

Radiation-induced fibrosis in breast cancer: A protocol for an observational cross-sectional pilot study for personalised risk estimation and objective assessment

Norman R. Williams^{a,d,*}, Sarah Williams^b, Muholan Kanapathy^{c,d}, Naghmeh Naderi^{c,d}, Vasileios Vavourakis^e, Afshin Mosahebi^{c,d}

^a Surgical & Interventional Trials Unit, University College London, UK

^b Division of Plastic Surgery, Charing Cross Hospital, Fulham Palace Road, London, UK

^c Division of Plastic Surgery, Royal Free Hospital, Pond Street, Hampstead, London, UK

^d UCL Division of Surgery and Interventional Science, University College London, London, UK

^e Department of Mechanical & Manufacturing Engineering, University of Cyprus, Nicosia, Cyprus

ARTICLE INFO

Article history:

Received 23 December 2018

Received in revised form 5 February 2019

Accepted 11 February 2019

Available online 13 February 2019

Keywords:

Breast cancer

Radiation induced fibrosis

Radiation therapy

Predictive model

ABSTRACT

Introduction: About 30% of patients request breast reconstruction following surgery for breast cancer, but radiation therapy negatively influences the outcome. Post-reconstruction radiotherapy is associated with more complications, including more severe capsular contracture and inferior cosmetic results. In general, less fibrosis is seen if autologous reconstruction is performed after radiotherapy, so surgeons will often delay reconstruction until after radiotherapy is complete. Drawbacks to this approach include additional surgery, recuperation, cost, and an extended reconstructive process. Randomised clinical trials are required to determine the best approach.

Methods and analysis: The aim of this cross-sectional pilot study is to see if it is feasible to recruit women, and gather the required data. This information will be used to design a subsequent, larger study whose aim is to identify factors that increase the risk of radiation-induced fibrosis, and use these to develop a personalised risk-prediction tool, to enable the clinician and patient to have a more informed discussion when treatment for breast cancer is being discussed. Identification of the risk factors will also enable the development of methods to minimise the risk, which would have applications in other medical conditions where fibrosis is a problem. In addition, the project will develop objective methods of assessing fibrosis, and will determine the psychological and economic impacts that fibrosis has affected individuals. A better understanding of the long-term effects of radiotherapy on normal tissues such as the heart and lungs may also have applications in other medical conditions where fibrosis is a problem.

Ethics and dissemination: The study has been submitted for ethical approval (REC reference). Findings will be made available to patients and clinicians through presentations at national and international meetings, peer-reviewed publications, social media and patient support groups.

Trial registration: Registered on ClinicalTrials.gov (after REC approval).

Crown Copyright © 2019 Published by Elsevier Ltd on behalf of Surgical Associates Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Strengths and limitations

- This study will establish feasibility, assess patient acceptability, and inform the design of a randomised clinical trial to answer the question of the best approach to take when planning reconstructive surgery.

- The clinical team will work with engineers to develop an objective measure of radiation-induced fibrosis.
- Objective methods alone may not capture the full extent of radiation-induced fibrosis.
- Patient reported outcome measures will be included to provide a more comprehensive assessment of the effects of radiation-induced fibrosis.

* Corresponding author at: Surgical & Interventional Trials Unit (SITU), UCL Division of Surgery & Interventional Science, 3rd Floor, Charles Bell House, 43–45 Foley Street, London W1W 7JN, UK.

E-mail address: norman.williams@ucl.ac.uk (N.R. Williams).

1. Introduction

1.1. Context

Breast cancer is the most common cancer to affect women in Europe, having a lifetime risk of 1 in 9. It is an increasingly treatable disease, and 10-year survival now exceeds 80%. The primary treatment for breast cancer is surgery, which is often used in conjunction with adjuvant therapies such as radiotherapy. Given the high breast cancer survival rate, an increasing number of women will live for many years with the consequences of their surgical and therapeutic treatment [1].

Women who receive radiation therapy as part of their treatment for breast cancer are at risk of late side-effects including radiation-induced fibrosis. This is an irreversible condition where there is an excessive formation of fibrous connective tissue which causes structural and functional changes. Fibrosis of the breast can cause hardening; if severe, the breast can become noticeably smaller and firmer. Fibrosis of the lung can cause a dry cough or shortness of breath. Fibrosis of heart tissue can cause serious problems, including heart failure. These problems can adversely impact the physical, psychological, social and economic well-being of an individual.

Approximately 30% of patients request breast reconstruction following breast cancer surgery [2]. It is generally accepted that radiation negatively influences the outcome of reconstruction in relation to late complications and aesthetic outcome [3]. Advances in multimodality treatments and subsequent significant improvements in survival impose greater expectations from patients on the quality of their aesthetic surgical outcome. Several studies advocate avoidance of post-reconstruction radiotherapy due to higher prevalence of complications, unpredictable volume loss, and unsatisfactory aesthetic outcomes [4,5]. Post-reconstruction radiotherapy is associated with more complications, including more severe capsular contracture and inferior cosmetic results, in implant-based compared to autologous reconstruction [6,7], which can be successful, although patients with specific risk factors, such as diabetes mellitus and smoking, should be aware of increased complication rates [8]. In general, less fibrosis is seen if autologous reconstruction is performed after radiation therapy [9], so surgeons will often delay reconstruction until after radiation therapy is complete. Drawbacks to this approach include additional surgery and an extended reconstructive process.

1.2. Preliminary work

The commonly reported incidence of radiation-induced fibrosis (RIF) is 10–15% [10], although 23% has been reported [11]. Manifestations of RIF in the breast may result in pain and cosmetic deformities. 41–45% of patients with fibrosis experience breast pain. Furthermore, the severity of fibrosis is directly related to the degree of morbidity, ranging from mild skin changes such as firmness on palpation to severe handicapping sclerosis many years after radiation exposure [12]. The development of radiation-induced fibrosis is influenced by multiple factors, including the radiation dose and area, fractionation schedule, previous or concurrent treatments, genetic susceptibility, and comorbidities [13,14]. RIF can significantly impact patients' quality of life. Understanding the mechanisms of RIF-induced changes is essential to developing effective strategies to prevent long-term disability and discomfort following radiotherapy.

1.3. Study aims and outcomes

The aim of the RIF cross-sectional pilot study is to see if it is feasible to recruit women, and gather the required data. This

information will be used to design a subsequent, larger study whose aim is to identify factors that increase the risk of radiation-induced fibrosis, and use these to develop a personalised risk-prediction tool, to enable the clinician and patient to have a more informed discussion when treatment for breast cancer is being discussed. Identification of the risk factors will also enable the development of methods to minimise the risk, which would have applications in other medical conditions where fibrosis is a problem. In addition, the RIF project will develop objective methods of assessing fibrosis, and will determine the psychological and economic impacts that fibrosis has affected individuals.

Most of the data used in the project will be readily available from the patients' medical notes and assessments made during routine standard of care (e.g. MRI and other images; information about the tumour size, location, type; etc.). Study-specific assessments will include 2D and 3D imaging of the unclothed torso, and self-completed questionnaires.

The objective assessments of outcome will eventually enable standardisation over time and across geographic locations. The psychological and economic assessments will empower patients to appreciate the impact that this side effect may have on their life outside of hospital.

2. Methods and design

2.1. Study design

This is a cross-sectional observational study on a cohort of women who have completed treatment for early breast cancer more than one year ago (no upper time limit).

2.2. Setting

This study will take place at a single site (Royal Free Hospital, London, UK) in 2019 and 2020. All patient-specific research activities and data collection will be completed in less than one day; there will be no follow-up investigations.

2.3. Participants

See Fig. 1. Suitable patients will be identified from the hospital notes (paper and electronic). The patient will then be approached by a member of the team and the RIF study discussed with her. If she is still interested, the patient will be given an information leaflet and consent form to read and discuss with family and friends. Once the patient provides written informed consent she will be deemed a participant in the study, although participation can be terminated at any time by the patient with no adverse impact on her care.

2.4. Eligibility criteria

2.4.1. Inclusion criteria

- Women who have undergone breast surgery for early breast cancer (with or without reconstruction) and received radiotherapy more than one year ago (no upper limit).
- Written informed consent obtained.

2.4.2. Exclusion criteria

- Unable to provide written informed consent.
- Younger than 18 years.
- Benign breast disease.

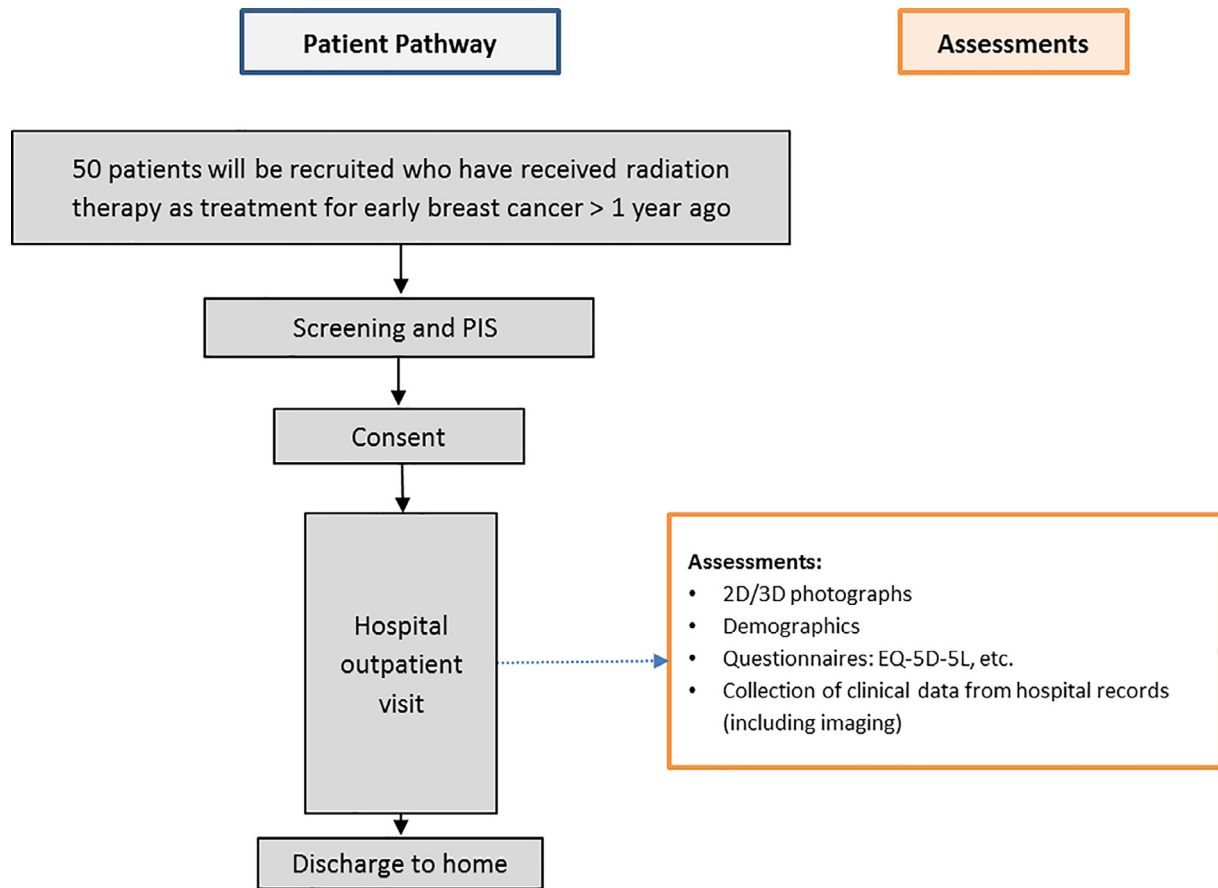


Fig. 1. Study Flow Chart.

2.5. Sample size

No formal sample size calculations have been performed for this pilot study. A sample size of 50 patients is considered sufficient to determine if patients can be recruited to a larger study in a reasonable period of time, and to determine if a complete set of data can be obtained on each patient, including the completion of all questionnaires. In addition, analysis of the data will enable estimation of the statistical power of a larger study designed with 90% power and two-sided 5% significance with a small standardised effect size [21].

2.6. Consent

The Patient Information Leaflet will be given to the patient during the recruitment process. Written informed consent will then be obtained using the consent form which will also be signed by the physician who explained the study to the patient. A copy of the consent form will be retained in site file, and a record of the consent process made in the patient's hospital notes.

2.7. Interventions & outcomes

After consent, each study patient will have the following assessments and interventions, including height, weight, and bra and cup size recorded by a member of the clinical team. The estimated time taken for photography and questionnaire completion is about 50 min. This will take place once per patient; there will be no follow-up.

2.7.1. Questionnaires

See Table 1.

2.7.2. Images

Each subject will have anonymised 2D (digital SLR) and 3D images taken of her unclothed torso (neck to navel) at various angles according to a pre-specified protocol.

Table 1
Patient-reported outcomes.

Questionnaire	Explanation
EQ-5D-5L	A standardised instrument developed by the EuroQol Group (https://euroqol.org/eq-5d-instruments/) as a measure of health-related quality of life used in a wide range of health conditions and treatments.
EORTC-QLQ-C30 & BR23	Developed in 1988, consists of a core generic questionnaire associated with the breast cancer specific module (https://eprovide.mapi-trust.org/instruments/eortc-quality-of-life-questionnaire-core-questionnaire).
ASI-R (composed of SES and MS subscales)	Appearance Schemas Inventory-Revised (ASI-R) is a 20-item measure with two subscales to measure cognitive-behavioural investment in one's own appearance—Self-Evaluative Salience (12 items) and Motivational Salience (8 items) (http://www.body-images.com/assessments/)
The Body Image Scale (Hopwood)	A short (10-item) body image scale (BIS) for use in clinical trials. (Hopwood et al. (2001) Eur J Cancer. 37(2):189–97)
Travel Questionnaire	A non-validated questionnaire asking about patient travel to hospital, for health care resource purposes.
Participation Questionnaire	A non-validated questionnaire asking about patient experience in the way study information was presented.

2.7.3. Outcome measures

The primary objective is to determine the rate at which eligible women can be identified and recruited into the study.

The secondary objective is to determine if it is feasible and acceptable to patients to gather the required clinical data, including 2D and 3D imaging and health-related quality of life questionnaires.

2.8. Participant withdrawal

If a participant, who has given informed consent, loses capacity to consent during the study, she will be withdrawn from the study. Identifiable data already collected with consent would be retained and used in the study. Participants who stop the study early will be replaced to maintain the sample size.

2.9. Patient and public involvement

The aim of this study is to see if it is feasible to collect the data, and if patients are happy with the assessments. If successful, there will be extensive public and participant involvement to assist in the design of a larger subsequent study.

2.10. Data collection

All data will be handled in accordance with the Data Protection Act 1998. The Case Report Forms (CRFs) will not bear the participant's name or other directly identifiable data. The participant's study identification number will be used for identification. The Staff Delegation of Responsibilities Log will identify all trial personnel responsible for data collection, entry, handling and managing the database. The data custodian for this study is the Chief Investigator (CI, Afshin Mosahebi).

2.11. Statistical analyses

No formal analysis of the primary outcome measure will be undertaken. Most of the analyses will be descriptive; continuous variables will be summarised using the mean, standard deviation, median, and interquartile range; categorical variables will be summarised as frequencies and proportions; all estimates will include confidence intervals. Data will be transformed if required.

Recruitment rate will be calculated as number of participants providing written informed consent divided by the time period. Numbers of patients recruited per month will be tabulated.

The completeness of data obtained from each patient will be estimated from the data actually obtained divided by the data expected to be obtained; this will be broken down into data source types (e.g. photographs, questionnaires, etc.).

Details of the number of eligible patients will be collected sufficient for the completion of a CONSORT diagram (<http://www.consort-statement.org/>).

A Statistical Analysis Plan (SAP) will be drafted and agreed before the first analysis. Any deviation(s) from the agreed plan will be described and justified.

2.12. Sources of bias

Sufficient information on all eligible patients will be collected to populate the CONSORT diagram; this will enable a description of the characteristics of the cohort in this population-based study, in order to determine if there had been selection bias, and to gauge the extent of non-response bias and volunteer bias. Use of objective measures will minimise ascertainment bias, but the patient-reported questionnaires will undoubtedly be prone to response

bias. Estimates of these biases will be invaluable for the design of a randomised clinical trial.

2.13. Study organisation and administration

The Study Management Group (SMG) will be responsible for the day-to-day management of the study, and will include the CI, Clinical Co-investigator, and statistician. The role of the group is to monitor all aspects of the conduct and progress of the study, ensure that the protocol is adhered to and take appropriate action to safeguard participants.

Members of the SMG will sign a Terms of Reference document that will specify elements such as composition of the group/quorum requirements, how meetings are convened and conducted, who is responsible for providing the group with information, etc.

2.14. Ethics and dissemination

The study has been submitted for ethical approval from the Research Ethics Committee (REC reference). The results of the study will be published in peer-reviewed publications and will be presented at relevant national and international conferences.

2.15. Availability of data

The SMG will control the final study dataset and any requests for access must adhere to the current SMG data sharing policy. The protocol, sample case report forms and participant information are available on upon request to the corresponding author.

2.16. Study status

The study is expected to be opened to recruitment in April 2019.

3. Discussion

Changes to appearance and body image as a consequence of breast cancer treatment can be extensive and enduring [15,16]. Women have reported that these changes are amongst the most difficult aspects of the disease [15,17]. Whilst a growing body of research has examined various aspects of breast cancer treatment on body image, to date, limited consideration has been given to the impact of radiation-induced fibrosis on body image amongst women with breast cancer. Assessment of the impact of any treatment on body image is needed [18].

This study is part of a programme designed to explore the impact of radiation-induced fibrosis on both quality of life and body image, and examine the sociodemographic, clinical and psychosocial factors that predict adjustment over time. A theory of adjustment to body images changes amongst patients with cancer [19] highlights the importance an individual places on appearance (appearance investment). The need to include assessment of the importance placed on appearance in research and clinical work with radiotherapy patients has been highlighted [20]. Patients who place greater importance on their appearance are more vulnerable to a poor adjustment when facing changes to appearance. Previous research [18] has shown that the level of investment in appearance predicts subsequent body image, so higher initial levels of investment in appearance would be associated with poor quality of life and body image.

The information from this study will be used to design a randomised clinical trial whose aim is to identify personalised strategies to reduce the risk of radiation-induced fibrosis. This work will have implications in other medical conditions where fibrosis is a

problem such as the long-term effects of radiation therapy on normal tissues such as the heart and lungs.

Ethical approval

Currently under consideration.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Departmental funding only.

Author contribution

Conception and design of the study: AM, NN, VV and NW.

Protocol/Patient Information Sheet: AM, NN, SW and MK.

Writing of manuscript: NW, SW, MK, NN, VV and AM.

All authors have read and approved the final manuscript. The study will comply with the authorship criteria recommended by the International Committee of Medical Journal Editors.

Conflict of interest statement

Nothing to declare.

Guarantor

Norman Williams.

Research Registration Number

Registration will be made soon after ethics approval.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.isjp.2019.02.002>.

References

- [1] L.A. Torre, F. Bray, R.L. Siegel, J. Ferlay, J. Lortet-Tieulent, A. Jemal, Global cancer statistics, 2012, *CA Cancer J. Clin.* 65 (2) (2015) 87–108, <https://doi.org/10.3322/caac.21262>, PubMed PMID: 25651787.
- [2] American Society of Plastic Surgeons 2000/2001/2002 National Plastic Surgery Statistics, 2002. Available from: http://www.plasticsurgery.org/public_education.
- [3] D.M. Harcourt et al., The psychological effect of mastectomy with or without breast reconstruction: a prospective, multicenter study, *Plast. Reconstr. Surg.* 111 (3) (2003) 1060–1068.
- [4] M.V. Schaverien, R.D. Macmillan, S.J. McCulley, Is immediate autologous breast reconstruction with postoperative radiotherapy good practice? A systematic review of the literature, *J. Plast. Reconstr. Aesthet. Surg.* 66 (12) (2013) 1637–1651.
- [5] B.T. Lee et al., Postmastectomy radiation therapy and breast reconstruction: an analysis of complications and patient satisfaction, *Ann. Plast. Surg.* 64 (5) (2010) 679–683.
- [6] J.S. Chatterjee et al., Effect of postoperative radiotherapy on autologous deep inferior epigastric perforator flap volume after immediate breast reconstruction, *Br. J. Surg.* 96 (10) (2009) 1135–1140.
- [7] T. Berry et al., Complication rates of radiation on tissue expander and autologous tissue breast reconstruction, *Ann. Surg. Oncol.* 17 (Suppl. 3) (2010) 202–210.
- [8] F.P. Albino et al., Irradiated autologous breast reconstructions: effects of patient factors and treatment variables, *Plast. Reconstr. Surg.* 126 (1) (2010) 12–16.
- [9] J. Berbers et al., 'Reconstruction: before or after postmastectomy radiotherapy?' A systematic review of the literature, *Eur. J. Cancer* 50 (16) (2014) 2752–2762.
- [10] M. Overgaard et al., The value of the NSD formula in equation of acute and late radiation complications in normal tissue following 2 and 5 fractions per week in breast cancer patients treated with postmastectomy irradiation, *Radiother. Oncol.* 9 (1) (1987) 1–11.
- [11] C.D. Lyngholm, P.M. Christiansen, T.E. Damsgaard, J. Overgaard, Long-term follow-up of late morbidity, cosmetic outcome and body image after breast conserving therapy. A study from the Danish Breast Cancer Cooperative Group (DBCG), *Acta Oncol.* 52 (2) (2013) 259–269, <https://doi.org/10.3109/0284186X.2012.744469>, PubMed PMID: 23215829.
- [12] S. Collette et al., Predictors of the risk of fibrosis at 10 years after breast conserving therapy for early breast cancer: a study based on the EORTC Trial 22881–10882 'boost versus no boost', *Eur. J. Cancer* 44 (17) (2008) 2587–2599.
- [13] A. Toledano et al., Concurrent administration of adjuvant chemotherapy and radiotherapy after breast-conserving surgery enhances late toxicities: long-term results of the ARCOSEIN multicenter randomized study, *Int. J. Radiat. Oncol. Biol. Phys.* 65 (2) (2006) 324–332.
- [14] S. Collette et al., Predictors of the risk of fibrosis at 10 years after breastconserving therapy for early breast cancer: a study based on the EORTC Trial 22881–10882 'boost versus no boost', *Eur. J. Cancer* 44 (17) (2008) 2587–2599.
- [15] V. Lehmann, M. Hagedoorn, M.A. Tuinman, Body image in cancer survivors: a systematic review of case-control studies, *J. Cancer Surv.* 9 (2) (2015) 339–348.
- [16] S.M. Rosenberg, R.M. Tamimi, S. Gelber, et al., Body image in recently diagnosed young women with early breast cancer, *Psychooncology* 22 (2013) 1849–1855.
- [17] R. Helms, E. O'Hea, M. Corso, Body image issues in women with breast cancer, *Psychol. Health Med.* 13 (3) (2007) 313–325.
- [18] H. Moreira, M.C. Canavarro, A longitudinal study about the body image and psychosocial adjustment of breast cancer patients during the course of the disease, *Eur. J. Oncol. Nurs.* 14 (2010) 263–270.
- [19] C. White, Body image dimensions and cancer: a heuristic cognitive behavioural model, *Psycho-Oncol.* 9 (2000) 183–192.
- [20] P. Hopwood, J. Haviland, J. Mills, G. Sumo, J.M. Bliss, The impact of age and clinical factors on quality of life in early breast cancer: an analysis of 2208 women recruited to the UK START Trial (Standardisation of Breast Radiotherapy Trial), *Breast* 16 (3) (2007) p241–p251.
- [21] A.L. Whitehead, S.A. Julious, C.L. Cooper, M.J. Campbell, Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable, *Stat. Methods Med. Res.* 25 (3) (2016) 1057–1073, <https://doi.org/10.1177/0962280215588241>, Epub 2015 Jun 19. PubMed PMID: 26092476; PubMed Central PMCID: PMC4876429.