible amongst six patients. Three of these six patients had their tattoos applied by the same operator. These tattoos were reapplied if there was confident agreement between two radiographers of the location. Where there was any ambiguity, the assumed location was marked and covered with Tegaderm™ and reapplied upon confirmation during standard routine image verification on day 1 of treatment. No patients required replanning.

Day 1 of treatment (both groups)

The first treatment fraction was on average 22 days post-application of the skin marks (range 12 - 34).

Standard Tattoos:

Fraction 1 tattoo visibility data was recorded for 64% (n = 36) of control arm patients and 108 tattoos. 100% of the tattoos were either easily visible (98%; n = 106) or difficult to visualise but adequate (2%; n = 2).

Test arm Tattoos:

Fraction 1 tattoo visibility data was recorded for 100% of the test arm patients and 173 tattoos. 94% of the tattoos were either easily visible (75%; n = 130) or difficult to visualise but adequate (19%; n = 33). Ten tattoos (6%) amongst six

patients were not adequately visible and required reapplication. One patient required reapplication of all three tattoos. This patient failed to attend their 2-week post application visibility assessment, but all were described as easy to visualise at the time of application. Two patients required both lateral tattoos to be reapplied and three patients needed one lateral tattoo to be reapplied.

The localisation of the tattoo re-application point was achieved by aligning the in-room lasers to the assumed (faint and considered inadequate) tattoo(s), with the visible tattoo(s) and all other patient set-up data (that reference the tattoo positions from anatomical landmarks and breast board scale) and verifying this with the standard day 1 treatment verification imaging protocol. No patients required replanning.

During treatment (test arm)

The last treatment fraction was on average 34 days post-application of the skin marks (range 16 - 56).

98% of patients (n = 57) did not require reapplication of any of the tattoos between the second and last treatment fraction. One patient required re-application of the tattoos during the treatment course; both lateral tattoos were considered inadequate to visualise at fraction 5 of 15. They were remarked following standard daily image verification. The patient did not require replanning.

3-Months post application (test arm)

This outcome measure allows assessment of the new tattoo method for longer-course radiotherapy that may continue for up to 12-weeks following the planning CT when tattoos are applied.

3-month post-application radiographer visibility assessments were performed on 38 (66%) of the test arm patients, and 114 tattoos. 93% of the tattoos were either easily visible (67%; n = 76) or difficult to visualise but adequate (26%; n = 30). Eight tattoos (7%) amongst 6 patients were not visible. Four patients had one invisible lateral tattoo, both lateral tattoos were invisible for two patients, and no

patients had all three tattoos become invisible. All medial tattoos were visible (figure 48).

Figure 48: 3-month radiographer tattoo visibility assessment

	Frequency	%	Valid %	Cumulative %
Medial Tattoo				
Easy	34	59	90	90
Difficult but adequate	4	7	10	100
Total	38	66	100	
Not done	20	34		
Total	58	100		
Left Lateral Tattoo				
Easy	21	36	55	55
Difficult but adequate	11	19	29	84
Not adequately visible	6	10	16	100
Total	38	65	100	
Not done	20	35		
Total	58	100		
Right Lateral Tattoo				
Easy	21	36	55	55
Difficult but adequate	15	26	40	95
Not adequately visible	2	3	5	100
Total	38	65	100	
Not done	20	35		
Total	58	100		

6 -Months post application (test arm)

6-month post-application radiographer visibility assessments were performed on 53 (92%) of the test arm patients, and 158 tattoos. 80% of the tattoos were either easily visible (52%; n = 83) or difficult to visualise but adequate (28%; n = 44). Thirty-one tattoos (20%) amongst 20 patients were not visible. Ten patients had one invisible lateral tattoo, both lateral tattoos were invisible for eight patients, and in two patients, none of their tattoos were visible, (medial, left and right lateral tattoos) (figure 49).

Of the 108 tattoos that were assessed at both 3- and 6-months, 30% (n = 32) reduced in visibility, from easy to visualise to difficult to visualise or invisible (n = 20), or from difficult to visualise to invisible (n = 12), demonstrating the ability of the test arm tattoos to fade over time. I interrogated the difference in visible versus

invisible tattoos when assessed a 3- versus 6-months post-application, using a McNamar's related samples test (figure 50). This revealed a statistically significant difference in distribution of tattoo visibility at 3- and 6-months ($p = 0.016$ and $p = 0.004$) for the left and right lateral tattoos. This supports the finding that the test arm tattoos are more likely to become invisible over time. The low number of paired data due to the poor attendance of the visibility assessment, at the 3-month time-point, may have contributed to no statistically significant difference in the frequency of the medial tattoo becoming invisible ($p = 1.0$), as in only 2 was this observed at the 6-month assessment. The data also suggests that the medial test arm tattoos are less likely to become invisible or take longer to become invisible compared to the lateral test arm tattoos.

Figure 49: 6-month radiographer tattoo visibility assessment

	Frequency	%	Valid %	Cumulative %
Medial Tattoo				
Easy	39	67	74	74
Difficult but adequate	12	21	23	96
Not adequately visible	2	3	3	100
Total	53	91	100	
Not done	5	9		
Total	58	100		
Left Lateral Tattoo				
Easy	21	36	40	40
Difficult but adequate	17	30	32	72
Not adequately visible	15	25	28	100
Total	53	91	100	
Not done	2	9		
Total	58	100		
Right Lateral Tattoo				
Easy	23	40	44	44
Difficult but adequate	15	26	29	73
Not adequately visible	14	24	27	100
Total	52	90	100	
Not done	6	10		
Total	58	100		

Figure 50: Difference in distribution of tattoo visibility at 3- and 6-months

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.[a,b]	Decision
1	The distributions of different values across Medial Tattoo Visible 3 mth Y N and Medial Tattoo Visible 6 mth Y N are equally likely.	Related-Samples McNemar Change Test	1.000[c]	Retain the null hypothesis.

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.[a,b]	Decision
1	The distributions of different values across Left Tattoo Visible 3 mth Y N and Left Tattoo Visible 6 mth Y N are equally likely.	Related-Samples McNemar Change Test	.016[c]	Reject the null hypothesis.

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.[a,b]	Decision
1	The distributions of different values across Right Tattoo Visible 3 mth Y N and Right Tattoo Visible 6 mth Y N are equally likely.	Related-Samples McNemar Change Test	.004[c]	Reject the null hypothesis.

Equipment Acceptance

All questionnaires were distributed and returned within 1 month of the final test-arm patient completing their radiotherapy course to ensure adequate recollection of their experience of the test arm tattoos.

Radiographer demographics

The equipment acceptance questionnaire was completed and returned by fifteen therapeutic radiographers: five from the pre-treatment team, and ten from the treatment team. The median number of years qualified for the cohort was seven years (range 2 - 29 years). 20% (n = 1) of the pre-treatment radiographers had been qualified less than 5 years, compared to 40% (n = 5) of the treatment radiographers. Both groups had radiographers with ten or more years' experience. 60% of both the pre-treatment and treatment respondents (n = 3, n = 6) had tattooed or treated more than ten patients with the new method. 20% of each group had tattooed or treated between five and ten patients (n = 2, n = 1), and the remaining 20% (n = 2, n = 1) less than five.

Perceived patient impact

93% (n = 14) either agreed or strongly agreed that the new tattoo method is useful for breast cancer patients and increases the quality of patient care. One pre-treatment radiographer disagreed with both statements. 80% (n = 12) agreed (n

= 5) or strongly agreed (n = 7) that the new tattoo's improve patient care and management. Of those that disagreed with this statement, one was from the pre-treatment team and two from the treatment team.

Training

93% agreed or strongly agreed with the statements that the new tattoo method is easy to learn and that they felt adequately trained and confident in using them. One respondent felt inadequately trained; and another did not feel confident using the new tattoos; both were treatment radiographers.

Clinical performance

100% agreed or strongly agreed that the new tattoo method was easy to use, and 20% (n = 2) disagreed that it fits well with the existing hardware and protocols. 100% agreed or strongly agreed with the statement that the new tattoo method is adaptable for other treatment sites (in addition to breast radiotherapy).

40% (n = 4) of the treatment radiographers agreed that the new tattoos would enhance the effectiveness of treatment set-up, and 20% (n = 2) agreed that patient set-up would be easier. 87% (n = 13) of the entire cohort disagreed that the new tattoo method would improve work efficiency.

None of the pre-treatment team agreed that the new tattooing method would make their job easier, and 90% of the treatment radiographers disagreed that it would make it easier to align the patients.

Social influence

93% agreed (n = 10) or strongly agreed (n = 4) that the department supports the use of the new tattoo method. One radiographer disagreed that the breast clinical oncologists were supportive of the new tattoo method. 47% agreed (n = 5) or strongly agreed (n= 2) that they would be more likely to use the new tattoo method if other departments were also using it. 67% (n = 10) agreed that all of their team members support the new tattoo method.

Free-text comments

Seven themes emerged from the free-text comments of the fifteen respondents. Three related to the visibility of the new tattoos; concerns regarding fading during treatment (n = 3), that they can be difficult to see (n = 2), and that they sometimes need reapplying (n = 2). The impact of increasing treatment sessions was highlighted by two respondents, with seven suggesting that tattoo visibility and durability improve with training and experience. One respondent suggested that recorded training would support the facilitation of the new tattoo method and four respondents stated that the extra time and work is worth it for the improved patient care.

5.5 Discussion

The long and established use of permanent Indian ink radiotherapy tattoos over the past five decades has contributed to the avoidance of meaningful challenge and change of this practice by the members of the radiotherapy team. This is despite the absence of medical device certification; evidence of feasible alternatives; the inequitable visibility on all skin colours that increases treatment times for patients with brown and black skin [leading to negative radiotherapy patient experience]; and the high visibility on white and lighter skin colours in the surviving decades after treatment [contributing to negative body image] (109,112,115,116,119,124,141).

It can be reasonably suggested that the appetite of therapeutic radiographers to implement an alternative to permanent Indian ink radiotherapy tattoos may be more receptive if the solution is only marginally removed from the standard of care; tattoos, but with the natural-coloured, non-permanent ink that is widely used in the field of medical tattooing in breast cancer cosmetic management. This skin-marking technique will satisfy the institutionalised belief of therapeutic radiographers that tattoos are simply the *gold standard* for patient alignment in the absence of surface guidance technology, compared to other identified solutions (that have failed to be implemented) such as pen marks or henna (119).

The hardware used in the medical tattooing field of breast cancer management has the potential to be translated into the radiotherapy domain if the appropriate medical device certification is achieved. However, this technology has not been subject to previous investigation or evaluation in terms of the medical purpose of radiotherapy tattoo application. This supported the concept of a feasibility trial to evaluate if radiotherapy tattoos applied with natural non-permanent ink pigments and micropigmentation technology are fit for purpose, i.e. do they fulfil their fundamental purpose of supporting patient alignment for accurate radiotherapy delivery; can these tattoos be applied as part of the standard pre-treatment pathway; are they visible on all skin colours; do they remain visible for the duration of a radiotherapy treatment course? Here I have presented the results of the NEAT trial which aimed to answer these questions.

The NEAT trial protocol underwent rigorous peer review, involving all members of the breast multidisciplinary team, public and patient representatives, statisticians and experts in clinical research. The result was that I was successful in being awarded the full grant, NEAT was adopted onto the NIHR portfolio, and I was granted favourable ethical opinion. Recruitment rates were excellent, demonstrating the value that patients attributed to this research question.

The sample size of the NEAT cohort was over double that of similar studies evaluating reproducibility of set-up when using an alternative device in breast radiotherapy patient alignment (117,163). Reflecting on my many years of planning and treating breast radiotherapy patients, as well as leading the breast radiotherapy technique development and audit at my centre over the past fifteen years, I consider the breast radiotherapy cohort to be a very heterogenous group. There is a wide variation in age, surgical technique, body habitus, anxiety, and compliance and comfort in the treatment position in a breast radiotherapy population. All of which can have a significant impact on set-up error (the primary endpoint of NEAT), supporting the widely regarded opinion that the standard recommended requirement of twenty patients when auditing a new radiotherapy technique, should be at least doubled if conducting an audit on breast radiotherapy techniques or equipment, in order to quantify the true effect. I was therefore pleased when the sample size calculation was large at 114 patients, as I was optimistic that this would give adequate power for some of the important secondary outcomes, and also ensure that we would include a wide range of ethnicities that is representative of our central London population.

I observed with interest the dialogue around permanent Indian ink radiotherapy tattoos that this trial instigated amongst the pre-treatment therapeutic radiographers and their patients, whilst not data that was collected as part of the trial. For the first time in over twenty-five years, I observed my colleagues acknowledging the potential negative impact of Indian Ink tattoos, discussing this with patients in a more detailed way, showing respect of their views and meeting their concerns with empathy. An example was related to a young patient (28-years-old), who was hoping for randomisation to the test arm tattoos, having expressed her concern of the impact that the visibility of the standard green/blue tattoos would have on her following treatment. The radiographers admitted to

“keeping their fingers crossed that she would get the test arm tattoos” (also demonstrating the importance of removing bias via the independent randomisation system used). This is in stark contrast to the time predating the NEAT trial, where I have consistently observed (throughout several radiotherapy departments) patient concerns or refusal to have permanent Indian ink radiotherapy tattoos causing frustration, minimisation and apathy amongst the team.

Radiographer support and successful challenge to institutionalise beliefs from participation in the NEAT trial, was also demonstrated in the equipment acceptance results. Despite 87% of respondents denying any improvements in efficiency with the new tattoo method, 47% commented that this would improve over time with training and experience, and 27% stated that the extra time and work is worth it for improved patient care. 93% agreed that the department were supportive of the new tattoo method, and that it increased the quality of patient care and outcomes.

Accurate patient alignment supports radiotherapy reproducibility, which is determined according to set-up error. Set-up error is quantified in three directions: vertical, longitudinal and lateral, according to on-treatment image verification, by comparing the anatomical position of the treatment isocentre at the planning CT scan to the time of treatment delivery. It is therefore important that any alternative or new method of patient alignment is evaluated in terms of the impact on set-up error. Corrective on-line imaging protocols have reduced the impact of poor initial patient alignment, as the isocentre position can be realigned with corrective couch shifts. However, patient alignment remains an important component of accurate treatment set-up, to localise the initial isocentre and associated image dose as closely as possible to the treatment target and reduce the degree of any deformative set-up which is more challenging, and often impossible to completely correct with table shifts.

Whilst statistically significant differences in set-up error was detected between the groups for both systematic and random error, these were not clinically significant. Lateral systematic error was in favour of the test arm tattoos, with a mean difference of 0.13 cm, and vertical random set-up error was in favour of the

standard tattoos, with a mean difference of 0.03 cm. The variance between the groups for both variables was very small at only 6% and 4.5% respectively, concluding that there was no meaningful difference between the tattoo methods, positively answering the primary endpoint of the trial.

The time to apply the test arm tattoos was greater than for the standard tattoos, with a difference in the median time of 3 minutes. However, despite this increase in time and large effect size (r = 0.75), the application of the new tattoos was feasible within the standard CT scanning slot for all patients and was considered by 100% of the pre-treatment radiographers as easy to learn and important for improved patient outcomes.

Successful tattoo visibility was achieved for all patients across all skin colours using the range of three non-permanent ink pigments that were selected for the trial. The small range selected (coconut, truly hazel and black tourmaline) was at the advice of the pigmentation experts that provided the equipment and delivered the radiographer training (Finishing Touches Group (168)). There was no consultation with patient representatives regarding the ink pigments selected, which I strongly recommended if selecting a range of ink colours to be certified for radiotherapy use. Biotic Phocea Laboratoires do manufacture and distribute radiotherapy certified ink pigments; but the range of colours available (red, black and green) are not considered appropriate in terms of addressing the clinical and patient-reported limitations of Indian tattoo ink, as they remain unnatural in colour and may not achieve adequate contrast on black skin.

Both the Ho & Robinson and Fitzpatrick scales (161,162) have a 1–6-point scale and have been referred to within the healthcare setting interchangeably. My study is the first to compare the two scales in a single cohort according to patient reported skin colour. Whilst there was a strong positive correlation between the scales, the shared variance was low at 38%, suggesting that the scales are not matched or equivalent, which is important evidence to be acknowledged with regard to baseline assessment during radiotherapy skin care management. The Ho and Robinson scale is perceived to have the greater sensitivity of the two skin colour scales, with a recent increase in its application in clinical settings such as wound management and radiotherapy skin care (169–171).

Pain is not generally acknowledged by the radiotherapy team in terms of the application of radiotherapy tattoos, with topical anaesthetic creams not utilised, even in paediatric patients. To my knowledge, this is the first study to record the pain of radiotherapy tattoo application, which was significant in both tattoo groups. 96% of patients reported painful tattoo application, with no difference according to tattoo arm. 32% of the tattoos applied were rated as moderately to very painful. The results from my proceeding research (112) identified pain as an important outcome in the thematic analysis of the free-text comments of a large survey of over 200 women that had permanent Indian ink tattoos for breast cancer radiotherapy. However, this negative theme was identified in only 2% of the respondents, which highlights the variability in findings when asking open versus closed questions. This data is meaningful for radiographers when counselling and supporting patients regarding the procedure and may support the justification of topical anaesthetics.

There was a statistically significant increase in the time for the treatment radiographers to align the new tattoos compared to the standard tattoos, with a median difference of 30 seconds. This is not clinically significant, supported by the small effect size (r = 0.12). 20% of the treatment radiographers had concerns that treatment session times may be increased in their equipment acceptance questionnaires. However, the same range of tattoo alignment times (1-10 minutes) was reported for both groups, demonstrating a commonly observed feature of breast cancer radiotherapy; that due to a number of factors such as body habitus, patient tension, compliance and radiographer skill; some tattoo alignments are rapid, and others can be significantly longer. The difference in the interquartile range of 1 minute between the groups may still be considered justifiable in acknowledgement of the negative impact on body image of permanent Indian ink tattoos, and the amount that other factors independent of tattoo type can have on in-room treatment times.

The ability to localise radiotherapy skin marks at each treatment fraction is an important factor when assessing the feasibility of a new tattoo method. The early run-in data suggested that the pre-treatment radiographers were selecting the test-arm ink pigment that provided the highest contrast (black tourmaline), rather than what would provide adequate contrast with a patient's skin colour. This is

possibly related to their institutionalised beliefs around Indian ink tattoos regarding the high visibility of alignment marks being the gold standard. The rate selecting the hazel ink pigment increased significantly after this notification.

The comparative rate of 'lost' or 'invisible' test arm tattoos at 2-weeks post-application (7%), treatment fraction 1 (6%) and during treatment (1%), support the opinion that tattoo application compliance was most likely the cause for inadequately visible tattoos. This was highlighted during the feasibility run-in phase and instigated the successful re-training of specific operators. The inadequate deposition of ink pigment into the skin is therefore the assumed cause of inadequately visible tattoos prior to and during treatment, as opposed to an unacceptable rate of these ink pigments fading over time. This poses a very important consideration when implementing any new tattooing technique; that the training of a new technique is crucial, and the audit of compliance to identify any specific training requirements or technology issues is highly recommended.

Standard imaging protocols were able to confirm and localise the alignment point location for the reapplication of the test arm tattoos if required. Only one patient had all three tattoos considered not adequately visible at fraction 1. Despite this, the tattoos were successfully reapplied without any requirement for additional imaging or replanning based on the very faint visibility that remained.

With only 4% of the study participants reporting their skin colour as five or six (according to the Ho & Robinson skin colour scale (162)), it may be that the population was not adequately sensitive to demonstrate an improvement in tattoo visibility in dark skin tones. This may have positively impacted treatment session length compared to standard tattoos, which are associated with poor visibility on black skin. Only 2% of the standard tattoo group had difficult but adequately visible skin marks, compared to 19% of the test arm group.

All of the radiographers completing the equipment acceptance questionnaire agreed that the new tattoos could be used for other treatment sites, in addition to breast radiotherapy. Breast radiotherapy is amongst the lowest course length in terms of radical treatment (typically five to fifteen fractions, delivered over one to three weeks), with other sites such as gynaecological, prostate and oesophageal

radiotherapy prescribed treatment courses that extend over as much as six to seven weeks. To demonstrate feasibility for longer-course radiotherapy, test arm tattoo visibility was assessed 3-months post application. Between the second and last treatment fraction (i.e. following fraction 1 re-application if required), 99% of the test-arm tattoos remained easy or difficult to visualise but adequate. This reduced to 93% at the 3-month assessment, with a greater number (26%) being difficult to visualise but adequate. Despite this demonstrating a greater number of tattoos becoming inadequate by 3-months post-application, my study has demonstrated that daily assessment of the tattoos during the treatment course, and standard image verification can facilitate remarking of the tattoos if they are considered inadequate on any treatment day, and therefore can be considered for longer-course radiotherapy.

The medical tattoo ink pigments, whilst acknowledged as fading with the potential to disappear over time; hence the terminology *semi-permanent* tattoos, do not have any available data regarding the rate at which a 1-2 mm dot fades or becomes invisible. This is important data regarding the patient information, choice of terminology (e.g. semi-permanent, sometimes permanent, time when they may disappear completely etc) and informed consent were this technique be implemented into clinical practice. The most important measure of tattoo visibility beyond the clinical requirement of visibility (3-months post-application), is patient-reported visibility. What matters is whether the recipient can see the tattoos, and how they subsequently feel about them. For example, there are several instances where a patient may report not having any permanent Indian ink radiotherapy tattoos when they attend for subsequent treatment; whereby the radiographer; with the benefit of insight and experience can identify these immediately. Patient-assessed tattoo visibility (monthly up to 18-months post-application) and the impact on body image will be reported separately from this report once the data is available. Therefore, within the constraints of this report, only the 6-month radiographer visibility assessments as a means of evaluating changes in visibility longer-term is included.

At 6-months post-application, the rate of tattoos becoming invisible had increased compared to the 3-month assessment (20% versus 7%), demonstrating the potential for these tattoos to disappear over time. There was

also evidence of tattoo visibility reducing, with easy to localise tattoos reducing from 67% to 52%. In contrast, Indian ink tattoos remain visible forever, and may increase in size over time as the tattoo ink disperses into the surrounding tissues.

The rate of becoming invisible by 6-months was not consistent between the medial and lateral tattoos, with only 3% of the medial tattoos being invisible compared to 28% and 27% of the left and right lateral tattoos. There was, however, evidence of the medial tattoos starting to fade, with 23% being difficult to see at 6-months compared to 10% at 3-months. The skin over the sternum is often more tense, with a lower depth of fat over the bone compared to the lateral tattoos. This is likely to result in a different deposition of ink when using the same technique compared to the lateral tattoos. It may also be that the rate of dispersal of the ink that leads to fading is lower in different areas of the body and warrants further investigation.

5.6 Conclusion

The NEAT trial is the first randomised controlled trial to evaluate the feasibility of a new tattoo method utilising the micropigmentation technology and natural semi-permanent ink pigments that are used in the medical cosmesis field; and to collect new and meaningful data on standard permanent Indian ink tattoos. Participation in this trial has challenged the ingrained beliefs of therapeutic radiographers that permanent Indian ink tattoos are inconsequential to patients following treatment, and that there may be feasible alternatives worth considering. The therapeutic radiographers were overwhelmingly supportive of the positive impact this new tattoo method could have on the quality of care that we offer our patients.

Therapeutic radiographers are key to the successful implementation of a new tattoo method; whereby their acceptance or rejection will directly impact whether this is adopted as standard of care. New methods of tattooing can take longer in the initial phases whilst training and experience grows, but the radiographers in our study were supportive despite this. There was no indication that CT or treatment session length would need to be increased.

Painful application of radiotherapy alignment tattoos has been quantified for the first time in this large cohort of breast radiotherapy patients and warrants further consideration of how this can be reduced. The use of topical anaesthetic, or microneedles may provide a solution, and should be evaluated across a range of tattoo locations and patient cohorts (e.g. paediatric and needle phobic patients).

The NEAT trial has demonstrated feasibility of using the natural-coloured semi-permanent inks and micropigmentation technology recognised widely in the medical tattooing of nipple areolas following nipple sacrificing mastectomy and reconstruction for radiotherapy tattoos. This method has been demonstrated as facilitating effective and accurate patient alignment within established tolerance levels, with no clinically significant difference with standard tattoos.

Whist a limitation of the study is the low proportion of patients reporting their skin colour as five or six (according to the Ho & Robinson skin colour scale (162)), the

study did however show that from a three-pigment range, adequate contrast with all skin colours was achieved.

It is important that ink pigments that are visible yet acceptable to patients of all skin colours are selected if proceeding with medical device certification. To satisfy the latter, it is recommended that patient focus groups should be conducted, inviting participants of all skin colours, to deepen the understanding of the types of colours and level of contrast between tattoo and skin that is acceptable to patients. This is important if aiming to reduce the negative impact on body image that has been reported, particularly if the new tattoos may take many months or years to become invisible.

The patient-reported tattoo visibility assessments of the test arm tattoos will be fundamental in quantifying the visibility duration of this tattoo method and will inform patient information and choice of terminology if these are to be clinically implemented. Comparing the impact on body image between the tattoo groups will be valuable data in support of any application to pursue the commercialisation of this alternative radiotherapy tattoo method.

The medical device directive provides a robust system for the certified use of equipment or software that is involved in a therapeutic intervention. However, the regulatory process of taking the equipment used in the NEAT trial though to commercialisation, is both a long and expensive path. This, however, should not be a deterrent if demonstrated as improving patient outcomes, and will require close partnership between the medical teams, patients, research institutions and industry, to ensure that the right colours are selected, and meaningful improvements to quality of life are achieved regarding side effects of radiotherapy skin marking.

Chapter 6

Defining a radiotherapy tattoo ink pigment range that is visible and acceptable for all people

6.1 Introduction

My previous two chapters have demonstrated the significant negative impact that permanent Indian ink radiotherapy tattoos can have on people in the years and decades following breast cancer treatment. A significant theme was the unnatural colour of the tattoos and prolonged high visibility resulting in the permanent marks serving as a constant negative reminder of the breast cancer diagnosis and treatment, affecting the clothing choices of 15% of the respondents (112).

The NEAT trial confirmed the feasibility (in terms of set-up accuracy and duration of visibility) of using the natural-coloured non-permanent ink pigments used in medical tattooing for the purpose of radiotherapy skin marking. I suggest that this alternative approach will satisfy two significant limitations of Indian ink tattoos; firstly to provide a greater contrast with brown and black skin tones to facilitate equitable visibility during treatment compared to white and lighter skin tones; and secondly, to be less impactful on body image as they are a more natural colour and fade over time compared to Indian ink tattoos.

However, the Medical Device Directive (172) restricts the use of medical devices only to their certified purpose, and therefore for these ink pigments to be used for the purpose of radiotherapy skin marking, they first must be regulated and certified as such. This is a long, complex and costly process, of which neither I, nor the Translational Research Office (TRO) at University College London (UCL) has prior specific experience; potentially making the process even longer and even more expensive. A fundamental first step in working towards the objective of having a range of radiotherapy tattoo ink pigments that are visible yet acceptable for all people, is to ask the end user – the patient – which colours these should be to eventually take through the process of medical device certification.

6.2 Study aim

To engage with patient representatives to learn about what coloured ink pigments are acceptable in terms of the ink visibility in relation to natural skin colour.

6.3 Materials and methods

6.3.1 Charitable partners

I was contacted by the Macmillan Cancer Support Radiotherapy Advisor, and offered an invitation to meet with the Director of Innovation and Commercial Partnerships to discuss how Macmillan could support the future commercialisation of natural-coloured semi-permanent radiotherapy tattoos. Following a successful meeting whereby Macmillan agreed in principle to support this project, and add it to their project worklist, they requested a summary and key milestone document (appendix 34), which I drafted, was reviewed and approved by the UCL TRO, and submitted to Macmillan accordingly.

Following successful completion of aims one and two (to determine the process of certifying new ink pigments for radiotherapy tattoos, and to identify a manufacturer to be the licence holder), aim three (to conduct a series of patient workshops to identify acceptable ink pigments for people of all skin colours) required close collaboration with a number of charitable organisations.

I reached out to several charities; outlining the aim of the patient workshops and to ask whether each charity would be supportive in terms of inviting their communities to participate. All of the charities I approached confirmed their support, facilitating representation from a wide range of ethnic groups:

- Macmillan
- Leanne Pero Foundation; Black Women Rising
- British Asian Cancer Charity
- Sakoon Through Cancer Charity
- South Asian Supernovas

Macmillan Cancer Support offered me the services of their Innovation Engagement Team to facilitate and analyse the data of the patient workshops, and they therefore managed the research methodology in terms of the results that were yielded to meet my study aim, hence the unconventional way I have presented this information under the *materials and methods* subheading.

Macmillan Cancer support also invited me to apply for a research grant to support the workshop costs. They pledged to fulfil their role as workshop facilitator at no cost, which included a written report following their analysis of the findings, that would be 'gifted' to me at the conclusion, with me the named owner of the outcome data.

The legal team at Macmillan required a confidentiality agreement with all parties (UCL/UCLH and Biotic Phocea Laboratoires) involved in the patient workshops (appendix 35).

Participants completed a project consent form (provided by Macmillan). Macmillan were satisfied that ethical approval was not required as I confirmed that:

> *"We have shared discussions internally and made the decision not to submit an amendment to the NEAT trial protocol as this tattoo ink regulatory and commercialisation work is not related to the primary or secondary objectives of the NEAT trial… The workshops will therefore be considered PPI focus groups as a part of research development, prior to ethics application as defined by the HRA https://www.hra.nhs.uk/planning-and-improving-research/best-practice/public-involvement/resources/*

6.3.2 Workshop funding

I completed and submitted a Macmillan project grant application in September 2024 (appendix 37), and following review by the panel was awarded the full amount in October 2024. The Macmillan support grant would cover the venue hire, refreshments, participant travel and workshop materials. Due to the terms and conditions of the grant, alternative funding would be required for payment of industry partner fees and participant thank you gifts. Therefore, to cover these

excluded costs, I approached the Society and College of Radiographers which agreed that the underspend of the CoRIPS award (NEAT trial) could be used to cove these excess workshop costs.

6.3.3 Existing Industry-based knowledge and experience

Medical device regulation requires a named manufacturer to be the license holder. During the set-up and recruitment phases of the NEAT trial, I was supported by a medical tattoo company, the Finishing Touches Group. Despite not producing radiotherapy certified ink pigments, their medical tattooing division offers training to breast care nurses and breast oncology surgeons. Finishing Touches provided the radiographer training, micropigmentation machine, needles and inks, with the range of ink pigments selected for the trial based on their advice.

At a radiotherapy conference, I was introduced to Biotic Phocea Laboratoires as a manufacturer with existing experience of the regulatory processes and certification of radiotherapy ink pigments for alignment tattoos. I subsequently identified this company as a viable option as the manufacturer for a natural-coloured radiotherapy ink pigment range.

Biotic Phocea Laboratoires hold the certification for a small range of three radiotherapy 'RADSAFE®' ink pigments, red, green and black (138). Having already navigated the path of medical device certification for these ink pigments, I, following consultation with the UCL TRO, approached the company to present an opportunity for a knowledge and skills exchange, as a first step towards potentially increasing the range of RADSAFE® inks, to include those that would be visible yet acceptable for all skin colours.

Biotic Phocea Laboratoires were interested in such a partnership but informed the UCLH and UCL teams that due to the requirements of the upcoming Medical Device Directive 2027, they were undergoing huge transformation and update of the certifications to ensure compliance of all of their medical devices. This meant that they were unable to increase their portfolio of medical devices at this time. However, they did accept my presentation that the current ink colour range may

not address all of the clinical limitations of Indian ink radiotherapy tattoos and were motivated to commencing a relationship to solve this problem together (appendix 36).

6.3.4 Knowledge exchange

The UCL contract team established non-disclosure agreement and knowledge exchange agreements with Biotic Phocea Laboratoires. The purpose of these contracts is to protect all involved parties; to ensure that any progression to commercialisation of the natural-coloured radiotherapy tattoos that has been as a result of the knowledge and skills to enable said progress, continues to be a joint venture.

The knowledge and skills offered by UCL and UCLH was my experience in protocol development for clinical trials, insight into patient perception of radiotherapy tattoos and radiographer acceptance of new technology, understanding the requirements of NHS business case requirements in terms of the justification of the implementation of a new medical device (at cost), and links to charitable organisations who had expressed an interest in supporting and funding this project to achieve commercialisation; and the TRO's understanding and experience in industry partnerships, contracts and navigating the Medical Device Regulatory process.

The knowledge and skills from Biotic Phocea Laboratories, was their understanding and experience of certifying ink pigments as medical devices for radiotherapy skin marking, and expert knowledge of tattoo ink pigmentation, and the infrastructure within their research team and laboratories to develop and produce suitable pigments that comply with the European Union REACH Regulations (151).

6.4 Results

I led the teams at UCLH, UCL and Macmillan, who worked over a period of several months to design the patient workshop. Having consulted with advisors in the field of treating patients from ethnic minority groups, I proposed that each workshop would invite the members of one charitable organisation at a time. This was in acknowledgement of differences around the use of skin colour terminology and the identification of a workshop location that was known and comfortable environment to the participants.

6.4.1 Target demographic and recruitment

I contacted the Leanne Pero Foundation; Black Women Rising group lead, who had previously confirmed their support of the concept of the patient workshop. I introduced them to the Macmillan Innovation Engagement team, and we subsequently worked together to produce an involvement briefing to invite the Black Women Rising members; all of whom had a lived experience of breast cancer.

Of the sixteen Black Women Rising members that expressed an interest and received the pre-reading information, twelve participants were recruited and attended the workshop, hosted at Future Dreams House, London. This was a meeting hub that I knew was used regularly for events hosted by the Leanne Pero Foundation, and so likely to be familiar in terms of travel to- and environment to the attendees.

6.4.2 Workshop planning

The main aim of the workshop was to learn about what colour tattoos are considered acceptable in people with brown and black skin, to support the choice of colour range if progressing to medical device certification and commercialisation.

This is particularly important when considering that this is the patient group in whom are possibly less likely to have visible radiotherapy tattoos when applied with Indian ink, and even though this will improve localisation and the issues surrounding this during treatment, may increase the impact on body image if not acceptable to patients.

In addition to learning about what coloured ink are acceptable, it was also important to learn about whether there was a colour of ink, or level of contrast (be that lighter or darker than the natural skin tone) that was not acceptable to patients.

In the lead-up to the workshop, I worked closely with the Macmillan team to advise and formulate a workshop session plan, facilitator support notes and session breakout questions (appendices 37 and 38) that would address the aims of the workshop and provide a positive participant experience.

I created A1-sized posters for each of the breakout groups with the available natural-coloured ink pigments from the medical tattooing range displayed. Each participant would first be asked what colour their own skin is according to the Ho & Robinson skin colour chart (162), and then annotate on the posters which tattoo colours they would and would not accept as radiotherapy skin marks; acknowledging that they may not reduce in intensity or disappear completely (as there is no high-level evidence available to support this).

Having consulted with an expert in the field, I provided specific training to the facilitators in terms of appropriate language when referring to skin colour, to reduce the risk of causing offense to any of the attendees.

6.4.3 Workshop outcomes

All participants had a lived experience of breast cancer, and most had received permanent Indian ink tattoos as part of their breast radiotherapy treatment.

Macmillan collected the comments of the breakout groups through a combination of digital recording and note-taking. The ink colour posters were also a source of

data collection pertaining to the views of the participants, relative to their self-reported skin colour. A report was produced and handed to me as the owner of the final reported outcome data, with permission to publish these results, appropriately acknowledging the role and contribution of Macmillan Cancer Support (appendix 40).

Various themes emerged from the break-out discussions, and were based around three broad themes, with several subthemes identified from the thematic analysis:

Experience of radiotherapy tattoos

Three subthemes emerged: lack of choice, understanding of radiotherapy tattoos and tattoo visibility.

Lack of choice was most commonly mentioned and supports my previous findings of Chapter 4 (112), whereby even though they provided their consent for the tattoos, they did not feel that they could refuse them, and therefore had to accept them.

The report also supports the theory that the small size of the tattoos does not reduce the impact of them remaining visible. Not understanding that the tattoos would be permanent or knowing the purpose of them. Recalling painful application and religious-based concerns was also described; echoing two rare theme that I identified in the questionnaire cohort (112).

Participants shared the impact on them feeling vulnerable, exposed and helpless, associated with the radiographers having difficulty in locating their tattoos during treatment due to the low contrast with their skin colour.

Emotional impact of radiotherapy tattoos

Positive themes emerged that were common with those of my questionnaire study (112), that a minority of participants reported that the tattoos were reassuring during treatment, or that they had feelings of pride about them. However, the majority of participants referred to their tattoos as serving as a

constant negative reminder of their breast cancer experience, remaining visible to them, particularly due to the unnatural ink colour used.

Ink colour preferences

Total consensus was voiced by the participants that being involved in choosing the ink colour was hugely important to reduce the negative impact of tattoos.

Some said that they would choose an ink colour that would blend with their existing skin blemishes, and being able to mix their own colour like with makeup would achieve personalisation that would be empowering. Others stated that they would select bolder colours that they associate with feeling empowered. The potential for the tattoos to fade was considered favourably.

The few participants that were happy with their existing Indian ink tattoo colour, explained that this was due to it looking similar to their natural skin blemishes. The degree of contrast between skin colour and the ink pigment was the single most important measure of colour acceptability, with no particular preference of lighter or darker, as long as it was of the least contrast possible yet adequately visible for effective treatment alignment, i.e. discrete.

The use of supporting material for the consent process of radiotherapy tattoos was highlighted as important, with a need to see the available ink colours presented on an inclusive spectrum of skin colours.

The post workshop feedback was 100% positive. Participants described feeling reassured and acknowledged by the presence of the industry partners, and also the familiarity of the workshop venue supporting them in feeling relaxed. The participants described having enjoyed the session, finding it interesting and feeling that their views were important and heard. One participant concluded the session by thanking the facilitators and researchers for “caring about me and my skin as much as I do”. At this, all of the participants applauded in support of this statement.

6.5 Discussion

This inaugural patient workshop demonstrated the highly valuable format of bringing all stakeholders together in the planning and delivery of a patient and public involvement event if aiming to deliver a positive experience to the participants, as well as satisfying the aims and objectives of the session. This included members of the radiotherapy clinical team, hospital-based and academic researchers, industry partners, charity partners and patient representatives.

The template of this workshop will be used as the foundation for all subsequent workshops that are planned with each individual charitable community that have expressed their support, representing a wide range of ethnicities. Adaptation will likely be required in terms of venue, method of initial engagement and language use. I will seek the advice and insight of the respective charity leaders during each planning stage. The outcomes of all of the workshops combined will help to advise which ink colours are required for medical certification and provide confidence that the investment made in the regulatory processes will address the current unmet need, protecting the commercial venture.

The presence of the Industry partners (Biotic Phocea) which enabled them to hear first-hand from people with a lived experience of breast cancer and radiotherapy tattoos was incredibly impactful. Despite having shared numerous conversations where I have described the negative impact of the unnatural colour of the Indian tattoo ink, which would also apply to their current RADSAFE® range of black, red and green, it was only following the workshop that our industry partners acknowledged this and described feeling deeply motivated to develop a natural-coloured range.

Observing the highly experienced Macmillan team facilitate the workshop gave me such valuable insight into this process. Due to restructuring within the Macmillan organisation, they are currently unable to support any further patient engagement, but have shared all of the workshop materials and given permission for me to use these as a template for all subsequent workshops. They have also

advised possible methods of workshop facilitation; either by me and my clinical team, or using a third party organisation. Although a third-party facilitator would come at a cost, having seen the value added by experienced facilitators, I would certainly consider this for the second workshop, whilst my clinical team gain further experience in this field.

Prior to this workshop, I had preconceived ideas of what ink colours would be 'preferred' by people with brown or black skin. I was wrong, again demonstrating the importance of patient and public involvement. I had assumed that people with brown or black skin would not accept ink pigments that were lighter than their own skin colour. This view was based on my previous conversations with my patients. When I learnt that there was a white ink pigment available (RADSAFE® ink pigment subsequently removed from the market) I asked many of the black women that I was treating what they thought about this. 100% told me that they would refuse white tattoos. However, we learnt through the patient workshop that it isn't whether a tattoo is lighter or darker than the natural skin colour, but the degree of contrast so that it looks natural. It will be interesting to learn via the subsequent patient workshops whether this is a consistent finding independent of ethnicity or skin colour.

6.6 Conclusion

Patient and public involvement may in the past have been perceived by some researchers as a simple ‘box-ticking’ exercise to meet funding requirements. However, if aiming to conduct meaningful and insightful research that can inform medical device development so that it meets not only the clinical objectives, but also the impact on the end user (the patient), this will contribute heavily to protecting any future investment and commercialisation.

Bringing together the knowledge and skills of all stakeholders when conducting patient and public involvement is the most effective way of delivering outcomes that are meaningful, impactful, and realised following positive interactions that leave all participants (attendees, facilitators, researchers and industry partners) feeling positive and motivated.

Chapter 7

Future plans and final conclusions

7.1 Next steps

7.1.1 Heart and lung dose surrogates

My department continue to use the virtual simulation dose surrogates (%HIF and %ILF) that I have identified and validated in my research as standard practice for all patients when virtually simulating breast/chest wall +/- nodal radiotherapy to guide field placement and technique selection. This has had a significant impact on the efficiency of our breast radiotherapy pathway, which releases resources and motivation of the radiotherapy team to further develop and improve our breast radiotherapy service. We continue to evolve this practice to meet changes in dose and fractionation (for example if FAST Forward Nodal extends the 26 Gy in 5 fraction schedule for nodal radiotherapy). We have also recently identified more efficient methods to create the *field* contour from which the HIF and ILF volumes are derived, streamlining this process even further. I would like to see this method used by more radiotherapy departments. I hope to reach out to those in our cancer network not utilising this method in the first instance, to support them in implementing this time-saving step to the their virtual simulation processes.

I will continue to work with the PARABLE trial working group to investigate and develop a tool to accurately predict mean heart dose from diagnostic imaging data sets. If successful (i.e. clinically acceptable confidence interval for predicting MHD), not only will this facilitate a more efficient breast proton beam pathway but can also be used for the breast photon pathway to identify which patients may require IMAT as opposed to tangential radiotherapy. There are still a proportion of radiotherapy departments that are unable to deliver IMAT in DIBH, and refer patients to a secondary radiotherapy department when this is indicated (if the patient 'fails' tangential planning), leading to a delay in the patient pathway.

We have a significant breast sarcoma practice at UCLH which uses higher dose and fractionation schedules to early breast cancer, yet also relies on virtual simulation for field placement. Although the heart and lung tolerance doses are greater when treating breast sarcoma, there are instances when heart dose may be unacceptably high and IMAT or PBT is considered. Early identification in the

pathway has the same efficiency-savings as with early breast cancer. The %HIF thresholds and calculations can be easily provided using the data from 20 retrospectively selected data sets from this patient cohort with regard to the range of fractionation schedules used and relevant tolerance dose levels.

7.1.2 Radiotherapy tattoo ink pigments

My aim is to complete all the proposed patient workshops, one for each of the charitable group community members. I will adapt the inaugural workshop template design to meet the needs of each representative group, such as location and terminology to be used. Feedback from participants and facilitators from the first and all subsequent workshops will be used to guide future workshops.

Another important objective is to publish the outcomes from the portfolio of completed workshops, to share good practice and demonstrate how collaborative working between all stakeholders (clinical, academic, charitable, industry and patients) can deliver high-value, high-quality patient and public involvement to help shape research ideas and product development to achieve maximum patient benefit.

A range of ink colours to be certified as medical devices with the purpose of radiotherapy skin marking will be identified following completion of the workshops. I will present this to Biotic Phocea Laboratoires within the knowledge sharing agreement, supported by the UCL TRO, to inform them of an appropriate future range of RADSAFE® ink pigments that will be visible yet acceptable on all skin colours, and hopefully fade over time.

Through the continued collaboration with Biotic Phocea Laboratoires, my aim is to produce a protocol and have the appropriate funding in place to provide the patient data required to satisfy the requirements of the medical device certification. Although Biotic Phocea are limited in terms of progressing this to through the regulatory procedures until 2027, the data can be collected and safety file build in advance. The required parameters for this will be identified by Biotic Phocea Laboratoires to ensure compliance with the 2027 Medical Device Directive.

My final objective is to produce a business case template for all radiotherapy departments (who do not offer tattoo-less radiotherapy, e.g. with SGRT) to support the rapid implementation of non-permanent natural coloured ink pigments in place of permanent Indian ink tattoos, in terms of health economics and benefits to patient survivorship and quality of life. An alternative approach may be to engage with breast cancer and paediatric charities to explore if a grant could be accessed to provide this equipment and training to all UK radiotherapy centres at zero cost to each Trust.

7.2 Final conclusion

The work that I have conducted within this thesis has contributed significantly to the field of breast cancer radiotherapy, with clinical impact already being observed on both a local and national level.

Having identified virtual simulation surrogates that are for the first time truly predictive of resulting heart and lung doses (with very narrow confidence intervals), I have facilitated significant efficiency savings within my centre and others within our cancer network. On a national and international basis, the easy-to-follow methodology I have provided to calculate and validate this model affords all radiotherapy departments the opportunity to make significant efficiency savings and raise the quality of their virtual simulation practice when planning their largest patient cohort, breast radiotherapy. This work has also paved the way to investigate how this concept can be used to streamline other radiotherapy pathways, such as those patients that may benefit from proton beam therapy due to unacceptable heart and/or lung dose with photons. I do not believe that this would have been considered (or the subsequent working party established), had my work not been successfully conducted and the impact clearly identified, both through the journal publication and my role as a PARABLE working party member.

In terms of permanent skin marking with Indian-ink tattoo, my work is the largest to report the negative impact of this practice on people following breast cancer radiotherapy due to the high- or low-contrast, unnatural colour. My research is also the first to present the data with the patient voice being at the centre; providing verbatim quotes alongside the statistical data. Communicating the findings in this way has resonated strongly with those at the centre of this practice, the therapeutic radiographers and the radiotherapy tattoo ink manufacturers. This has paved the way for me to form an industry network that includes all stakeholders that are now working together to commercialise a fully regulated natural coloured ink pigment range. I have achieved this by forging strong industry partnerships, bolstered by my clinical expertise and the

knowledge of my academic colleagues within the UCL Translational Research Office.

The impact of my work in this field in the short terms is the growing recognition and acknowledgement by therapeutic radiographers that Indian-ink tattoos are commonly associated with strongly negative effects on our patients both during and after treatment; in the mid-term is the demand for a feasible alternative solution by the oncology team; and the long term aim is for all radiotherapy departments that are not able to offer tattoo-less radiotherapy, to be equipped to offer natural-coloured skin marking that is visible and acceptable for people of all skin colours. The basis for this now realistic objective, is underpinned by the research that I have conducted in quantifying the impact and identifying a feasible alternative.

Regarding my on-going career as a consultant therapeutic radiographer, entering my 10th year in this role, I will continue to acknowledge and work within all four pillars of consultant practice. In terms of the research and development pillar, I hope to utilise the knowledge and skills that I have developed over the course of the PhD programme to continue to evaluate scientifically, and refine the radiotherapy delivered to breast cancer patients, taking into account both the physical and technical aspects, and the psychological elements of patient care. I will use the experience and resilience I have gained to train and mentor more junior therapeutic radiographers, encouraging them to take an academic interest beyond simply the delivery of standard care. I also hope to inspire my specialist and consultant therapeutic radiographer colleagues to protect, nurture and fulfil the research and development pillar of their practice, as we are in a very privileged role in terms of our high patient contact and links with our manufacturers and industry partners. We have specific technical insight as radiographers of what our equipment can do not just now, but in the future, to address not only improving survival, but also the quality of life of our existing and future patients.

Chapter 8

References

1. Cancer Research UK. Cancer Research UK. 2015 [cited 2024 Dec 10]. Breast cancer statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer

2. National Institute for Health and Clinical Excellence. Overview | Early and locally advanced breast cancer: diagnosis and management | Guidance | NICE [Internet]. NICE; 2018 [cited 2024 Dec 10]. Available from: https://www.nice.org.uk/guidance/ng101

3. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. The Lancet [Internet]. 2000 May [cited 2024 Dec 10];355(9217):1757–70. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673600022637

4. Tomé WA, Steeves RA, Paliwal BP. On the use of virtual simulation in radiotherapy of the intact breast. J Appl Clin Med Phys [Internet]. 2000 Mar 1 [cited 2024 Dec 10];1(2):58–67. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5726150/

5. International Commission on Radiation Units and Measurements. ICRU Report 50, Prescribing, Recording, and Reporting Photon Beam Therapy – ICRU [Internet]. [cited 2024 Dec 10]. Available from: https://www.icru.org/report/prescribing-recording-and-reporting-photon-beam-therapy-report-50/

6. International Commission on Radiation Units and Measurements. ICRU Report 62, Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU 50) – ICRU [Internet]. [cited 2024 Dec 10]. Available from: https://www.icru.org/report/prescribing-recording-and-reporting-photon-beam-therapy-report-62/

7. Maddams J, Utley M, Møller H. Projections of cancer prevalence in the United Kingdom, 2010–2040. Br J Cancer [Internet]. 2012 Sep 25 [cited 2024 Dec 10];107(7):1195–202. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3461160/

8. 2020 - Clinical oncology UK workforce census 2020 report.pdf [Internet]. [cited 2024 Dec 10]. Available from: https://www.rcr.ac.uk/media/trib5qrs/clinical_oncology_census_report_2020.pdf

9. The NHS Plan. A plan for investment. A plan for reform. 1998.pdf [Internet]. [cited 2024 Dec 10]. Available from: https://pns.dgs.pt/files/2010/03/pnsuk1.pdf

10. Department of Health. Meeting the challenge: a strategy for the allied health professionals.pdf [Internet]. [cited 2024 Dec 10]. Available from: http://www.nursingleadership.org.uk/publications/meetingthechallenge.pdf

11. Department of Health. Making a difference: strengtheneing the nursing, midwifery and health visiting contribution to health and healthcare.pdf [Internet]. [cited 2024 Dec 10]. Available from: http://www.nursingleadership.org.uk/publications/nurstrat.pdf

12. Department of Health. Radiography Skills Mix: A Report on the Four-Tier Service Delivery Model – ScienceOpen [Internet]. 2003 [cited 2024 Dec 10]. Available from: https://www.scienceopen.com/document?vid=027b2eb7-a198-427d-8477-c4eadabdebb8

13. Department of Health. Cancer refrom strategy.pdf [Internet]. [cited 2024 Dec 10]. Available from: https://data.parliament.uk/DepositedPapers/Files/DEP2007-0203/DEP2007-0203.pdf

14. Tsang Y, Roberts N, Wickers S, Nisbet H. Embracing Skill Mix in the Clinical Oncology Workforce – Capturing Impacts of Consultant Therapeutic Radiographers in the UK. Clinical Oncology [Internet]. 2021 May [cited 2024 Dec 10];33(5):e239–42. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0936655521000443

15. import-high-planning-pack-version-4-0-final-23052013-edited.pdf [Internet]. [cited 2024 Dec 10]. Available from: https://www.icr.ac.uk/media/docs/default-source/default-document-library/import-high-planning-pack-version-4-0-final-23052013-edited.pdf?sfvrsn=6d2c2169_0

16. Association of Breast Surgery at - 2009 - Surgical guidelines for the management of breast c.pdf [Internet]. [cited 2024 Dec 10]. Available from: https://www.ejso.com/action/showPdf?pii=S0748-7983%2809%2900027-4

17. Coles C, Yarnold J. Localising the Tumour Bed in Breast Radiotherapy. Clinical Oncology [Internet]. 2010 Feb [cited 2024 Dec 10];22(1):36–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0936655509002738

18. Bedwinek J. Breast conserving surgery and irradiation: The importance of demarcating the excision cavity with surgical clips. International Journal of Radiation Oncology*Biology*Physics [Internet]. 1993 Jul 15 [cited 2024 Dec 10];26(4):675–9. Available from: https://www.sciencedirect.com/science/article/pii/0360301693902876

19. Krawczyk JJ, Engel B. The importance of surgical clips for adequate tangential beam planning in breast conserving surgery and irradiation. Int J Radiat Oncol Biol Phys. 1999 Jan 15;43(2):347–50.

20. Coles CE, Griffin CL, Kirby AM, Titley J, Agrawal RK, Alhasso A, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. Lancet. 2017 Sep 9;390(10099):1048–60.

21. Brunt AM, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. The Lancet [Internet]. 2020 May 23 [cited 2024 Dec 12];395(10237):1613–26. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30932-6/fulltext

22. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, et al. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med [Internet]. 2015 Jul 23 [cited 2024 Dec 11];373(4):307–16. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1415340

23. Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, et al. Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. N Engl J Med [Internet]. 2015 Jul 23 [cited 2024 Dec 11];373(4):317–27. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1415369

24. Poortmans PM, Weltens C, Fortpied C, Kirkove C, Peignaux-Casasnovas K, Budach V, et al. Internal mammary and medial supraclavicular lymph node chain irradiation in stage I–III breast cancer (EORTC 22922/10925): 15-year results of a randomised, phase 3 trial. The Lancet Oncology [Internet]. 2020 Dec [cited 2024 Dec 11];21(12):1602–10. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1470204520304721

25. Dodwell D, Taylor C, McGale P, Coles C, Duane F, Gray R, et al. Abstract GS4-02: Regional lymph node irradiation in early stage breast cancer: An EBCTCG meta-analysis of 13,000 women in 14 trials. Cancer Research [Internet]. 2019 Feb 15 [cited 2024 Dec 11];79(4_Supplement):GS4-02. Available from: https://doi.org/10.1158/1538-7445.SABCS18-GS4-02

26. Postoperative radiotherapy for breast cancer: UK consensus statements | The Royal College of Radiologists [Internet]. [cited 2024 Dec 11]. Available from: https://www.rcr.ac.uk/our-services/all-our-publications/clinical-oncology-publications/postoperative-radiotherapy-for-breast-cancer-uk-consensus-statements/

27. Early and locally advanced breast cancer diagnosi.pdf [Internet]. [cited 2024 Dec 11]. Available from: https://www.nice.org.uk/guidance/ng101/resources/early-and-locally-advanced-breast-cancer-diagnosis-and-management-pdf-66141532913605

28. Duane FK, McGale P, Teoh S, Mortimer C, Broggio J, Darby SC, et al. International Variation in Criteria for Internal Mammary Chain Radiotherapy. Clin Oncol (R Coll Radiol) [Internet]. 2019 Jul [cited 2024 Dec 11];31(7):453–61. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6575151/

29. Ranger A, Dunlop A, Hutchinson K, Convery H, Maclennan MK, Chantler H, et al. A Dosimetric Comparison of Breast Radiotherapy Techniques to Treat Locoregional Lymph Nodes Including the Internal Mammary Chain. Clin Oncol (R Coll Radiol). 2018 Jun;30(6):346–53.

30. Locke I, Drinkwater K. Implementation of Royal College of Radiologists Consensus Statements and National Institute for Health and Care Excellence Guidance: Breast Radiotherapy Practice in the UK. Clinical Oncology [Internet]. 2021 Jul 1 [cited 2024 Dec 11];33(7):419–26. Available from: https://www.sciencedirect.com/science/article/pii/S0936655521000406

31. Breast Cancer Now. Breast Cancer Now. [cited 2024 Dec 11]. Breast Cancer Statistics. Available from: https://breastcancernow.org/about-us/why-we-do-it/breast-cancer-facts-and-statistics/

32. Bornstein BA, Cheng CW, Rhodes LM, Rashid H, Stomper PC, Siddon RL, et al. Can simulation measurements be used to predict the irradiated lung volume in the tangential fields in patients treated for breast cancer? International Journal of Radiation Oncology*Biology*Physics [Internet]. 1990 Jan 1 [cited 2024 Dec 11];18(1):181–7. Available from: https://www.sciencedirect.com/science/article/pii/036030169090282O

33. Kong FM, Klein EE, Bradley JD, Mansur DB, Taylor ME, Perez CA, et al. The impact of central lung distance, maximal heart distance, and radiation technique on the volumetric dose of the lung and heart for intact breast radiation. International Journal of Radiation Oncology*Biology*Physics [Internet]. 2002 Nov 1 [cited 2024 Dec 11];54(3):963–71. Available from: https://www.sciencedirect.com/science/article/pii/S0360301602037410

34. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, et al. Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer. N Engl J Med [Internet]. 2013 Mar 14 [cited 2024 Dec 11];368(11):987–98. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1209825

35. Bartlett FR, Colgan RM, Donovan EM, Carr K, Landeg S, Clements N, et al. Voluntary Breath-hold Technique for Reducing Heart Dose in Left Breast Radiotherapy. J Vis Exp

[Internet]. 2014 Jul 3 [cited 2024 Dec 11];(89):51578. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4211647/

36. Bartlett FR, Yarnold JR, Donovan EM, Evans PM, Locke I, Kirby AM. Multileaf Collimation Cardiac Shielding in Breast Radiotherapy: Cardiac Doses are Reduced, But at What Cost? Clinical Oncology [Internet]. 2013 Dec 1 [cited 2024 Dec 11];25(12):690–6. Available from: https://www.sciencedirect.com/science/article/pii/S0936655513003373

37. Bartlett FR, Yarnold JR, Kirby AM. Breast Radiotherapy and Heart Disease — Where Are We Now? Clinical Oncology [Internet]. 2013 Dec 1 [cited 2024 Dec 11];25(12):687–9. Available from: https://www.sciencedirect.com/science/article/pii/S0936655513003075

38. Korreman SS, Pedersen AN, Josipović M, Aarup LR, Juhler-Nøttrup T, Specht L, et al. Cardiac and pulmonary complication probabilities for breast cancer patients after routine end-inspiration gated radiotherapy. Radiotherapy and Oncology [Internet]. 2006 Aug 1 [cited 2024 Dec 11];80(2):257–62. Available from: https://www.sciencedirect.com/science/article/pii/S0167814006003008

39. Stranzl H, Zurl B. Postoperative irradiation of left-sided breast cancer patients and cardiac toxicity. Does deep inspiration breath-hold (DIBH) technique protect the heart? Strahlenther Onkol. 2008 Jul;184(7):354–8.

40. Borst GR, Sonke JJ, den Hollander S, Betgen A, Remeijer P, van Giersbergen A, et al. Clinical results of image-guided deep inspiration breath hold breast irradiation. Int J Radiat Oncol Biol Phys. 2010 Dec 1;78(5):1345–51.

41. Vikström J, Hjelstuen MHB, Mjaaland I, Dybvik KI. Cardiac and pulmonary dose reduction for tangentially irradiated breast cancer, utilizing deep inspiration breath-hold with audio-visual guidance, without compromising target coverage. Acta Oncol. 2011 Jan;50(1):42–50.

42. Hayden AJ, Rains M, Tiver K. Deep inspiration breath hold technique reduces heart dose from radiotherapy for left-sided breast cancer. J Med Imaging Radiat Oncol. 2012 Aug;56(4):464–72.

43. poster-walsh-breast-estro-2015.pdf [Internet]. [cited 2024 Dec 11]. Available from: https://www.dynr.com/wp-content/uploads/2017/07/poster-walsh-breast-estro-2015.pdf

44. Eldredge-Hindy H, Lockamy V, Crawford A, Nettleton V, Werner-Wasik M, Siglin J, et al. Active Breathing Coordinator reduces radiation dose to the heart and preserves local control in patients with left breast cancer: report of a prospective trial. Pract Radiat Oncol. 2015;5(1):4–10.

45. Teoh M, Clark CH, Wood K, Whitaker S, Nisbet A. Volumetric modulated arc therapy: a review of current literature and clinical use in practice. Br J Radiol. 2011 Nov;84(1007):967–96.

46. Hoekstra N, Fleury E, Merino Lara TR, van der Baan P, Bahnerth A, Struik G, et al. Long-term risks of secondary cancer for various whole and partial breast irradiation techniques. Radiother Oncol. 2018 Sep;128(3):428–33.

47. Lapen K, Yamada Y. The Development of Modern Radiation Therapy. Curr Phys Med Rehabil Rep [Internet]. 2023 Jun 1 [cited 2024 Nov 13];11(2):131–8. Available from: https://doi.org/10.1007/s40141-023-00395-6

48. Ares C, Khan S, Macartain AM, Heuberger J, Goitein G, Gruber G, et al. Postoperative proton radiotherapy for localized and locoregional breast cancer: potential for clinically relevant improvements? Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3):685–97.

49. Jimenez RB, Goma C, Nyamwanda J, Kooy HM, Halabi T, Napolitano BN, et al. Intensity modulated proton therapy for postmastectomy radiation of bilateral implant reconstructed breasts: a treatment planning study. Radiother Oncol. 2013 May;107(2):213–7.

50. Stick LB, Lorenzen EL, Yates ES, Anandadas C, Andersen K, Aristei C, et al. PV-0046 Patient selection for proton therapy of early breast cancer - the DBCG phase II study strategy. Radiotherapy and Oncology [Internet]. 2019 Apr [cited 2024 Dec 11];133:S15–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0167814019304669

51. Settatree S, Dunlop A, Mohajer J, Brand D, Mooney L, Ross G, et al. What Can Proton Beam Therapy Achieve for Patients with Pectus Excavatum Requiring Left Breast, Axilla and Internal Mammary Nodal Radiotherapy? Clin Oncol (R Coll Radiol). 2021 Dec;33(12):e570–7.

52. Ashraf A. Radiopaedia. [cited 2024 Nov 13]. Severe pectus excavatum | Radiology Case | Radiopaedia.org. Available from: https://radiopaedia.org/cases/severe-pectus-excavatum

53. NHS England. NHS commissioning » Proton beam therapy [Internet]. [cited 2024 Nov 13]. Available from: https://www.england.nhs.uk/commissioning/spec-services/highly-spec-services/pbt/

54. proton-beam-therapy-clinical-commissioning-policy.pdf [Internet]. [cited 2024 Nov 13]. Available from: https://www.england.nhs.uk/wp-content/uploads/2020/10/proton-beam-therapy-clinical-commissioning-policy.pdf

55. 1787-Policy_Updated-policy.pdf [Internet]. [cited 2024 Nov 13]. Available from: https://www.england.nhs.uk/wp-content/uploads/2021/06/1787-Policy_Updated-policy.pdf

56. parable-protocol_v4-0-22feb2024_clean4c7d5ecb659564f3a772ff0000325351.pdf [Internet]. [cited 2024 Nov 13]. Available from: https://www.icr.ac.uk/media/docs/default-source/default-document-library/parable-protocol_v4-0-22feb2024_clean4c7d5ecb659564f3a772ff0000325351.pdf?sfvrsn=d6e83a69_0

57. Kirby AM, Haviland JS, Mackenzie M, Fleming H, Anandadas C, Wickers S, et al. Proton Beam Therapy in Breast Cancer Patients: The UK PARABLE Trial is Recruiting. Clinical Oncology [Internet]. 2023 Jun 1 [cited 2024 Nov 13];35(6):347–50. Available from: https://www.sciencedirect.com/science/article/pii/S0936655523000626

58. NHS England. Standard operatig procedure: Process for applying for proton beam therapy and subsequent treatment allocation for eligible patients. 2019 Mar;

59. Cohen J. Statistical power analysis for the behavioural sciences. 2nd ed. Hillsdale NJ: Lawrence Erlbaum Associates; 1988.

60. Pallant J. SPSS Survival manual. 5th ed. New York, NY: Open University Press; 2013.

61. Tang DD, Ye ZJ, Liu WW, Wu J, Tan JY, Zhang Y, et al. Survival feature and trend of female breast cancer: A comprehensive review of survival analysis from cancer registration data. Breast. 2024 Dec 15;79:103862.

62. National Institue for Health and Care Excellence. Early and locally advanced breast cancer: diagnosis and management. 2024;

63. multi-professionalframeworkforadvancedclinicalpracticeinengland.pdf [Internet]. [cited 2024 Dec 11]. Available from: https://www.hee.nhs.uk/sites/default/files/documents/multi-professionalframeworkforadvancedclinicalpracticeinengland.pdf

64. Lorenzen EL, Brink C, Taylor CW, Darby SC, Ewertz M. Uncertainties in estimating heart doses from 2D-tangential breast cancer radiotherapy. Radiother Oncol [Internet]. 2016 Apr [cited 2024 Dec 11];119(1):71–6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4871929/

65. Kong FM, Klein EE, Bradley JD, Mansur DB, Taylor ME, Perez CA, et al. The impact of central lung distance, maximal heart distance, and radiation technique on the volumetric dose of the lung and heart for intact breast radiation. International journal of radiation oncology, biology, physics [Internet]. 2002 Nov 1 [cited 2024 Dec 11];54(3):963–71. Available from: http://www.scopus.com/inward/record.url?scp=0036835101&partnerID=8YFLogxK

66. Hall EJ, Wuu CS. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. Int J Radiat Oncol Biol Phys. 2003 May 1;56(1):83–8.

67. Grantzau T, Overgaard J. Risk of second non-breast cancer after radiotherapy for breast cancer: A systematic review and meta-analysis of 762,468 patients. Radiotherapy and Oncology [Internet]. 2015 Jan [cited 2024 Dec 11];114(1):56–65. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0167814014004125

68. Morton LM, Gilbert ES, Hall P, Andersson M, Joensuu H, Vaalavirta L, et al. Risk of treatment-related esophageal cancer among breast cancer survivors. Ann Oncol [Internet]. 2012 Dec [cited 2024 Dec 11];23(12):3081–91. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3501231/

69. Zhang Q, Liu J, Ao N, Yu H, Peng Y, Ou L, et al. Secondary cancer risk after radiation therapy for breast cancer with different radiotherapy techniques. Sci Rep [Internet]. 2020 Jan 27 [cited 2024 Dec 12];10(1):1220. Available from: https://www.nature.com/articles/s41598-020-58134-z

70. Raphael MJ, Saskin R, Singh S. Association between Waiting Time for Radiotherapy after Surgery for Early-Stage Breast Cancer and Survival Outcomes in Ontario: A Population-Based Outcomes Study. Current Oncology [Internet]. 2020 May 1 [cited 2024 Nov 13];27(2):216–21. Available from: https://www.mdpi.com/1718-7729/27/2/5629

71. Wickers S, Thould C, Keeble J, Bodey R, Harsanyi C, Royle G, et al. Identifying Surrogates for Heart and Ipsilateral Lung Dose to Guide Field Placement and Treatment Modality Selection during Virtual Simulation of Breast Radiotherapy. Clinical Oncology [Internet]. 2021 Apr 1 [cited 2024 Nov 13];33(4):224–9. Available from: https://www.sciencedirect.com/science/article/pii/S0936655520304477

72. Franken NAP, Oei AL, Kok HP, Rodermond HM, Sminia P, Crezee J, et al. Cell survival and radiosensitisation: modulation of the linear and quadratic parameters of the LQ model (Review). Int J Oncol. 2013 May;42(5):1501–15.

73. Barnett GC, West CML, Dunning AM, Elliott RM, Coles CE, Pharoah PDP, et al. Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. Nat Rev Cancer. 2009 Feb;9(2):134–42.

74. Withers HR. Biological basis of radiation therapy for cancer. Lancet. 1992 Jan 18;339(8786):156–9.

75. Ray KJ, Sibson NR, Kiltie AE. Treatment of Breast and Prostate Cancer by Hypofractionated Radiotherapy: Potential Risks and Benefits. Clin Oncol (R Coll Radiol). 2015 Jul;27(7):420–6.

76. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013 Oct;14(11):1086–94.

77. Whelan TJ, Kim DH, Sussman J. Clinical experience using hypofractionated radiation schedules in breast cancer. Semin Radiat Oncol. 2008 Oct;18(4):257–64.

78. van Leeuwen CM, Oei AL, Crezee J, Bel A, Franken NAP, Stalpers LJA, et al. The alfa and beta of tumours: a review of parameters of the linear-quadratic model, derived from clinical radiotherapy studies. Radiation Oncology [Internet]. 2018 May 16 [cited 2024 Dec 12];13(1):96. Available from: https://doi.org/10.1186/s13014-018-1040-z

79. Appelt AL, Vogelius IR, Bentzen SM. Modern hypofractionation schedules for tangential whole breast irradiation decrease the fraction size-corrected dose to the heart. Clin Oncol (R Coll Radiol). 2013 Mar;25(3):147–52.

80. Borst GR, Ishikawa M, Nijkamp J, Hauptmann M, Shirato H, Bengua G, et al. Radiation pneumonitis after hypofractionated radiotherapy: evaluation of the LQ(L) model and different dose parameters. Int J Radiat Oncol Biol Phys. 2010 Aug 1;77(5):1596–603.

81. Withers HR, Thames HD, Peters LJ. A new isoeffect curve for change in dose per fraction. Radiother Oncol. 1983 Nov;1(2):187–91.

82. Aznar MC, Duane FK, Darby SC, Wang Z, Taylor CW. Exposure of the lungs in breast cancer radiotherapy: A systematic review of lung doses published 2010-2015. Radiother Oncol. 2018 Jan;126(1):148–54.

83. Lee BM, Chang JS, Kim SY, Keum KC, Suh CO, Kim YB. Hypofractionated Radiotherapy Dose Scheme and Application of New Techniques Are Associated to a Lower Incidence of Radiation Pneumonitis in Breast Cancer Patients. Front Oncol [Internet]. 2020 Feb 11 [cited 2024 Dec 12];10. Available from: https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2020.00124/full

84. Coronavirus disease (COVID-19) – World Health Organization [Internet]. [cited 2024 Dec 12]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019

85. Lillie PJ, Samson A, Li A, Adams K, Capstick R, Barlow GD, et al. Novel coronavirus disease (Covid-19): The first two patients in the UK with person to person transmission. J Infect. 2020 May;80(5):578–606.

86. Wider Impacts of COVID-19 [Internet]. [cited 2024 Dec 12]. Available from: https://analytics.phe.gov.uk/apps/covid-19-indirect-effects/

87. Brunt AM, Wheatley D, Yarnold J, Somaiah N, Kelly S, Harnett A, et al. Acute skin toxicity associated with a 1-week schedule of whole breast radiotherapy compared with a standard 3-week regimen delivered in the UK FAST-Forward Trial. Radiother Oncol. 2016 Jul;120(1):114–8.

88. guidelines-for-breast-rt-during-covid-19_rcr_v2.pdf [Internet]. [cited 2024 Dec 12]. Available from: https://associationofbreastsurgery.org.uk/media/ihpe1ekf/guidelines-for-breast-rt-during-covid-19_rcr_v2.pdf

89. Coles CE, Aristei C, Bliss J, Boersma L, Brunt AM, Chatterjee S, et al. International Guidelines on Radiation Therapy for Breast Cancer During the COVID-19 Pandemic. Clin Oncol (R Coll Radiol). 2020 May;32(5):279–81.

90. Yumpu.com. yumpu.com. [cited 2024 Dec 12]. Planning Pack for the FAST-Forward Trial. Available from: https://www.yumpu.com/en/document/view/3824248/planning-pack-for-the-fast-forward-trial

91. Piroth MD, Baumann R, Budach W, Dunst J, Feyer P, Fietkau R, et al. Heart toxicity from breast cancer radiotherapy : Current findings, assessment, and prevention. Strahlenther Onkol. 2019 Jan;195(1):1–12.

92. M. Bentzen, J. Z. Skoczylas, J. Ber S. Quantitative clinical radiobiology of early and late lung reactions. International Journal of Radiation Biology [Internet]. 2000 Jan [cited 2024 Dec 12];76(4):453–62. Available from: http://www.tandfonline.com/doi/full/10.1080/095530000138448

93. Glatstein E. The omega on alpha and beta. Int J Radiat Oncol Biol Phys. 2011 Oct 1;81(2):319–20.

94. Joiner MC, Kogel A van der. Basic Clinical Radiobiology. 4th ed. London: CRC Press; 2009. 375 p.

95. Veronesi U, Saccozzi R, Del Vecchio M, Banfi A, Clemente C, De Lena M, et al. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. N Engl J Med. 1981 Jul 2;305(1):6–11.

96. START Trialists' Group, Bentzen SM, Agrawal RK, Aird EGA, Barrett JM, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol. 2008 Apr;9(4):331–41.

97. START Trialists' Group, Bentzen SM, Agrawal RK, Aird EGA, Barrett JM, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet. 2008 Mar 29;371(9618):1098–107.

98. Chatterjee S, Chakraborty S, HYPORT Adjuvant Author Group. Hypofractionated radiation therapy comparing a standard radiotherapy schedule (over 3 weeks) with a novel 1-week schedule in adjuvant breast cancer: an open-label randomized controlled study (HYPORT-Adjuvant)-study protocol for a multicentre, randomized phase III trial. Trials. 2020 Sep 30;21(1):819.

99. Yarnold J, Haviland J. Hypofractionated adjuvant whole breast radiotherapy: progress and prospects. Acta Oncol. 2010 Nov;49(8):1288–92.

100. Tsang Y, Ciurlionis L, Kirby AM, Locke I, Venables K, Yarnold JR, et al. Clinical impact of IMPORT HIGH trial (CRUK/06/003) on breast radiotherapy practices in the United Kingdom. Br J Radiol [Internet]. 2015 Dec [cited 2024 Dec 13];88(1056):20150453. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4984937/

101. Boyages J, Baker L. Evolution of radiotherapy techniques in breast conservation treatment. Gland Surg [Internet]. 2018 Dec [cited 2024 Sep 18];7(6):576–95. Available from: http://gs.amegroups.com/article/view/22840/22074

102. Ginzton EL, Nunan CS. History of microwave electron linear accelerators for radiotherapy. International Journal of Radiation Oncology*Biology*Physics [Internet]. 1985 Feb [cited 2024 Sep 18];11(2):205–16. Available from: https://linkinghub.elsevier.com/retrieve/pii/0360301685901415

103. Zenger, I [Internet]. [cited 2024 Sep 19]. Available from: https://www.medmuseum.siemens-healthineers.com/en/stories-from-the-museum/pioneers-of-radiotherapy

104. Thwaites DI, Tuohy JB. Back to the future: the history and development of the clinical linear accelerator. Phys Med Biol [Internet]. 2006 Jul 7 [cited 2024 Sep 19];51(13):R343–62. Available from: https://iopscience.iop.org/article/10.1088/0031-9155/51/13/R20

105. Harris JR. Fifty Years of Progress in Radiation Therapy for Breast Cancer. American Society of Clinical Oncology Educational Book [Internet]. 2014 May [cited 2024 Sep 18];(34):21–5. Available from: https://ascopubs.org/doi/10.14694/EdBook_AM.2014.34.21

106. Radiotherapy data [Internet]. [cited 2024 Sep 18]. Available from: https://nhsd-ndrs.shinyapps.io/rtds_episodes_and_attendances/

107. Gardner A, Bagshaw MA, Page V, Karzmark CJ. Tumor localization, dosimetry, simulation and treatment procedures in radiotherapy: the isocentric technique. American Journal of Roentgenology [Internet]. 1972 Jan [cited 2024 Sep 18];114(1):163–71. Available from: https://ajronline.org/doi/10.2214/ajr.114.1.163

108. Hutchings RE. “Invisible” field skin marking on radiotherapy patients. BJR [Internet]. 1986 Nov [cited 2024 Sep 18];59(707):1135–1135. Available from: https://academic.oup.com/bjr/article/59/707/1135/7442396

109. Townend C, Landeg S, Thorne R, Kirby AM, McNair HA. A review of permanent marking for radiotherapy in the UK. Radiography [Internet]. 2020 Feb [cited 2024 Sep 18];26(1):9–14. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1078817419301142

110. Naidoo W, Leech M. Feasibility of surface guided radiotherapy for patient positioning in breast radiotherapy versus conventional tattoo-based setups- a systematic review. Technical Innovations & Patient Support in Radiation Oncology [Internet]. 2022 Jun [cited 2024 Sep 18];22:39–49. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2405632422000105

111. Rigley J, Robertson P, Scattergood L. Radiotherapy without tattoos: Could this work? Radiography [Internet]. 2020 Nov [cited 2024 Oct 1];26(4):288–93. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1078817420300171

112. Wickers S, Taylor RM, Royle G, Gaze MN. Permanent Indian ink tattoos for breast cancer radiotherapy: A United Kingdom study of the emotional impact on patients following radiotherapy. Radiography [Internet]. 2024 Aug 30 [cited 2024 Oct 11]; Available from: https://www.sciencedirect.com/science/article/pii/S1078817424002025

113. Jumeau R, Péguret N, Zulliger C, Moeckli R, Bourhis J, Ozsahin EM. Optimization of re-irradiation using deformable registration: a case study. BJR Case Rep [Internet]. 2016 May 6 [cited 2024 Sep 19];2(2):20150412. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6180895/

114. Hall DE, Prochazka AV, Fink AS. Informed consent for clinical treatment. CMAJ [Internet]. 2012 Mar 20 [cited 2024 Oct 2];184(5):533–40. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3307558/

115. Clow B, Allen J. Psychosocial impacts of radiation tattooing for breast cancer patients: A critical review. Canadian Woman Studies. 2010;28(2–3):46–52.

116. Probst H, Dodwell D, Gray JC, Holmes M. An evaluation of the accuracy of semi-permanent skin marks for breast cancer irradiation. Radiography [Internet]. 2006 Aug [cited 2024 Sep 18];12(3):186–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1078817405001094

117. Landeg SJ, Kirby AM, Lee SF, Bartlett F, Titmarsh K, Donovan E, et al. A randomized control trial evaluating fluorescent ink versusdark ink tattoos for breast radiotherapy. The British Journal of Radiology [Internet]. 2016 Dec 1 [cited 2024 Sep 18];89(1068):20160288. Available from: https://academic.oup.com/bjr/article/doi/10.1259/bjr.20160288/7445889

118. Lim LH, Pang EPP, Sultana R, Kusumawidjaja G, Wong RX, Yeo RMC, et al. A Prospective Randomized Controlled Trial to Compare the Use of Conventional Dark-Ink Tattoo and Ultraviolet-Ink Tattoo for Patients Undergoing Breast Radiation Therapy. Practical Radiation Oncology [Internet]. 2021 Nov [cited 2024 Sep 18];11(6):463–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1879850021002095

119. Wickers S, Probst, H, Julken-Anderson, N, Harris, R. Safer Radiotherapy Guest Editorial. Radiotherapy alignment tattoos with Indian tattoo ink: Time for challenge and change? [Internet]. 2023. Available from: https://www.ukhsa-protectionservices.org.uk/cms/assets/gfx/content/resource_5339cs2ba61cc3a8.pdf

120. Development of learning from radiotherapy errors.pdf [Internet]. [cited 2024 Sep 18]. Available from: https://assets.publishing.service.gov.uk/media/5a7f4a80e5274a2e87db4f51/DL_guidance_finalNB211216.pdf

121. Malvezzi M, Carioli G, Bertuccio P, Boffetta P, Levi F, La Vecchia C, et al. European cancer mortality predictions for the year 2019 with focus on breast cancer. Annals of Oncology [Internet]. 2019 May [cited 2024 Sep 19];30(5):781–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0923753419311561

122. Breast Cancer Now [Internet]. [cited 2024 Sep 19]. Available from: https://breastcancernow.org/sites/default/files/breast_cancer_facts_and_figures_-_final.pdf

123. Macmillan Cancer Support [Internet]. [cited 2024 Sep 19]. Available from: https://www.macmillan.org.uk/cancer-information-and-support/treatment

124. Moser T, Creed M, Walker R, Meier G. Radiotherapy tattoos: Women's skin as a carrier of personal memory—What do we cause by tattooing our patients? Breast J [Internet]. 2020 Feb [cited 2024 Sep 19];26(2):316–8. Available from: https://onlinelibrary.wiley.com/doi/10.1111/tbj.13591

125. Freislederer P, Kügele M, Öllers M, Swinnen A, Sauer TO, Bert C, et al. Recent advances in Surface Guided Radiation Therapy. Radiation Oncology [Internet]. 2020 Jul 31 [cited 2024 Oct 1];15(1):187. Available from: https://doi.org/10.1186/s13014-020-01629-w

126. Beer KT. Introduction of SGRT in clinical practice. Technical Innovations & Patient Support in Radiation Oncology [Internet]. 2022 Mar [cited 2024 Oct 1];21:27–30. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2405632422000038

127. Mueller B, Song Y, Chia-Ko W, Hsu HY, Zhai X, Tamas P, et al. Accuracy and Efficiency of Patient Setup Using Surface Imaging versus Skin Tattoos for Accelerated Partial Breast Irradiation. Adv Radiat Oncol [Internet]. 2023 Jan 26 [cited 2024 Oct 1];8(3):101183. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9991531/

128. Batista V, Gober M, Moura F, Webster A, Oellers M, Ramtohul M, et al. Surface guided radiation therapy: An international survey on current clinical practice. Tech Innov Patient Support Radiat Oncol [Internet]. 2022 Mar 30 [cited 2024 Oct 1];22:1–8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8984757/

129. Wurstbauer K, Sedlmayer F, Kogelnik HD. Skin markings in external radiotherapy by temporary tattooing with henna: Improvement of accuracy and increased patient comfort. International Journal of Radiation Oncology*Biology*Physics [Internet]. 2001 May [cited 2024 Sep 18];50(1):179–81. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0360301601014390

130. Breast Cancer Now. Breast Cancer Now. [cited 2024 Oct 1]. Breast Cancer Now: Who we are. Available from: https://breastcancernow.org/about-us/who-we-are/

131. Cohen J. Statistical power analysis for the behavioral sciences. 2. ed., reprint. New York, NY: Psychology Press; 2009. 567 p.

132. Corden A, Sainsbury R. Exploring 'Quality': research participants' perspectives on verbatim quotations. International Journal of Social Research Methodology. 2006 Apr;9(2):97–110.

133. FitzpatrickSkinType.pdf [Internet]. [cited 2024 Oct 1]. Available from: https://www.arpansa.gov.au/sites/default/files/legacy/pubs/RadiationProtection/FitzpatrickSkinType.pdf

134. University College London Hospitals NHS Foundation Trust [Internet]. [cited 2024 Oct 4]. Series No 2 - Radiotherapy to the Breast. Available from: https://www.uclh.nhs.uk/patients-and-visitors/patient-information-pages/series-no-2-radiotherapy-breast

135. rcr-breast-cancer-radiotherapy-consent-form.pdf [Internet]. [cited 2024 Oct 4]. Available from: https://www.rcr.ac.uk/media/ajnh3df2/rcr-breast-cancer-radiotherapy-consent-form.pdf

136. Shimizu-Niwa M, Suzuki J, Matsunaga T, Komori M. Evaluation of the clinical implementation of a tattoo-free positioning technique in breast cancer radiotherapy using ExacTrac. Physica Medica [Internet]. 2022 Jun [cited 2024 Sep 18];98:81–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1120179722019706

137. The Medical Devices (Amendment) (Great Britain) Regulations 2023.

138. BIOTIC Phocea [Internet]. [cited 2024 Oct 4]. RADSAFE® - Marking in Radiotherapy. Available from: https://www.biotic.fr/en/33-radsafe-marking-in-radiotherapy

139. Ho BK, Robinson JK. Color bar tool for skin type self-identification: A cross-sectional study. Journal of the American Academy of Dermatology [Internet]. 2015 Aug [cited 2024 Oct 1];73(2):312-313.e1. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0190962215017235

140. Black Women Rising. Black Women Rising. [cited 2024 Oct 1]. Black Women Rising, About Us. Available from: https://www.blackwomenrisinguk.org/about-us

141. Okyere, Pamela. A nurse's comment about my breast cancer confirmed all my suspicions | Metro News [Internet]. 2024 [cited 2024 Oct 1]. Available from: https://metro.co.uk/2024/08/24/breast-cancer-journey-a-constant-battle-adequate-treatment-21412925/

142. Becker S, Proctor M, Cassisi JE. The Application of Medical Tattooing in Cosmetic Breast Surgery. Plast Reconstr Surg Glob Open [Internet]. 2022 Apr 15 [cited 2024 Oct 11];10(4):e4272. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10106240/

143. Finishing Touches Group [Internet]. [cited 2024 Oct 11]. Medical Micropigmentation Training Course. Available from: https://www.finishingtouchesgroup.com/pages/medical-micropigmentation-training

144. Uscher, Jen. Breast Cancer Now. [cited 2024 Oct 11]. Nipple Tattoos or Nipple Reconstruction: Which Is Best for You? Available from: https://www.breastcancer.org/treatment/surgery/breast-reconstruction/types/nipple-reconstruction-tattoos

145. Finishing Touches Group [Internet]. [cited 2024 Oct 11]. Areola Pigments. Available from: https://www.finishingtouchesgroup.com/collections/areola-pigments

146. Biotic Phocea. BIOTIC Phocea. [cited 2024 Oct 11]. ICONIC COLLECTION Areola & Skin Palette. Available from: https://www.biotic.fr/en/areolas-and-scars/90-areola-skin-pigments-iconic-palette-truly-reach.html

147. Cosmetic tattooing following breast reconstruction surgery.pdf [Internet]. [cited 2024 Oct 11]. Available from: https://www.wwl.nhs.uk/media/.leaflets/6225dd4d17b370.00019052.pdf

148. Levites HA, Fourman MS, Phillips BT, Fromm IM, Khan SU, Dagum AB, et al. Modeling Fade Patterns of Nipple Areola Complex Tattoos Following Breast Reconstruction. Annals of Plastic Surgery [Internet]. 2014 Dec [cited 2024 Oct 11];73:S153. Available from:

https://journals.lww.com/annalsplasticsurgery/fulltext/2014/12001/modeling_fade_patterns_of_nipple_areola_complex.8.aspx

149. Flood AB, Wood VA, Swartz HM. Using India Ink as a Sensor for Oximetry: Evidence of its Safety as a Medical Device. Adv Exp Med Biol [Internet]. 2017 [cited 2024 Oct 11];977:297–312. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5973822/

150. Medical Device Regulation [Internet]. [cited 2024 Oct 11]. Available from: https://www.gov.uk/guidance/regulating-medical-devices-in-the-uk

151. European Chemicals Agency [Internet]. [cited 2024 Oct 11]. Available from: https://echa.europa.eu/hot-topics/tattoo-inks

152. Biotic Phocea RadSafe Inks [Internet]. [cited 2024 Oct 4]. Available from: https://www.biotic.fr/en/33-radsafe-marking-in-radiotherapy

153. College of Radiographers. CoRIPS | CoR [Internet]. [cited 2024 Nov 1]. Available from: https://www.collegeofradiographers.ac.uk/research-grants-and-funding/corips

154. Lane et al. - 2022 - MRC: Short Guide: Trial Steering Committees (TSCs).pdf [Internet]. [cited 2024 Nov 5]. Available from: https://www.ukri.org/wp-content/uploads/2022/03/MRC-170322-ShortGuideTrialSteeringCommittees.pdf

155. Health Research Authority. Health Research Authority. [cited 2024 Nov 5]. Roles and responsibilities. Available from: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/roles-and-responsibilities/

156. GOV.UK. Clinical investigations guidance - GOV.UK [Internet]. [cited 2024 Nov 5]. Available from: https://www.gov.uk/guidance/notify-mhra-about-a-clinical-investigation-for-a-medical-device#how-to-notify-the-mhra-of-your-clinical-investigation

157. Riva JJ, Malik KM, Burnie SJ, Endicott AR, Busse JW. What is your research question? An introduction to the PICOT format for clinicians. The Journal of the Canadian Chiropractic Association [Internet]. 2012 Sep [cited 2024 Nov 8];56(3):167. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3430448/

158. Sealed Envelope | Randomisation [Internet]. [cited 2024 Nov 5]. Available from: https://www.sealedenvelope.com/randomisation/

159. On target: ensuring geometric accuracy in radiotherapy.

160. Ho_Robinson_2015_Color bar tool for skin type self-identification.pdf.

161. Ward WH, Lambreton F, Goel N, Yu JQ, Farma JM. TABLE 1, Fitzpatrick Classification of Skin Types I through VI [Internet]. Codon Publications; 2017 [cited 2024 Nov 6]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK481857/table/chapter6.t1/

162. Ho BK, Robinson JK. Color bar tool for skin type self-identification: A cross-sectional study. J Am Acad Dermatol. 2015 Aug;73(2):312-313.e1.

163. Probst H, Reed H, Stanton A, Simpson RM, Walters SJ, Simpson H, et al. A Randomised Clinical Feasibility Trial of a Breast Immobilisation Device: The SuPPORT 4 All Bra. Clinical Oncology [Internet]. 2023 Dec [cited 2024 Nov 6];35(12):801–10. Available from: https://linkinghub.elsevier.com/retrieve/pii/S093665552300328X

164. Holden RJ, Karsh BT. The technology acceptance model: its past and its future in health care. J Biomed Inform. 2010 Feb;43(1):159–72.

165. Health Research Authority. Health Research Authority. [cited 2024 Nov 7]. Good Clinical Practice. Available from: https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/good-clinical-practice/

166. Venugopalan HN, Moinuddin S, Simoes R, Wickers S. 1394: Introduction of kV corrective imaging protocol for breast radiotherapy. Radiotherapy and Oncology [Internet]. 2024 May [cited 2024 Nov 7];194:S5541–2. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0167814024017997

167. Pallant J. SPSS Survival Manual: A Step By Step Guide to Data Analysis Using SPSS Program. 6th ed. London: McGraw-Hill Education; 2016.

168. Finishing Touches Group [Internet]. 2024 [cited 2024 Nov 12]. Micropigmentation Training & Product Supplies. Available from: https://www.finishingtouchesgroup.com/

169. Andrews E, Nair HKR, Pearson J, Dhoonmoon L, Wijeyaratne M, Waheed M, et al. Wound care and skin tone: Signs, symptoms and terminology for all skin tones – Wounds International [Internet]. 2023 [cited 2024 Nov 12]. Available from: https://woundsinternational.com/consensus-documents/wound-care-and-skin-tone-signs-symptoms-and-terminology-for-all-skin-tones/

170. Radiotherapy skin reactions: what they are and how to spot them in different skin tones [Internet]. 2024 [cited 2024 Nov 12]. Available from: https://www.flenhealth.co.uk/news/radiotherapy-skin-reactions-what-they-are-and-how-to-spot-them-in-different-skin-tones/radiotherapy-skin-reactions-what-they-are-and-how-to-spot-them-in-different-skin-tones

171. Julka-Anderson - Equity with Radiation Induced Reaction Assessment.pdf [Internet]. [cited 2024 Dec 13]. Available from: https://rmpartners.nhs.uk/wp-content/uploads/2024/04/Equity-with-Radiation-Induced-Reaction-Assessment.pdf

172. GOV.UK [Internet]. 2024 [cited 2024 Oct 11]. Regulating medical devices in the UK. Available from: https://www.gov.uk/guidance/regulating-medical-devices-in-the-uk