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Review

Opportunities and priorities for breast surgical research

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ABSTRACT

Background: The Breast Cancer Campaign Gap analysis (2013) established breast cancer research priorities without specific focus on surgical research nor the role of surgeons. The majority of breast cancer patients encounter a surgeon at diagnosis or during treatment, thus surgical involvement in design and delivery of high-quality research to improve patient care is critical. This review aims to identify opportunities and priorities for breast *surgical* research to complement the previous gap analysis.

Methods: Research-active breast surgeons met and identified topic areas for breast surgical research which mapped to the patient pathway. These included diagnosis, neoadjuvant treatment, surgery, adjuvant therapy and special groups (e.g. risk-reducing surgery). Section leads were identified based on research interests with invited input from experts in specific areas, supported by consultation with the Association of Breast Surgery (ABS) membership and Independent Cancer Patients' Voice (ICPV). The document was iteratively modified until participants were satisfied that key priorities for surgical research were clear.

Results: Key research gaps were identified for each topic area including: (1) issues surrounding overdiagnosis and treatment; (2) optimising selection for neoadjuvant therapies and subsequent surgery; (3) reducing re-operation rates for breast conserving surgery; (4) generating evidence for the clinical and cost-effectiveness of breast reconstruction and mechanisms for evaluating novel interventions; (5) determining optimal axillary management, especially post-neoadjuvant treatment; (6) defining and standardising indications for risk-reducing surgery. Strategies for resolving these knowledge gaps are proposed.

Conclusions: Surgeons are ideally placed for a central role in breast cancer research and should foster a culture of engagement and participation in research to benefit patients and the NHS. Development of infrastructure and surgical research capacity together with appropriate allocation of research funding will be needed to successfully address the key clinical and translational research gaps highlighted in this analysis within the next two decades.

Keywords: breast cancer; surgery; review; gap analysis

INTRODUCTION

Breast cancer is the most common malignancy in the UK and the second commonest cancer worldwide¹. More than 53,000 new cases are diagnosed annually in the UK, with one in eight women affected at some point in their lives². Breast cancer incidence continues to increase, and the disease constitutes a major public health issue with significant resource implications; estimates for healthcare costs per patient are in excess of £12,000 in the 15 months following diagnosis³. Identifying cost-effective treatments for breast cancer is therefore both a clinical and a research priority. Furthermore, significantly improved survival rates mean that long term post-surgical quality of life issues are increasingly important to patients.

In 2012, the Breast Cancer Campaign (BCC) facilitated a series of workshops with the aim of identifying gaps in knowledge and formulating strategies to address these. The resulting gap analysis⁴ prioritised areas for breast cancer research; however, there was minimal focus on surgical research or the potential role of surgeons in effective design and delivery of studies.

Surgeons are uniquely placed for a pivotal role in breast cancer research. Most patients see a surgeon at diagnosis and the majority undergo surgery as primary treatment. Surgical engagement is crucial for identifying and recruiting patients to research at almost all stages of the treatment pathway. Involving surgeons in development of research strategies may optimise trial design, facilitate recruitment and ensure that trials successfully accrue to time and target.

Historically, the pioneers in changing treatment paradigms for breast cancer were surgeons but nonetheless the quality of much surgical research has been variable⁵. Less than 5% of all government healthcare research funding is currently spent on surgical projects⁶. The Royal College of Surgeons in the UK has recently invested in infrastructure to promote surgical research and secure additional funding⁷, aiming to improve quality and value of surgical research, enabling all surgeons to embrace research as a means of enhancing surgical practice and patient care.

The Association of Breast Surgery (ABS) has recognised the need to increase engagement with breast cancer research. The ABS Academic and Research (A&R) Committee was convened in 2014 with the aim of “enhancing care and outcomes for patients with breast disease through the promotion and support of (surgical) research and innovation”. A key intention was to identify areas where surgeons could make significant research contributions, complementing the BCC gap analysis. This paper outlines opportunities and priorities for breast surgical research highlighted by this exercise.

METHODS

The ABS A&R committee comprises research-active breast surgeons, trainees and patient representation. The committee agreed key topics on which to focus this surgical gap analysis and convened a workshop in May 2016. Chosen topics map to the patient care pathway and are listed as follows: a) diagnosis b) neoadjuvant therapy c) surgical treatment of the breast and axilla (including reconstructive and oncoplastic surgery) d) adjuvant therapy e) risk-reducing surgery and f) special groups (elderly, young women; breast cancer in pregnancy, male breast cancer and survivorship). For the purpose of this review, “surgical research” was not confined to studies of surgical procedures or techniques; it also included areas relevant to surgical practice where surgeons could contribute to successful design, conduct and completion of breast cancer-related projects to complement the BCC gap analysis.

Section leads were identified based on individual interests and expertise, had responsibility for enlisting further experts in each area and were tasked with providing a summary comment of:

- existing knowledge
- key surgical research questions in each area
- proposed future research to address these gaps.

The document was iteratively modified until all contributors considered that key themes and research priorities had been identified. Consultation with ABS membership and Independent Cancer Patients’ Voice (ICPV) included presentation at the ABS Annual Conference in May 2017 and a survey, prior to preparation of the final document.

The Gap Analysis survey was developed by members of the A&R Committee (RIC, SMcl, SP and MWR) based on key gaps identified by section leads and contributing experts (Appendix 1). Respondents were asked to rate the importance of research gaps in four areas (diagnosis and assessment (n=5); neoadjuvant therapy (n=7); surgical management (n=5) and special groups (n=5) on a 10-point Likert scale from 1 (not important) to 10 (most important) and to identify any additional research gaps that should be included in the analysis.

The survey was circulated to the ABS membership by email and at conference and was open for six weeks between 15th May and 30th June 2017. E-mail reminders were sent on two occasions to optimise response rates. Survey Monkey software (www.surveymonkey.com) was used for data collection.

All responses were summarised using simple summary statistics. Thematic analysis of free-text was used to explore whether any key gaps had been omitted.

RESULTS

A provisional document for consultation including 22 proposed research gaps was developed with input from 35 research-active surgeons and invited experts (ABS Gap Analysis Working Group, appendix 2). The ABS Gap Analysis survey was completed by 40 additional ABS members, 98% (n=39) of whom felt that there were gaps in breast surgical research that would benefit from additional research. All 22 identified gaps received a median score of between 7 and 9 and so all were retained. No additional gaps were identified, although reference was made to some gaps discussed in the 2013 BCC analysis. Consistent with our stated aims these have not been reiterated here. The principal surgical gaps identified are summarised in Table 1 and discussed below.

DIAGNOSIS AND ASSESSMENT

Screen-detected breast cancer

Approximately one third of breast cancer cases in England present through the National Health Service Breast Screening Programme (NHSBSP)² and addressing overdiagnosis (defined as detection of cancers that would never have been found were it not for the screening test) and overtreatment of

screen-detected breast cancer has been identified as a research priority in a recent independent review⁸.

Addressing overtreatment

Surgeons have a key role in screening studies as traditionally they have been responsible for excision of screen-detected lesions. Use of vacuum-assisted biopsy (VAB) to obtain larger samples for histological assessment has replaced excision biopsy for many women with 'B3' lesions (of uncertain malignant potential)⁹ but lack of randomised evidence has prevented universal uptake of the technique. The natural history of some B3 lesions (e.g. lobular carcinoma in situ (LCIS), flat epithelial atypia (FEA), and atypical ductal hyperplasia [ADH]) remains uncertain, and RCTs are required to determine the optimal management of indeterminate lesions.

Whilst there is agreement (albeit without supporting randomised evidence) that high-grade ductal carcinoma in situ (DCIS) requires surgical intervention, there is more uncertainty regarding management of low and intermediate grade DCIS¹⁰. LORIS (Low Risk DCIS) is a phase III trial comparing active monitoring with surgery for patients with screen-detected low risk DCIS, with the primary end-point being development of ipsilateral invasive breast cancer. The non-inferiority design aims to demonstrate whether active monitoring is not inferior to standard surgery in this group of women¹¹. Similar studies are underway worldwide^{12 13}, and translational studies to identify candidate biomarkers of disease progression are integral to these trials.

Symptomatic breast cancer

Streamlining referral and diagnostic pathways for symptomatic breast patients

Over half of breast cancers are diagnosed in symptomatic clinics following triple assessment¹⁴⁻¹⁶ although over 90% of patients presenting to symptomatic breast clinics do not have cancer¹⁷. Alternative assessment methods, including radiology-led triple-assessment services or primary care open access schemes, may be more cost-effective than the current model, but require robust evaluation to demonstrate acceptable sensitivity, specificity and reliability before introduction.

Advanced and emerging breast imaging modalities

Research is needed to establish the role of breast magnetic resonance imaging (MRI) for specific scenarios such as assessing operability, clarifying local extent and planning complex breast conserving surgery¹⁸, as well as determining which patient groups may benefit from imaging with novel modalities such as contrast-enhanced mammography and digital breast tomosynthesis¹⁹. More sophisticated imaging may result in increased detection of previously subclinical ipsi- and contralateral breast lesions, mandating further radiological and pathological evaluation and potential excision²⁰. There is a need to elucidate the clinical/biological significance of such lesions, and the impact of occult multifocality/multicentricity on oncological outcomes, to determine whether such small, previously subclinical lesions require surgical intervention. Furthermore, the impact of detecting and investigating subclinical disease on psychological well-being of women warrants further investigation.

Staging investigations

Staging investigations for distant metastases are not routinely recommended for asymptomatic patients presenting with breast cancer. Current practice is variable²¹ and treatment decision making when lesions of uncertain clinical significance are identified can be challenging. Studies are needed to determine the most appropriate strategies and imaging modalities for staging and monitoring equivocal lesions.

MANAGEMENT

Management of breast cancer is multimodal and the BCC gap analysis⁴ recognises the need for a more personalised approach. Several areas of controversy relate to optimal selection and sequencing of treatment strategies in the neoadjuvant setting, including tailoring and sequencing local therapies (surgery and radiotherapy) after primary systemic therapy, and the potential role and outcomes of response-adapted surgery.

Neoadjuvant therapy

Neoadjuvant therapy is an established option in management of locally advanced breast cancer²², and can downsize larger cancers, permitting breast conservation. Neoadjuvant chemotherapy (NAC) is as effective as adjuvant chemotherapy in terms of overall survival for patients with operable cancer²³⁻²⁶. It allows disease down-staging, thereby potentially reducing the extent of surgery, although this may be

associated with increased rates of local recurrence, the reasons for which are unclear and warrant further investigation²³. Neoadjuvant endocrine therapy (NET) is an alternative to NAC in women with oestrogen receptor positive (ER+) breast cancer, and further work is needed to establish the optimal duration of treatment²⁷. Combination therapies (e.g. CDK4/6 inhibitors with aromatase inhibitors) may increase response rates, and are currently being explored in ongoing studies. There is less randomised evidence to support NET than for NAC in terms of impact on long-term survival. Of note, the POETIC trial demonstrated that response to short-term pre-operative aromatase inhibitor therapy did not impact time to recurrence²⁸.

Identifying patients who may benefit from neoadjuvant therapy

Benefits of NAC in certain disease subgroups are well-established, with pCR rates of up to 50% seen in triple negative breast cancer with some regimens²⁹. In HER2-positive disease, dual targeting with anti-HER2 therapies combined with chemotherapy can further increase pCR rates^{30,31}. A meta-analysis did not confirm pCR to be a surrogate for improved overall survival³², although pCR at an individual patient level was prognostic. However, improved ability to identify patients likely to respond favourably to neoadjuvant therapies remains a key research focus and will guide clinical decision-making on sequencing of chemotherapy and surgery.

The optimal selection of neoadjuvant therapy (NAC or NET) in post-menopausal patients with ER positive disease remains to be determined. The role of molecular assays has yet to be fully elucidated³³ although early results with the 21 gene assay suggest possible clinical utility³⁴. Likewise, a 4-gene signature has recently been proposed to allow patients to be classed as likely long-term responders or non-responders within 2 weeks of starting endocrine therapy³⁵. Further high-quality prospective evidence is necessary to determine the value of such biomarkers.

Monitoring response to neoadjuvant therapy

Response can be assessed either clinically or radiologically and improved techniques for detection of early response may permit treatment strategies to be adjusted in non-responders (e.g. change of neoadjuvant regimen or proceed to surgery)³⁶. Accurate prediction of response may increase the reliability of surgical decision-making when evaluating potential down-staging for breast conservation. Techniques to optimise monitoring of response may include novel imaging modalities, e.g. drug-induced

apoptosis has been described as a possible functional imaging technique in this context³⁷. Further validation will however be required before such approaches can be utilised in the clinical setting.

Management of patients with a complete pathological response in the breast

The necessity for surgery in patients achieving pCR following neoadjuvant treatment remains to be addressed, and robust minimally-invasive methods to confirm pCR prior to surgery are needed. The NOSTRA trial aims to address this question by examining the need for surgery in HER-2 positive patients achieving pCR following combination NAC and dual anti-HER-2 therapy. In the feasibility phase all patients will undergo surgery, to determine whether patients with a pCR can be identified pre-operatively with multiple ultrasound-directed tumour-bed biopsies. In the main trial, patients with apparent pCR will be randomised to either surgery and radiotherapy or radiotherapy alone. This trial may demonstrate that surgery can be safely omitted in selected patients where the absence of residual disease can be accurately and reliably identified. Long-term follow-up will clearly be essential to monitor outcomes. Similar studies are ongoing internationally to address this question³⁸.

Management of the axilla in patients undergoing neoadjuvant chemotherapy

Two key questions remain to be resolved in management of the axilla in the context of NAC: the timing of SLNB in patients clinically and radiologically node-negative at diagnosis, and the surgical management of patients who are initially biopsy-proven node-positive, but apparently convert to node-negative status following NAC.

In patients node-negative at presentation, current options are SLNB pre-treatment, or following NAC. Upfront SLNB potentially overtreats patients with subclinical nodal involvement which may be downstaged by NAC, as positive pre-treatment SLNB usually commits a patient to additional axillary treatment (surgery or radiotherapy). Between 40%-75% of patients with axillary metastasis at diagnosis become node negative following NAC, raising the possibility of post-treatment SLNB in this group. Two prospective cohort studies^{39,40} have demonstrated high false negative rates in this setting. The sensitivity of SLNB was acceptable when post-treatment, nodes reverted to normal morphology on ultrasound, dual localisation techniques were used and a minimum of 3 nodes retrieved. The use of pre-treatment techniques for marking positive axillary lymph nodes prior to neoadjuvant therapy may improve accuracy by allowing targeted axillary dissection in this setting. This has been described using

a variety of methods including radioactive iodine seeds and clipping of positive node(s)⁴¹⁻⁴³ but these approaches require further evaluation and the question remains whether SLNB alone is safe in this setting, where there is potential risk of residual chemo-resistant axillary disease

With respect to neoadjuvant treatments, in the first instance, improved data are required to understand real world rates of conversion to breast conservation, change of chemotherapy regimen due to non-response, early abandonment of NAC in favour of early surgery, pCR rates, long-term local recurrence rates and overall survival.

Window of opportunity studies

Window of opportunity (WoO) studies utilise the short time interval between diagnosis and surgery to examine biological effects of novel treatments in the *in vivo* setting. Window studies can:

- a) demonstrate, confirm or validate (proposed) biological mechanism(s) of action
- b) identify resistance or sensitivity profiles pre- and post- treatment
- c) identify surrogate endpoints that may correlate with long-term outcomes (such as changes in specific biomarkers seen in biopsies at diagnosis and at surgery)

They require a fraction of the time, cost and patient exposure to test therapies, compared with adjuvant trials. The “post-neoadjuvant window” between completion of neoadjuvant chemotherapy and surgery in those patients who fail to respond completely to treatment represents a further novel therapeutic opportunity which has yet to be exploited. Repeat tumour biopsy at conclusion of treatment can be used to identify patients with residual disease who might be suitable for targeted therapies during this timeframe.

WoO studies may provide an evidence base for proceeding to phase III trials. Surgeons have a role in the design and delivery of such trials. Involving patient advocates is also vital to allow concerns surrounding the acceptability of such studies to be addressed. Examples include reassurance to research ethics committees regarding tissue collection pre-treatment and open discussion of the effects of trial participation on scheduling of surgery. For practical purposes, trial entry counts as treatment for the purposes of meeting health service waiting time targets⁴⁴.

Surgery for breast cancer

Surgery to the breast

Strategies to improve breast conserving surgery and to reduce re-excision rates

Surgical resection margins remain contentious, but there is broad consensus that a negative margin, regardless of extent, is key to reducing local recurrence for invasive disease⁴⁵. Currently, one in five women require further excision because of involved resection margins⁴⁶. This represents a significant burden for patients and healthcare providers, and strategies to reduce margin positivity are a research and clinical priority.

Intra-operative margin assessment

Technologies allowing intra-operative margin assessment offer further potential to reduce re-excision rates beyond routine specimen radiology⁴⁷. Intra-operative margin assessment techniques including imprint cytology and frozen section have not become routine practice due to resource limitations⁴⁸. Emerging technologies for margin assessment potentially offer rapid and reliable methods for reducing rates of margin positivity. These include the MarginProbe (radiofrequency reflection)⁴⁹, ClearEdge⁵⁰ (bio-impedance spectroscopy), and LightPath (Cerenkov Luminescence Imaging⁵¹). Other technologies such as Raman Spectroscopy⁵² and the iKnife Rapid Evaporative Ionisation Mass Spectrometry technology⁵³ are also being explored, Feasibility and validation studies are required for all these technologies to determine clinical utility and cost-effectiveness. Surgeon-led multi-centre trials are necessary for comparison of newer technologies with current margin assessment techniques. This in turn will determine relative impact on re-excision rates.

Tumour localisation for non-palpable lesions

The ideal localisation method should be safe, accurate, deliverable in advance of the planned operation date and cost-effective. New approaches to localisation include use of radioactive⁵⁴ and magnetic seeds⁵⁵. These may offer benefits over standard wire-guided techniques and are being validated in on-going studies with promising early results^{56,57}. However, magnetic seeds limit subsequent use of MRI for imaging unless completely removed, and further evaluation is essential before comparative studies can be undertaken.

Surgeons have clear responsibilities in trialling new devices and participating in adequately powered prospective collaborative studies to validate novel localisation techniques. The current European approach to device testing involves CE marking of the device with no regulatory requirement for post-market research. A coordinated approach mandating prospective data collection (post-CE marking) for new devices is necessary, and working closely with the Medicines and Healthcare products Regulatory Agency (MHRA) and equivalent international bodies to ensure more robust assessment and evaluation may be one way to achieve this.

Alternatives to surgical excision

Standard surgical excision may be unnecessary for small, low-grade screen-detected cancers for which percutaneous ablation techniques such as cryotherapy, radiofrequency ablation, high-intensity focused ultrasound and laser therapy may be appropriate. However, techniques that completely ablate cancers^{58,59} raise concerns about margin assessment and definitive histopathology. Hence percutaneous excisional techniques to remove tumours may be preferable in this respect. Further research will clarify which cancers are amenable to treatment with minimally-invasive techniques⁶⁰⁻⁶², who requires adjuvant radiotherapy, and what constitutes adequate axillary management for individual patients.

Appropriate end-points for de-escalation studies need to be clearly defined and include local or regional recurrence, disease-free and overall survival. Designing studies which provide definitive data may pose significant methodological challenges. Randomised controlled studies with non-inferiority design are the gold standard but may be challenging due to patient and clinician preferences in non-blinded studies. Large cohort or patient preference studies may be more acceptable in this context. Multidisciplinary working, alongside patient advocates, will be necessary to define appropriate end-points and deliver well-designed studies that address these key questions.

Adjuvant radiotherapy

Adjuvant radiotherapy is an integral part of loco-regional therapy and reduces local recurrence. Intra-operative radiotherapy may safely reduce the burden of treatment on the patient and enable more

accurate targeting of tissues at risk¹⁰¹ and the ongoing TARGIT-B trial will provide further data on potential benefits of this approach in terms of local tumour control and adverse effects. Avoidance of radiotherapy may be possible in some patient groups, particularly in light of the findings of the CALGB 9343 trial, which has confirmed low rates of ipsilateral recurrence at 10 years in patients ≥ 70 years of age with hormone receptor positive node negative tumours under 5cm treated with adjuvant hormone therapy alone after wide local excision⁶³. This question is being addressed by the ongoing PRIMETIME study⁶⁴.

Breast reconstruction and oncoplastic surgery

Breast reconstruction is offered to improve cosmesis, body image and quality of life for women undergoing mastectomy⁶⁵. Many reconstructive options are available, from implant-based techniques to autologous procedures. These can be performed at mastectomy or a later date. Decision-making for breast reconstruction can be complex, with reports of dissatisfaction and regret not uncommon^{66,67}. Decision aids may reduce decisional conflict and increase knowledge about options⁶⁸ but these must be based on high-quality evidence.

High-quality patient-centred short and long-term outcome data for different reconstructive techniques are currently lacking^{69,70}. Inconsistent and heterogeneous reporting of outcomes precludes comparison of results from different studies and there is an urgent need for a robust set of standardised outcomes, allowing comparisons across studies. Therefore, a core outcome set has been developed⁷¹, which includes 11 clinical, patient-reported and cosmetic outcomes important to both patients and healthcare professionals. Agreement regarding how to measure these outcomes is important before effective integration into research and clinical implementation. Development of a simple, reliable and valid method for assessing cosmetic outcomes of breast reconstruction is ongoing and includes use of three-dimensional imaging techniques⁷². Furthermore, inclusion of patient reported outcomes should be standard in all future research and well-validated tools are required for this purpose. One such tool is the BREAST-Q^{73,74}, which is comprehensive, includes domains for breast satisfaction together with psychosocial and sexual well-being and is finding universal application.

The incidence of multifocal and multicentric cancers has increased with MRI usage and screening. Despite limitations of studies addressing surgical treatment of multiple ipsilateral breast cancers, rates of local recurrence are low after oncoplastic breast conserving surgery with no survival detriment. This has prompted the first randomised trial evaluating therapeutic mammoplasty versus standard mastectomy for these cases⁷⁵.

With broadening indications for postmastectomy radiotherapy⁷⁶ (PMRT), further research is required to determine how to integrate radiotherapy into management plans to minimize surgical complications and adverse cosmetic outcomes in breast reconstruction^{77,78}. A well-designed randomised trial addressing this issue has previously failed to recruit⁷⁹ however a recent survey of European practice confirms that there remain controversies around the scheduling of PMRT in the context of reconstructive surgery⁸⁰. This question will be in part addressed by the PRADA trial (<https://clinicaltrials.gov/ct2/show/NCT02771938>), which is a non-randomised phase II trial exploring whether radiotherapy before mastectomy and autologous breast reconstruction is associated with improved aesthetic results without increasing post-operative complications secondary to upfront radiotherapy. Data from this study is awaited, although further research is required to resolve these issues and non-randomised studies with standardised outcome measures may be a pragmatic wayforward.

The optimal approach to implant-based breast reconstruction is another area of controversy. This is a rapidly evolving area and it is unclear what type of biological or synthetic mesh should be used and whether implants should be placed in the subpectoral or pre-pectoral plane. RCTs are challenging but the iBRA (implant Breast Reconstruction evaluation) study⁸¹ (ISRCTN37664281) has prospectively recruited over 2000 patients undergoing new approaches to implant-based reconstruction at 81 centres to inform the feasibility and design of a future trial.

New surgical techniques must be prospectively evaluated using robust methodology. There should be “no innovation without evaluation” and infrastructure should be in place to support the introduction of new procedures and devices in a controlled and monitored fashion, encouraging more efficient innovation whilst protecting patients. The IDEAL framework⁸² provides a methodology for achieving this. Adoption of innovation can be improved by collaborative approaches, linked to a network of high-volume centres willing and able to evaluate new devices and techniques. Engagement of industry and

regulators, as well as surgeons, in post-market surveillance of medical devices will be essential to deliver these innovation programmes in a timely and cost-effective fashion. Some aspects of best practice for devices and implants may be developed from regulatory processes for new medicinal products. Furthermore, in order to embed best practice in the context of complex procedures such as implant-based breast reconstruction, an improved understanding of the nature of adoption and implementation of such practice is necessary.

Management of the axilla

Management of the axilla has become increasingly conservative and high-quality imaging may in future replace SLNB in patients with low-risk cancers. The SOUND trial (Sentinel node versus Observation after axillary UltraSouND)⁸³ aims to address this, and recent work suggests this approach may be safe in selected patients⁸⁴. In addition, with increasing numbers of patients having SLNB, the feasibility of repeat SLNB in patients with local recurrence and optimal management of the axilla following isolated regional nodal recurrence needs to be addressed.

Patients with low volume nodal disease found by sentinel node biopsy

There is continued controversy over treatment of sentinel node macrometastases. ACOSOG Z0011 challenged the therapeutic benefit of ANC for this patient group. However, these findings have not been readily adopted into clinical practice in the U.K. This may in part be due to the fact that Z0011 did not include mastectomy patients, and that half of patients received high tangent radiotherapy fields which may have favoured equivalence of outcomes. Recent updated analysis at 10 years⁸⁵, confirming no significant difference in recurrence or survival, may go some way to addressing these concerns. The POSNOC trial⁸⁶ is exploring management of sentinel node macrometastases in both BCS and mastectomy patients, and will accrue 1900 patients, potentially providing more definitive answers on the safety of SLNB alone for patients with sentinel node macrometastases receiving adjuvant systemic therapies. Finally, the benefit of axillary dissection in patients with a clinically negative but needle biopsy positive axilla remains to be elucidated – these patients are eligible for entry into POSNOC and this may provide data to guide the management of this patient group.

Further advances in imaging technologies, percutaneous sampling techniques and systemic therapies for breast cancer may be forthcoming, and there is potential for elimination of surgical staging of the axilla in selected patients with node-negative and possibly some cases of node-positive disease.

SPECIAL GROUPS

Patients at high risk

Risk-reducing surgery

Management of women with a strong family history but no identified genetic mutation

The surgical management of high-risk women with germline BRCA mutations is well-established, with bilateral risk-reducing mastectomy achieving a significant reduction (>90%) in breast cancer incidence⁸⁷, although survival benefit remains unproven⁸⁸. The optimal management of women with a strong family history of breast cancer but no identifiable mutation in a predisposition gene remains unclear, with no consensus about when (or if) risk-reducing surgery should be offered. Surgical intervention is not without risk and may include adverse psychosocial sequelae, decisional regret and dissatisfaction⁸⁹. Well-designed studies using validated instruments for patient reported outcomes are lacking. Surgeons are often approached directly about risk-reducing surgery and are ideally placed to explore these issues alongside patients and psychologists.

Contralateral prophylactic mastectomy

Rates of contralateral prophylactic mastectomy (CPM) are increasing and more patients with unilateral breast cancer are requesting contralateral surgery with or without reconstruction either at initial diagnosis or subsequently⁹⁰. There is no clear evidence for survival benefit for CPM⁹¹ in the absence of a genetic predisposition. Despite recent guidelines⁹², there is no consensus for optimal management of this group⁹³⁻⁹⁵. There is a need to explore relative benefits and harms of CPM with accurate reporting of complications, long-term sequelae and validated patient-reported outcomes. Work to improve the effective communication of the competing risks (recurrence from the index primary and development of a new primary) will also be important to help with these complex decision-making processes and allow women to make fully informed choices.

Surgery for metastatic disease

A randomised trial⁹⁶ found no survival benefit from excision of the primary tumour in patients with metastatic disease. In the context of improved systemic and biological therapy for certain tumour subgroups, however, further research is required to identify specific patient subgroups which may benefit from excision of the primary tumour (such as those with isolated bone metastases⁹⁷ or with complete resolution of distant disease), and how this might impact on quality of life.

Further work is also needed to establish the magnitude of survival benefit from resection of breast cancer metastases. Non-randomised studies suggest that in selected patients, resection may be associated with significant survival benefit^{98,99} but RCTs are needed to definitively establish the value of this approach. Other treatment modalities including stereotactic radiotherapy, radioablation and cryoablation of metastatic lesions require robust clinical evaluation.

Surgery for lymphoedema

Lymphoedema following axillary surgery is disabling and adversely impacts quality of life. Surgery such as lymphaticovenous anastomosis and vascularised lymph node transfer may significantly improve outcomes for patients with severe symptoms¹⁰⁰ but further research is required to evaluate both the safety and effectiveness of these techniques and determine which patients derive symptom benefit while minimising donor site morbidity¹⁰¹.

Young women

Management of breast cancer in young women presents specific challenges and multidisciplinary guidelines for optimal management of this group have recently been published¹⁰². Data from the POSH¹⁰³ cohort study have shown that in the absence of a known pathogenic germline mutation, there is no survival advantage from mastectomy compared with BCS.

Research is required to explore how concerns specific to young women should be managed. These include issues relating to fertility, bone health, consequences of extended endocrine therapy, and the psychological impact of a breast cancer diagnosis not only on the patient, but also their partners and family. Indications for germline mutation testing remain to be defined and the probability threshold for testing in the UK has recently been decreased from 20% to 10%. The surgeon has an important role in engaging with clinical geneticists and other collaborators to answer these key questions.

Pregnancy associated breast cancer

Pregnancy-associated breast cancer (PABC) is estimated to affect 2.4-7.8 women per 100,000 live births. Two large on-going studies in the UK and Europe^{104 105} will explore the incidence and short-term outcomes of PABC. Surgeons working in collaboration with obstetricians are ideally placed to recruit patients to relevant studies.

Older women

The management of women with breast cancer diagnosed over the age of 70 years varies widely across the UK¹⁰⁶⁻¹⁰⁸, and is currently the subject of a national audit⁵¹. Older patients are more likely to be managed with primary endocrine therapy without surgery. Although several randomised trials have shown overall survival to be similar to combined surgery and adjuvant endocrine therapy, a Cochrane Review revealed that local control was significantly worse in the absence of surgical treatment¹⁰⁹. Furthermore, those offered surgery are more likely to undergo mastectomy without the potential benefit of downstaging from neoadjuvant therapies and axillary management is more likely to be non-guideline compliant in older patients.

Whilst adjuvant chemotherapy is widely employed in younger women, usage is more selective and variable in patients over 70 years¹¹⁰. Failure to include older patients in clinical trials and tendencies to overestimate comorbidity and frailty whilst underestimating therapeutic benefit collectively influence treatment recommendations in the older patient.

Randomised trials to address these questions have failed to recruit for several reasons including lack of equipoise on the part of both clinician and patient¹¹¹. However, both cohort¹¹² and qualitative studies¹¹³ investigating factors which influence patient choice and evaluate interventions to reduce treatment variation have been more successful.

Male breast cancer

Male breast cancer represents 0.5–1% of all breast cancers and has been understudied, with management decisions often extrapolated from studies of female breast cancer. This may be inappropriate as recent evidence suggests that these cancers may be biologically different. The majority of men with breast cancer will undergo primary surgery, and surgeons have a central role in recruiting these patients to on-going studies and promoting tissue collection for research.

RESEARCH METHODOLOGY

Multidisciplinary collaboration

Clinical research is multidisciplinary based and continued collaboration between breast surgeons and other disciplines is essential for ensuring advances in breast cancer research across the globe. Surgeons play roles as research leaders within their own areas of expertise, and are vital as collaborators within research teams. There is clear evidence of a changing culture and attitude in breast surgery in the UK with annual ABS Multidisciplinary Meetings bringing together experts to debate controversial topics and an increasingly visible surgical presence within national multidisciplinary research infrastructure such as the National Cancer Research Institute (NCRI) Breast Clinical Studies Group and the UK Breast Intergroup creating an environment where such collaborations can flourish. Consolidating and building on these successes will be crucial to increase research capacity and facilitate delivery of well-designed research to address gaps highlighted in this review.

Patient and public involvement

Patient and public involvement is central to the delivery of high-quality research and patients are key to any successful multidisciplinary collaboration. Patients should be involved in the design, development and delivery of studies to ensure that research is relevant and addresses questions with clear patient focussed outcomes. Shared decision making approaches to breast cancer treatment should be explored in clinical trials with inclusion of patient reported outcomes as standard. Breast cancer survivorship and secondary prevention are discussed in detail in the BCC gap analysis⁴. As surgeons have a significant role in the follow-up and ongoing management of patients with breast cancer they are well placed to work with patients to deliver research in these areas.

Clinical research

The surgeon is well placed to synthesise current evidence, formulate new hypotheses, identify and question inconsistencies in current approaches, and to help design and develop innovative clinical trials. The surgeon is central to patient recruitment, monitoring and sample collection and represents a key link between patient and translational scientist. Surgeons are responsible for the diagnostic process and are involved in treatment planning for most breast cancer patients, and thus are key to recruitment to biological studies in the perioperative period which are increasingly important in the development of stratified medicine. Surgeons are usually trusted for advice and information and need to be enthusiastic

advocates of clinical trials; ensuring patients have full and equal access to information and participation in clinical research studies.

Although well-designed, pragmatic randomised trials are considered the 'gold standard' for determining efficacy, they may not be possible in some areas including assessment of radiotherapy effects on breast reconstruction, risk-reducing surgery or in certain groups such as older patients. In these settings, prospective cohort studies may be a reasonable alternative with rapid creation of large and powerful datasets which allow hypotheses to be explored and key questions addressed. The trainee research collaborative model has emerged as a successful cost-effective way of conducting these types of studies. Engaging trainees also has the potential to augment research capacity by fostering a new generation of surgeons with an understanding of research methodology, patient and public involvement and engagement in trial recruitment¹¹⁴⁻¹¹⁶. The success of this approach has recently been evidenced by a trainee-delivered prospective audit evaluating current practice with respect to resection margins¹¹⁷. Collaboration with psychosocial and qualitative researchers may allow surgeons to develop studies to explore issues around topics such as risk-reducing mastectomy and CPM. Health economic participation is vital, for evaluation of emerging technologies and devices, as favourable cost-effectiveness data will support commissioning of future service provision.

Translational research

As acknowledged in the BCC gap analysis⁴, improved collection of tumour samples and blood from patients at all disease stages is essential for the ongoing development of personalised medicine. A culture change allowing routine collection and biobanking of samples at diagnosis and during treatment is urgently required. Consensus is required to optimise sample collection and preanalytical processing, allowing the assessment of fresh and formalin-fixed paraffin embedded samples appropriate for "omics" studies as well as techniques such as individualised cell culture analysis, single cell sequencing, and patient derived organotypic models and xenografts⁴.

Identification and validation of biomarkers which predict for local or "surgical" disease endpoints will be critical in the context of developing stratified medicine. Engaging surgeons to routinely participate in tissue banking and translational studies is an essential prerequisite for progression of biomarker driven research.

RESEARCH FUNDING

As highlighted above, currently only a small proportion of governmental research spend is directed towards surgical research. Recent investment in surgical research infrastructure such as the Royal College of Surgeons Surgical Trials Initiative which in partnership with the National Institute of Health Research (NIHR), the professional associations and charitable funders including Cancer Research UK and Breast Cancer Now has created a network of surgical trials units and Surgical Speciality Leads to increase the quality and number of surgical trials in the UK. This drive to place research at the centre of surgical culture includes increasing research capacity through developing existing clinical research networks, as well as in the training of current and future generations of surgeons in research methodology and Good Clinical Practice to ensure the high quality of future studies. The success of this initiative has already been demonstrated with a portfolio of 85 trials recruiting over 25,000 patients across 10 different specialities in the four years since inception¹¹⁸.

Further funding, however, will be needed and funding bodies responsible for supporting surgical and breast cancer research in the UK need to be cognisant that addressing the critical gaps in clinical and translation research outlined in this analysis will require significant investment over the next two decades to benefit patients, clinicians and healthcare providers. It is anticipated that as surgeons continue to embrace 'team science' by developing their multidisciplinary collaborations and building strong links with methodologists, the funding successes seen in surgically-led studies such as LORIS, POSNOC and SMALL will continue increase leading to well-designed and conducted studies that address these issues.

CONCLUSIONS

Surgeons are uniquely placed to design and deliver studies addressing the key gaps in our knowledge of breast cancer management. Historically, surgeons have played key roles in improving breast cancer outcomes, far beyond evolution of surgical techniques. The concept of 'surgical' research being restricted to devices or techniques is outdated and should reflect the spectrum of roles that surgeons have in contemporary multidisciplinary research. Evolving research platforms such as 'window of opportunity' studies and trainee collaboratives offer surgeons unrivalled opportunities to develop more

effective treatments, reduce overtreatment, and become involved in research. Open multidisciplinary collaboration will be vital to ensure progress in breast cancer research from an international perspective.

The key research gaps identified in this analysis are summarised in table 1 and include issues surrounding overdiagnosis and overtreatment, the selection of patients for neoadjuvant therapies and their subsequent surgical management and refining surgical techniques to improve re-operation rates in women having breast conserving surgery. Evidence should be generated to enable stratification, personalisation (patient selection criteria, the impact of adjuvant treatments and co-morbidities) and clinical and cost-effectiveness of breast reconstruction, including mechanisms for the evaluation of novel technologies and surgical approaches. Management pathways for the axilla should be further clarified particularly in the context of post-neoadjuvant treatment and the indications for risk-reducing surgery and contralateral prophylactic mastectomy should be more clearly defined and standardised.

Proposed strategic solutions to address these gaps include the integration of a research culture into surgical practice at all stages of training with breast surgeons becoming key proponents of scientific, translational and clinical research and the development of surgical leadership in design and delivery of clinical research. Surgical clinician scientists should be nurtured to accelerate translational research to address key surgical and clinical questions and an agreed framework for biobanking of clinical samples at key points in the patient treatment pathway should be developed to facilitate translational research studies. Finally there should be further development and optimisation of clinical trial methodologies relevant to address key surgical questions in breast cancer management.

High-quality research is essential to improve patient outcomes and should be embedded in surgical culture to engage and empower surgeons to participate in trials for the benefit of their patients. All surgeons should offer their patients the opportunity to enter well-designed trials, and research should remain at the heart of breast surgical practice.

Collaborators

Author contributions

RIC and MWR conceived the project; AG, SP, CCK, JH, AF, ARC, PF, RIC and RV were section leads and co-ordinated expert input; SP produced the first draft of the manuscript; RIC, SMcl, MWR and JB critically revised the manuscript; all authors reviewed and approved the manuscript prior to submission.

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Conflict of interest

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REFERENCES

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. 2013 (accessed 05/07/2016).
2. Cancer Research UK. <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer>; 2016.
3. Hall PS, Hamilton P, Hulme CT, et al. Costs of cancer care for use in economic evaluation: a UK analysis of patient-level routine health system data. *Br J Cancer* 2015; **112**(5): 948-56.
4. Eccles SA, Aboagye EO, Ali S, et al. Critical research gaps and translational priorities for the successful prevention and treatment of breast cancer. *Breast Cancer Res* 2013; **15**(5): R92.
5. Horton R. Surgical research or comic opera: questions, but few answers. *Lancet* 1996; **347**(9007): 984-5.
6. Royal College of Surgeons. Funding surgical research. <https://www.rcseng.ac.uk/about-the-rcs/support-our-work/funding-surgical-research/> (accessed 11/6/18 2018).
7. Morton D. RCS to expand surgical research infrastructure. *Annals of the Royal College of Surgeons of England (Supp)* 2012; **94**: 131-2.
8. Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. The benefits and harms of breast cancer screening: an independent review. *Br J Cancer* 2013; **108**(11): 2205-40.
9. Rageth CJ, O'Flynn EA, Comstock C, et al. First International Consensus Conference on lesions of uncertain malignant potential in the breast (B3 lesions). *Breast Cancer Res Treat* 2016; **159**(2): 203-13.
10. Mammary Fold Academic and Research Committee. Variation in the management of ductal carcinoma in situ in the UK: Results of the Mammary Fold National Practice Survey. *Eur J Surg Oncol* 2016; **42**(8): 1153-61.
11. Francis A, Fallowfield L, Rea D. The LORIS Trial: Addressing overtreatment of ductal carcinoma in situ. *Clin Oncol (R Coll Radiol)* 2015; **27**(1): 6-8.
12. Elshof LE, Tryfonidis K, Slaets L, et al. Feasibility of a prospective, randomised, open-label, international multicentre, phase III, non-inferiority trial to assess the safety of active surveillance for low risk ductal carcinoma in situ - The LORD study. *Eur J Cancer* 2015; **51**(12): 1497-510.
13. The COMET trial. 2017. <https://clinicaltrials.gov/ct2/show/NCT02926911> (accessed 19/6/2017 2017).
14. National Institute of Health and Care Excellence T. Breast Cancer - NICE quality standard QS12. 2016 2011. www.nice.org.uk/guidance/qs12 (accessed 29/08/2016 2016).
15. Department of Health. Best practice diagnostic guidelines for patients presenting with breast symptoms. 2010.
16. National Institute of Clinical Excellence. Breast cancer (early & locally advanced): diagnosis and treatment; 2009.
17. Wishart GC, Warwick J, Pitsinis V, Duffy S, Britton PD. Measuring performance in clinical breast examination. *Br J Surg* 2010; **97**(8): 1246-52.
18. Winters ZE, Horsnell J, Schmid P, et al. Time for a randomised clinical trial evaluating breast conserving surgery compared to mastectomy in ipsilateral multifocal breast cancer (MFBC)? *Breast* 2016; **26**: 149-50.
19. Peppard HR, Nicholson BE, Rochman CM, Merchant JK, Mayo RC, 3rd, Harvey JA. Digital Breast Tomosynthesis in the Diagnostic Setting: Indications and Clinical Applications. *Radiographics* 2015; **35**(4): 975-90.
20. Brennan ME, Houssami N, Lord S, et al. Magnetic resonance imaging screening of the contralateral breast in women with newly diagnosed breast cancer: systematic review and meta-analysis of incremental cancer detection and impact on surgical management. *J Clin Oncol* 2009; **27**(33): 5640-9.
21. Chand N, Cutress RI, Oeppen RS, Agrawal A. Staging Investigations in Breast Cancer: Collective Opinion of UK Breast Surgeons. *Int J Breast Cancer* 2013; **2013**: 506172.
22. Kummel S, Holtschmidt J, Loibl S. Surgical treatment of primary breast cancer in the neoadjuvant setting. *Br J Surg* 2014; **101**(8): 912-24.
23. Asselain B, Barlow W, Bartlett J, et al. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. *The Lancet Oncology*; **19**(1): 27-39.
24. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. *Journal of the National Cancer Institute Monographs* 2001; (30): 96-102.

25. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J Clin Oncol* 2008; **26**(5): 778-85.
26. Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol* 1997; **15**(7): 2483-93.
27. Kolberg HC, Aktas B, Liedtke C. Clinical Utility of Neoadjuvant Endocrine Therapy for Hormone Receptor Positive Breast Cancer. *Rev Recent Clin Trials* 2017; **12**(2): 67-72.
28. Robertson J, Dowsett M, Bliss J, et al. Abstract GS1-03: Peri-operative aromatase inhibitor treatment in determining or predicting longterm outcome in early breast cancer – The POETIC* Trial (CRUK/07/015). *Cancer Research* 2018; **78**(4 Supplement): GS1-03-GS1-.
29. von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. *Lancet Oncol* 2014; **15**(7): 747-56.
30. Schneeweiss A, Chia S, Hickish T, et al. Neoadjuvant Pertuzumab and Trastuzumab Concurrent or Sequential with an Anthracycline-Containing or Concurrent with an Anthracycline-Free Standard Regimen: A Randomized Phase II Study (TRYPHAENA). *Cancer Research* 2011; **71**(24 Supplement): S5-6-S5-6.
31. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012; **13**(1): 25-32.
32. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet* 2014; **384**(9938): 164-72.
33. Markopoulos C, van de Velde C, Zarca D, Ozmen V, Masetti R. Clinical evidence supporting genomic tests in early breast cancer: Do all genomic tests provide the same information? *Eur J Surg Oncol* 2017; **43**(5): 909-20.
34. Bear HD, Wan W, Robidoux A, et al. Using the 21-gene assay from core needle biopsies to choose neoadjuvant therapy for breast cancer: A multicenter trial. *J Surg Oncol* 2017; **115**(8): 917-23.
35. Turnbull AK, Arthur LM, Renshaw L, et al. Accurate Prediction and Validation of Response to Endocrine Therapy in Breast Cancer. *J Clin Oncol* 2015; **33**(20): 2270-8.
36. Lindenberg MA, Miquel-Cases A, Retel VP, et al. Imaging performance in guiding response to neoadjuvant therapy according to breast cancer subtypes: A systematic literature review. *Crit Rev Oncol Hematol* 2017; **112**: 198-207.
37. Nguyen QD, Challapalli A, Smith G, Fortt R, Aboagye EO. Imaging apoptosis with positron emission tomography: 'bench to bedside' development of the caspase-3/7 specific radiotracer [(18F)ICMT-11. *Eur J Cancer* 2012; **48**(4): 432-40.
38. Kuerer HM, Rauch GM, Krishnamurthy S, et al. A Clinical Feasibility Trial for Identification of Exceptional Responders in Whom Breast Cancer Surgery Can Be Eliminated Following Neoadjuvant Systemic Therapy. *Ann Surg* 2017.
39. Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncology* 2013; **14**(7): 609-18.
40. Boughhey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA* 2013; **310**(14): 1455-61.
41. Plecha D, Bai S, Patterson H, Thompson C, Shenk R. Improving the Accuracy of Axillary Lymph Node Surgery in Breast Cancer with Ultrasound-Guided Wire Localization of Biopsy Proven Metastatic Lymph Nodes. *Ann Surg Oncol* 2015; **22**(13): 4241-6.
42. Diego EJ, McAuliffe PF, Soran A, et al. Axillary Staging After Neoadjuvant Chemotherapy for Breast Cancer: A Pilot Study Combining Sentinel Lymph Node Biopsy with Radioactive Seed Localization of Pre-treatment Positive Axillary Lymph Nodes. *Ann Surg Oncol* 2016; **23**(5): 1549-53.
43. Caudle AS, Yang WT, Krishnamurthy S, et al. Improved Axillary Evaluation Following Neoadjuvant Therapy for Patients With Node-Positive Breast Cancer Using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection. *Journal of Clinical Oncology* 2016; **34**(10): 1072-8.
44. Gasson S, Bliss J, Jamal-Hanjani M, Krebs M, Swanton C, Wilcox M. The Value of Patient and Public Involvement in Trial Design and Development. *Clin Oncol (R Coll Radiol)* 2015; **27**(12): 747-9.

45. Houssami N, Macaskill P, Marinovich ML, Morrow M. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. *Ann Surg Oncol* 2014; **21**(3): 717-30.
46. Jeevan R, Cromwell DA, Trivella M, et al. Reoperation rates after breast conserving surgery for breast cancer among women in England: retrospective study of hospital episode statistics. *BMJ* 2012; **345**: e4505.
47. Layfield DM, May DJ, Cutress RI, et al. The effect of introducing an in-theatre intra-operative specimen radiography (IOSR) system on the management of palpable breast cancer within a single unit. *Breast* 2012; **21**(4): 459-63.
48. St John ER, Al-Khudairi R, Ashrafian H, et al. Diagnostic Accuracy of Intraoperative Techniques for Margin Assessment in Breast Cancer Surgery: A Meta-analysis. *Ann Surg* 2017; **265**(2): 300-10.
49. Allweis TM, Kaufman Z, Lelcuk S, et al. A prospective, randomized, controlled, multicenter study of a real-time, intraoperative probe for positive margin detection in breast-conserving surgery. *Am J Surg* 2008; **196**(4): 483-9.
50. Dixon JM, Renshaw L, Young O, et al. Intra-operative assessment of excised breast tumour margins using ClearEdge imaging device. *Eur J Surg Oncol* 2016; **42**(12): 1834-40.
51. Grootendorst MR, Cariati M, Pinder SE, et al. Intraoperative Assessment of Tumor Resection Margins in Breast-Conserving Surgery Using (18)F-FDG Cerenkov Luminescence Imaging: A First-in-Human Feasibility Study. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 2017; **58**(6): 891-8.
52. Deng K, Zhu C, Ma X, et al. Rapid Discrimination of Malignant Breast Lesions from Normal Tissues Utilizing Raman Spectroscopy System: A Systematic Review and Meta-Analysis of In Vitro Studies. *PLoS One* 2016; **11**(7): e0159860.
53. St John ER, Balog J, McKenzie JS, et al. Rapid evaporative ionisation mass spectrometry of electrosurgical vapours for the identification of breast pathology: towards an intelligent knife for breast cancer surgery. *Breast Cancer Res* 2017; **19**(1): 59.
54. Pouw B, de Wit- van der Veen LJ, Stokkel MPM, Loo CE, Vrancken Peeters M-JTFD, Valdés Olmos RA. Heading toward radioactive seed localization in non-palpable breast cancer surgery? A meta-analysis. *Journal of Surgical Oncology* 2015; **111**(2): 185-91.
55. Price ER, Khoury AL, Esserman LJ, Joe BN, Alvarado MD. Initial Clinical Experience With an Inducible Magnetic Seed System for Preoperative Breast Lesion Localization. *American Journal of Roentgenology* 2018; **210**(4): 913-7.
56. Ahmed M, Anninga B, Goyal S, et al. Magnetic sentinel node and occult lesion localization in breast cancer (MagSNOLL Trial). *Br J Surg* 2015; **102**(6): 646-52.
57. Cox CE, Garcia-Henriquez N, Glancy MJ, et al. Pilot Study of a New Nonradioactive Surgical Guidance Technology for Locating Nonpalpable Breast Lesions. *Ann Surg Oncol* 2016; **23**(6): 1824-30.
58. Fornage BD, Hwang RF. Current status of imaging-guided percutaneous ablation of breast cancer. *AJR Am J Roentgenol* 2014; **203**(2): 442-8.
59. Roubidoux MA, Yang W, Stafford RJ. Image-guided ablation in breast cancer treatment. *Tech Vasc Interv Radiol* 2014; **17**(1): 49-54.
60. Palussiere J, Henriques C, Mauriac L, et al. Radiofrequency ablation as a substitute for surgery in elderly patients with nonresected breast cancer: pilot study with long-term outcomes. *Radiology* 2012; **264**(2): 597-605.
61. Klimberg VS, Boneti C, Adkins LL, et al. Feasibility of percutaneous excision followed by ablation for local control in breast cancer. *Ann Surg Oncol* 2011; **18**(11): 3079-87.
62. Grotenhuis BA, Vrijland WW, Klem TM. Radiofrequency ablation for early-stage breast cancer: treatment outcomes and practical considerations. *Eur J Surg Oncol* 2013; **39**(12): 1317-24.
63. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol* 2013; **31**(19): 2382-7.
64. Kirwan CC, Coles CE, Bliss J, Group PPW, Group PPW. It's PRIMETIME. Postoperative Avoidance of Radiotherapy: Biomarker Selection of Women at Very Low Risk of Local Recurrence. *Clin Oncol (R Coll Radiol)* 2016; **28**(9): 594-6.
65. Harcourt DM, Rumsey NJ, Ambler NR, et al. The psychological effect of mastectomy with or without breast reconstruction: A prospective, multicenter study. *Plast Reconstr Surg* 2003; **111**(3): 1060-8.
66. Jeevan R, Cromwell D, Browne J, et al. National Mastectomy and Breast Reconstruction Audit 2011; 2011.

67. Sheehan J, Sherman KA, Lam T, Boyages J. Association of information satisfaction, psychological distress and monitoring coping style with post-decision regret following breast reconstruction. *Psychooncology* 2007; **16**(4): 342-51.
68. Nicholas Z, Butow P, Tesson S, Boyle F. A systematic review of decision aids for patients making a decision about treatment for early breast cancer. *Breast* 2016; **26**: 31-45.
69. Potter S, Brigid A, Whiting PF, et al. Reporting clinical outcomes of breast reconstruction: a systematic review. *J Natl Cancer Inst* 2011; **103**(1): 31-46.
70. Potter S, Harcourt D, Cawthorn S, et al. Assessment of cosmesis after breast reconstruction surgery: a systematic review. *Ann Surg Oncol* 2011; **18**(3): 813-23.
71. Potter S, Holcombe C, Ward JA, Blazeby JM, Group BS. Development of a core outcome set for research and audit studies in reconstructive breast surgery. *Br J Surg* 2015; **102**(11): 1360-71.
72. O'Connell RL, Stevens RJ, Harris PA, Rusby JE. Review of three-dimensional (3D) surface imaging for oncoplastic, reconstructive and aesthetic breast surgery. *Breast* 2015; **24**(4): 331-42.
73. Pusic AL, Klassen AF, Scott AM, Klok JA, Cordeiro PG, Cano SJ. Development of a new patient-reported outcome measure for breast surgery: the BREAST-Q. *Plastic & Reconstructive Surgery* 2009; **124**(2): 345-53.
74. Cano SJ, Klassen AF, Scott AM, Cordeiro PG, Pusic AL. The BREAST-Q: further validation in independent clinical samples. *Plast Reconstr Surg* 2012; **129**(2): 293-302.
75. Winters ZE, Benson JR. Surgical treatment of multiple ipsilateral breast cancers. *British Journal of Surgery* 2018; **105**(5): 466-8.
76. Ebtctg, McGale P, Taylor C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014; **383**(9935): 2127-35.
77. Ho AY, Hu ZI, Mehrara BJ, Wilkins EG. Radiotherapy in the setting of breast reconstruction: types, techniques, and timing. *Lancet Oncol* 2017; **18**(12): e742-e53.
78. Kuerer HM, Cordeiro PG, Mutter RW. Optimizing Breast Cancer Adjuvant Radiation and Integration of Breast and Reconstructive Surgery. *Am Soc Clin Oncol Educ Book* 2017; **37**: 93-105.
79. Winters ZE, Emson M, Griffin C, et al. Learning from the QUEST multicentre feasibility randomization trials in breast reconstruction after mastectomy. *Br J Surg* 2015; **102**(1): 45-56.
80. Aristei C, Kaidar-Person O, Tagliaferri L, et al. The Assisi Think Tank Meeting and Survey of post MAstectomy Radiation Therapy after breast reconstruction: The ATTM-SMART report. *Eur J Surg Oncol* 2018; **44**(4): 436-43.
81. Potter S, Conroy E, Williamson P, et al. The iBRA (implant Breast Reconstruction evAluation) Study: Protocol for a prospective multicentre cohort study to inform the feasibility, design and conduct of a pragmatic randomised clinical trial comparing new techniques of implant-based breast reconstruction. . *Pilot and Feasibility Studies* 2016; **in press**.
82. McCulloch P, Altman DG, Campbell WB, et al. Surgical Innovation and Evaluation 3 No surgical innovation without evaluation: the IDEAL recommendations. *Lancet* 2009; **374**(9695): 1105-12.
83. Gentilini O, Veronesi U. Abandoning sentinel lymph node biopsy in early breast cancer? A new trial in progress at the European Institute of Oncology of Milan (SOUND: Sentinel node vs Observation after axillary UltraSOUND). *Breast* 2012; **21**(5): 678-81.
84. O'Connell RL, Rusby JE, Stamp GF, et al. Long term results of treatment of breast cancer without axillary surgery - Predicting a SOUND approach? *Eur J Surg Oncol* 2016; **42**(7): 942-8.
85. Giuliano AE, Ballman KV, McCall L, et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. *Jama* 2017; **318**(10): 918-26.
86. Goyal A, Dodwell D. POSNOC: A Randomised Trial Looking at Axillary Treatment in Women with One or Two Sentinel Nodes with Macrometastases. *Clin Oncol-Uk* 2015; **27**(12): 692-5.
87. Hartmann LC, Lindor NM. The Role of Risk-Reducing Surgery in Hereditary Breast and Ovarian Cancer. *N Engl J Med* 2016; **374**(5): 454-68.
88. Ludwig KK, Neuner J, Butler A, Geurts JL, Kong AL. Risk reduction and survival benefit of prophylactic surgery in BRCA mutation carriers, a systematic review. *Am J Surg* 2016; **212**(4): 660-9.
89. Razdan SN, Patel V, Jewell S, McCarthy CM. Quality of life among patients after bilateral prophylactic mastectomy: a systematic review of patient-reported outcomes. *Qual Life Res* 2016; **25**(6): 1409-21.
90. Morrow M, Harris JR. More Mastectomies: Is This What Patients Really Want? *J Clin Oncol* 2009; **27**(25): 4038-40.

91. Jatoi I, Parsons HM. Contralateral prophylactic mastectomy and its association with reduced mortality: evidence for selection bias. *Breast Cancer Res Treat* 2014; **148**(2): 389-96.
92. Basu NN, Ross GL, Evans DG, Barr L. The Manchester guidelines for contralateral risk-reducing mastectomy. *World J Surg Oncol* 2015; **13**(1): 237.
93. Basu NN, Littlechild S, Evans G, Ross G, Barr L. Contralateral risk reducing mastectomy – A national survey of surgeons' practices and perceptions. *European Journal of Surgical Oncology (EJSO)* 2013; **39**(11): S64.
94. Basu NN, Littlechild S, Barr L, Ross GL, Evans DG. Attitudes to contralateral risk reducing mastectomy among breast and plastic surgeons in England. *Ann R Coll Surg Engl* 2016; **98**(2): 121-7.
95. Basu NN, Barr L, Ross GL, Evans DG. Contralateral risk-reducing mastectomy: review of risk factors and risk-reducing strategies. *Int J Surg Oncol* 2015; **2015**: 901046.
96. Badwe R, Hawaldar R, Nair N, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. *Lancet Oncol* 2015; **16**(13): 1380-8.
97. Soran A, Vahit O, Ozbas S, et al. A randomized controlled trial evaluating resection of the primary breast tumor in women presenting with de novo Stage 4 breast cancer: Turkish study (Protocol MF07-01). *J Clin Oncol* 2016; **34**(suppl;): abstr 1005.
98. Ruiz A, Wicherts DA, Sebahg M, et al. Predictive Profile-Nomogram for Liver Resection for Breast Cancer Metastases: An Aggressive Approach with Promising Results. *Ann Surg Oncol* 2017; **24**(2): 535-45.
99. Margonis GA, Buettner S, Sasaki K, et al. The role of liver-directed surgery in patients with hepatic metastasis from primary breast cancer: a multi-institutional analysis. *HPB (Oxford)* 2016; **18**(8): 700-5.
100. Allen RJ, Jr., Cheng MH. Lymphedema surgery: Patient selection and an overview of surgical techniques. *J Surg Oncol* 2016; **113**(8): 923-31.
101. Silva AK, Chang DW. Vascularized lymph node transfer and lymphovenous bypass: Novel treatment strategies for symptomatic lymphedema. *J Surg Oncol* 2016; **113**(8): 932-9.
102. Partridge AH, Pagani O, Abulkhair O, et al. First international consensus guidelines for breast cancer in young women (BCY1). *Breast* 2014; **23**(3): 209-20.
103. Maishman T, Cutress RI, Hernandez A, et al. Local Recurrence and Breast Oncological Surgery in Young Women With Breast Cancer: The POSH Observational Cohort Study. *Ann Surg* 2017; **266**(1): 165-72.
104. Loibl S, Schmidt A, Gentilini O, et al. Breast Cancer Diagnosed During Pregnancy: Adapting Recent Advances in Breast Cancer Care for Pregnant Patients. *JAMA Oncol* 2015; **1**(8): 1145-53.
105. Lambertini M, Kroman N, Ameye L, et al. Safety of pregnancy in patients (pts) with history of estrogen receptor positive (ER+) breast cancer (BC): Long-term follow-up analysis from a multicenter study. *Journal of Clinical Oncology* 2017; **35**(18_suppl): LBA10066-LBA.
106. Wyld L, Reed MW. The need for targeted research into breast cancer in the elderly. *Br J Surg* 2003; **90**(4): 388-99.
107. All-Party Parliamentary Group. APPG Report on Breast Cancer. <https://www.kcl.ac.uk/innovation/groups/earlypres/Publications/Age-is-just-a-number---APPG-report-on-older-people-and-breast-cancer.pdf> (accessed 21/06/2017).
108. Biganzoli L, Wildiers H, Oakman C, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol* 2012; **13**(4): e148-60.
109. Hind D, Wyld L, Reed MW. Surgery, with or without tamoxifen, vs tamoxifen alone for older women with operable breast cancer: Cochrane review. *Brit J Cancer* 2007; **96**(7): 1025-9.
110. Wyld L, Garg DK, Kumar ID, Brown H, Reed MWR. Stage and treatment variation with age in postmenopausal women with breast cancer: compliance with guidelines. *Br J Cancer* 2004; **90**(8): 1486-91.
111. Reed MW, Wyld L, Ellis P, et al. Breast cancer in older women: trials and tribulations. *Clin Oncol (R Coll Radiol)* 2009; **21**(2): 99-102.
112. Lavelle K, Sowerbutts AM, Bundred N, et al. Is lack of surgery for older breast cancer patients in the UK explained by patient choice or poor health? A prospective cohort study. *Br J Cancer* 2014; **110**(3): 573-83.
113. Ring A, Harder H, Langridge C, Ballinger RS, Fallowfield LJ. Adjuvant chemotherapy in elderly women with breast cancer (AChEW): an observational study identifying MDT perceptions and barriers to decision making. *Ann Oncol* 2013; **24**(5): 1211-9.
114. Bhangu A, Koliass AG, Pinkney T, Hall NJ, Fitzgerald JE. Surgical research collaboratives in the UK. *Lancet* 2013; **382**(9898): 1091-2.

115. Baker E, Kim B, Rattay T, et al. The TeaM (Therapeutic Mammoplasty) study: Protocol for a prospective multi-centre cohort study to evaluate the practice and outcomes of therapeutic mammoplasty. *International Journal of Surgery Protocols* 2016; **1**: 3-10.
116. Dave R, O'Connell R, Rattay T, et al. The iBRA-2 (immediate breast reconstruction and adjuvant therapy audit) study: protocol for a prospective national multicentre cohort study to evaluate the impact of immediate breast reconstruction on the delivery of adjuvant therapy. *BMJ Open* 2016; **6**(10): e012678.
117. Tang SS, Kaptanis S, Haddow JB, et al. Current margin practice and effect on re-excision rates following the publication of the SSO-ASTRO consensus and ABS consensus guidelines: a national prospective study of 2858 women undergoing breast-conserving therapy in the UK and Ireland. *Eur J Cancer* 2017; **84**: 315-24.
118. Royal College of Surgeons. Surgical Research Report 2018. <https://www.rcseng.ac.uk/standards-and-research/research/surgical-research-reports/> (accessed 11/6/18).