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Article Authors

Association of Breast Surgeons Working Group

On Behalf of the Academic Section of Association of Breast Surgeons

United Kingdom

Article Contributors

Ash Subramanian, Amtul R Carmichael, , Cliona C Kirwan,
John Benson, James Harvey, Matthew Green, Ramsey I Cutress, Stuart A McIntosh, , Shelley Potter, Romics Laszlo, Fenlon D.R., Pat Fairbrother, Sarah Holborn, Edward St John. Rachel O'Connell,
Chris Holcombe * , Daniel Leff PhD* & Raghavan Vidya*,
*= Joint senior authors

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Introduction

Breast cancer is the commonest cancer in women in the United Kingdom (UK), with over 50,000 new cases diagnosed each year. Over the next decade the evolving advances in science, technology and its applications will undoubtedly have a major influence on delivery of health care and training. Here we set out our vision on impact of innovations in science and technlogy on the future surgical management of breast cancer.

Genetics and Genomics for Improved Risk Profiling

Genomic medicine is likely to improve the selection of neoadjuvant and adjuvant systemic therapies for breast cancer. Increasing use of sequencing technologies will identify therapeutic targets at an individual level, making precision medicine for breast cancer patients a reality. Finally, liquid biopsies, will be in use for the quantification of circulating tumour DNA, and these will likely have utility for screening and early detection of breast cancer, as well as disease monitoring and early detection of recurrence [1].

While mutations in high-risk breast cancer predisposition genes such as BRCA1/2, TP53 and PALB2 have been identified , it seems unlikely that mutations in coding regions of additional genes will be identified to account for missing hereditability of breast cancer. Thus, it is likely that either non-coding and splice site mutations, or the contribution of multiple breast cancer-susceptibility alleles (with much lower effect sizes) will be studied, allowing development of polygenic risk scores. In turn, this will permit a more individualised approach to screening and prevention, as more sophisticated approaches to predicting risk for a given individual can be adopted, and this will have clear implications for the surgeons given that the risk management of these patients remains the province of the breast surgeon.

In genomic terms, the somatic mutational landscape of normal tissue (predating development of proliferative or malignant lesions), is not well understood, although in some tissue types it has been shown that within normal tissue a significant somatic mutational burden (comprising frequent known cancer driver mutations) can be identified [2]. More detailed study of this landscape will improve our understanding of tumour initiating events and possible pathways of tumourigenesis. This in turn will allow for more individualised approaches to prevention, as well as development of

temporal biomarkers of genomic instability in high-risk patients, aiding surgeons to guide the optimal timing of risk-reduction surgery.

Early Lesion Localisation and Minimally Invasive Therapies

In the future, we anticipate less invasive procedures being able to adequately treat breast cancers, using techniques ith proven success in the treatment of other solid tumors. Specifically, percutaneous ablation procedures including radiofrequency ablation (RFA), cryoablation, interstitial laser therapy, microwave thermotherapy, and high intensity focused ultrasound (HIFU) ablation are all able to successfully induce coagulative necrosis with a low side-effect profile but complete ablation is not achieved consistently (1). RFA, which is the most frequently applied, is a short procedure with a relatively high complete ablation rate of breast cancer especially under 2 cm (2, 3). HIFU is a relatively novel technique with the lowest complication rate of all, it is entirely non invasive requiring no incision at all and its human application under MRI guidance is under investigation (MR-HIFU) although cost effectiveness has been questioned mainly due to the length of the procedure (4). In addition, non-surgical ablation when combined with immune modulator treatment may be beneficial to induce abscopal effect in metastatic breast cancer in particular after cryoablation (5). As cryotherapy is the only ablative method, which leaves tumor-associated antigens intact it is in the focus of interest of studies on treatment strategies that combine checkpoint blockade with local therapies. Potentially favourable intratumoral and systemic antitumour immunologic effects can be induced when cryotherapy in combination with immune modulator therapy is applied prior to definitive surgical treatment too (6). Potential advantages of these non-surgical ablative procedures include the ability to perform this procedure under local anesthesia on an outpatient basis, reducing the complication rate and severity of these, reducing recovery time and reducing scarring, therefore potentially improving patients' quality of life. It may also reduce treatment cost, and adjuvant therapy may be administered faster after ablative treatment, in the absence of a wound requiring healing. In addition these procedures could be considered as a possibility for downsizing the effect of overdiagnosis and overtreatment, thus following a less aggressive approach to breast cancer therapy.

HIFU: High intensity focused ultrasound (HIFU) (e.g. EchoPulse™, Theraclion, Malakoff, France), is where focused ultrasound beams act as a high-frequency pressure wave to rapidly heats tissue (60-95 degrees centigrade) causing precise denaturisation and coagulative necrosis. HIFU ablation of fibroadenomas has demonstrated decreased pain and lesion volume compared to controls[26,27] but data is still inconsistent with regards to treatment of breast cancer.[28]

- Cryotherapy: A probe is introduced into a lesion and an iceball is formed to rapidly freeze tissue. Liquid nitrogen cryotherapy systems are being used to treat patients with fibroadenomas, performed under ultrasound guidance in an outpatient environment. The low temperature has analgesic effects. A multicentre phase II trial to treat invasive breast carcinoma demonstrated that of 86 patients, 75.9% of the cancers were successfully ablated.[29]
- Laser: A focused beam of energy causes direct heating of the targeted tissue. Novilase™ (Novian Health, Illinois, USA) has received FDA 510(k) clearance for the treatment of fibroadenomas (≤2 cm), benign breast tumors, and ablation of soft tissue. Small studies have evaluated use of lasers for the treatment of fibroadenoma[30] and breast cancer[31]. Results revealed 97% of fibroadenomas reduced in size on follow up[30] and complete pathological ablation was achieved in 88% of tumours smaller than 2cm, but only 17% in tumours greater than 2cm[31]. Multicentre trials to further evaluate the use of laser ablation for breast cancer are ongoing (e.g. BR-002, "Ablate and Resect" Study of Novilase® Interstitial Laser Therapy for the Ablation of Small Breast Cancers and "Laserbreast1", Study of local treatment by thermic Destruction of primitive breast cancer.)
- Radiofrequency Ablation (RFA): Electrosurgical ablation uses high frequency current via needle electrodes under ultrasound guidance causing coagulative necrosis to the surrounding tissues. Studies investigating the use of RFA for breast cancer have demonstrated complete ablation in 85%-92.5% of lesions (<2cm)[32-34]. However, during a direct comparison, authors preferred the use of cryotherapy due to increased patient compliance and the inherent analgesic effects as a result of freezing.[33]

Microwave ablation: This technique uses electromagnetic waves to produce tissue heating resulting in localised necrosis. Recent studies have demonstrated successful ablation of benign breast lesions (82-100%)[35,36] and high rates of complete pathological malignant tumour ablation (90%)r.[37]

- Minimally invasive lesion excision techniques (e.g. Vacuum assisted biopsy). Vacuum assisted biopsy (VAB) allows image-guided removal of a larger quantities of tissue compared to the conventional core biopsy technique. Mammotome (Johnson & Johnson, New Jersey, USA) was the first commercially available vacuum device but now there are many others including the BARD EnCore (Bard Biopsy Systems, Arizona, USA) and the Hologic Suros Atec (Hologic Inc, Massachusetts, USA).[38] As well as the diagnostic role of VAB in achieving optimal tissue biopsy specimens, it has also been used for the complete excision of breast lesions. Successful management of B3 lesions has been demonstrated with first line management of VAB, where 62% of patients avoided surgical exicsion.[39] Excision of selected B3 lesions with VAB has been supported by more recent international consensus regarding the management of B3 lesions.[40] The Intact™ breast lesion excision system (Medtronic, USA) uses an automated radiofrequency electrosurgical system to excise, capture and retrieve breast specimens.

Surgical Avoidance & Non-Operative Therapies

The concept of non-operative therapy of breast cancer or DCIS is an evolving new paradigm. If it is proved to be safe and effective, has the potential to eliminate postsurgical complications, improve quality of life, and decrease healthcare costs. There has been dramatic improvement in pathologic complete response rates after neo-adjuvant systemic treatment in the past decade, especially among triple-negative and human epidermal growth factor receptor 2-positive breast cancers. This questions the paradigm for the necessity of breast and nodal surgery in all cases, particularly when the patient will be receiving adjuvant local therapy with radiotherapy (1).

Current trials have commenced looking at omission of breast surgery, the ultimate breast conserving strategy, in exceptional responders after neo-adjuvant systemic treatment (2). Such trials will, however, rely on developments in post-

treatment high quality imaging and / or image-guided percutaneous large-volume biopsy with an adequate sampling of residual imaging abnormalities to select patients appropriately for avoidance of breast surgery. This however will require limiting patients for this potential approach with either a complete radiologic response or near-complete radiologic response for adequate pathologic assessment for residual disease. The concept of de-escalating axillary surgery is currently trialed, too. In the context of neo-adjuvant treatment, ongoing studies are currently questioning whether completion axillary dissection can be safely substituted with axillary radiotherapy in patients who demonstrate axillary response to neo-adjuvant chemotherapy (3). In the future, neo-adjuvant systemic therapy may also provide the unique opportunity to avoid axillary staging altogether in women who undergo breast conserving therapy with adjuvant radiation after achieving pathologic complete response in the breast.

In the modern context of sentinel lymph node surgery, ongoing trials explore the added value of sentinel lymph node biopsy over avoidance of any axillary surgery when the axilla is both clinically and ultrasonographically negative (4). In ductal *carcinoma-in-situ* (DCIS) current trials are aiming to determine whether screen-detected low nuclear grade DCIS can safely be managed by an active surveillance strategy (with ot without hormonal therapy only) or that the conventional treatment - including surgical resection - should remain the standard of care (5, 6).

Systemic or locally administered agents that are taken up by tumours to guide intraoperative tumour localisation may represent a future tool to assist surgeons. Nanotechnology is the development of materials in the nanometer (10^9m) size range. The potential of cancer nanotechnology lies in the ability to engineer vehicles that penetrate tumours with high specificity. Active targeting involves linking ligands to nanoparticles that are tumour specific. Passive targeting exploits the inherent size of nanoparticles and the wide fenestrations between endothelial cells in tumour vasculature. For example**,** Gold nanoparticles conjugated to EGFR antibodies facilitate biopsy of precancerous lesions in cervical cancer. This technique could potentially have efficacy in breast cancer, in terms of localisation, and even in directing non-surgical excision of small lesions, possibly even using techniques such as photothermal ablation. Surgical techniques including local infiltration of radiotherapy-sensitising chemicals, such as gold nanoparticles, may allow more targeted radiotherapy, facilitating higher dose delivery to relevant tissues whilst sparing surrounding normal tissue.

Adequately powered and prospectively conducted cohort trials are required to confirm complete pathological ablation in all patients as all ablative techniques are generally being evaluated in small, often uncontrolled studies that are unlikely to change clinical practice or provide the basis for phase III trials (7, 8). Once efficacy to achieve complete pathological ablation is confirmed, randomized controlled trials comparing the most promising ablative technique to surgical excision as well as comparison of ablative techniques with each other can be conducted to determine long-term treatment related and cancer specific complications. In addition trials needs to be planned for the potential utilization of the techniques for ductal carcinoma *in situ* as all the trials treated patients with invasive breast cancer or breast recurrences due to the lack of reliable imaging tools for treatment planning and assessment of response to treatment in ductal carcinoma *in situ*. Nevertheless, the disadvantage of all these techniques is that surgical axillary staging is still required in patients with early breast cancer so surgery cannot be avoided completely at the moment.

Optimising Breast Conserving Surgery & Minimising Re-operative Interventions

A plethora of techniques are emerging to inform the surgeon about the surgical margin status intra-operatively and enable immediate action to reduce margin positivity and reoperation rates. Broadly, there are four categories:

1. Imaging techniques: High frequency ultrasound is capable of high resolution imaging with pilot data suggesting it can be used to differentiate malignant and benign breast tissue with a sensitivity of 76.9% and specificity of 85.2%.[1] Three dimensional, high resolution, specimen images can be captured using miniaturised specimen CT imaging systems, known as Micro-CT[2] or portable MRI scanner.[3]
2. Optical techniques: Raman spectroscopic probes use scattering of light to measure molecular vibrations to determine the structural fingerprints of normal and malignant breast tissue.[4,5] Optical Coherence tomography (OCT) measures the speed and reflection of infrared light waves, to produce high resolution non-invasive images of tissue microstructure which has been successfully piloted for specimen margin status.[6,7] Confocal microscopy can provide real-time highly magnified surface level images allowing intraoperative non-invasive breast

margin histopathological examination.[8,9] Fluorescence techniques are being used to target and identify breast cancer with potential towards margin assessment.[10,11] While Cerenkov luminescence imaging (CLI) detects light emitted from positron emission tomography (PET) imaging agents, and is under investigation for use in breast margin detection.[12]

3. Bio impedance: The electrical impedance of tissue can be measured in relation to an applied electric field. This enables immediate specimen examination to determine tissue type. MarginProbe™ is commercially available and its use has demonstrated reduction in re-excision rates[13,14], and ClearEdge™ is undergoing clinical evaluation.[15]
4. Mass spectrometry: Mass spectrometers measure the mass/charge of ions and can be used to provide detailed chemical analysis of tissues. The intelligent knive (iKnife) has been used to analyse diathermy smoke during breast surgery in real-time with promising results[16] whilst the MasSpec pen uses a probe based approach to provide tissue surface analysis.[17]

Neoadjuvant Therapy- Surgical Precision and Active Monitoring

Translational science is leading us into an era of more personalised breast cancer treatment. Increasingly neoadjuvant therapies are being used not just to downstage tumours prior to surgery, but increasingly to trial the efficacy of systemic therapies on individual patients to allow a more individualised approach. Early breast cancer treatment is increasingly likely to require surgeons to work even more closely with oncologists to facilitate trial and re-biopsy of consecutive systemic therapies prior to definitive surgical excision. With increasing rates of tumour response to neoadjuvant therapies, for example with dual anti-Her2 therapies, there is a need to accurately determine residual tumour size to allow precise, and not excessive, surgical excision. In certain cicumstances of complete clinical, radiological and 'pathological' response (as determined by multiple core biopsies) it may be possible to avoid surgery entirely in lieu of active monitoring .

Neoadjuvant treatment for breast cancer has become an increasingly utilised treatment modality over the last three decades. At an individual level, response to treatment is prognostic[1]; however, this correlation has not been seen at a trial level,

and benefits of neoadjuvant treatment have not always translated to a clinically meaningful overall or recurrence free survival benefit in the adjuvant setting[2, 3].

It has been demonstrated that with careful patient selection, high rates of complete pathological response can be obtained[4, 5]. Future development in this area is likely to focus on improved patient selection for neoadjuvant treatments, whether cytotoxic or targeted therapies. It is likely that such developments will be predicated on improved understanding of the genomic landscape of breast cancer, with increasingly widespread adoption of next generation sequencing technologies leading to the identification of additional therapeutic targets for novel agents.

In this context, it is likely that some patients will no longer require surgery following neoadjuvant systemic therapy. Trials have commenced looking at omission of surgery in exceptional responders [6, 7]. Such trials will, however, rely on developments in post-treatment imaging and biopsy to identify and predict complete response. Where a complete response to neoadjuvant treatment is not seen, it is likely that re-biopsy of residual disease, using next generation sequencing technologies to identify additional drug targets in residual disease, will provide information to guide additional systemic therapies, either before definitive surgery or in the adjuvant setting.

Finally, neoadjuvant radiotherapy remains an under-exploited treatment modality, although there is increasing interest in this area. It is likely that radiotherapy will feature in future trials of neoadjuvant treatment, either alone, or in combination with agents such as immune checkpoint inhibitors to exploit effects such as the abscopal effect[8]. Developments in neoadjuvant treatment have clear implications for breast surgeons, who require to be aware of these to make optimal treatment decisions for their breast cancer patients; it is possible that breast surgery may evolve to become an adjuvant therapy following personalised selection of primary systemic therapies.

Technologies for Improved Breast Cancer Staging & Axillary De-escalation

Sentinel lymph node (SLN) biopsy has been embraced around the world as a standard of care for breast cancer patients and incorporates dual localization techniques using a combination of blue dye and radioisotope (1). There are potential drawbacks from radioisotopes as a tracer agent for SLN localization including cumulative radiation exposure for healthcare workers, surgical waste disposal and restrictions on access to radioisotopes secondary to mandatory licensing. These radioisotopes are a bi-product

of a contracting nuclear industry and supply might become unpredictable with more widespread usage, particularly within emerging economies of Asia. Localization techniques using non-radioactive tracers warrant further investigation and in the longer term there is a need to explore novel agents. These include fluorescence mapping with indocyanine green (ICG) and magnetic nanoparticles that have each been evaluated and deemed to be non-inferior to standard tracer agents (2,3). Alternative tracers such as these might eventually be used as single agents for SLN biopsy; they combine many of the advantages of blue dye and radioisotope without the disadvantages and might be relevant once more clinical experience as part of a dual localization strategy has accrued (4).

Improvements in adjuvant systemic therapy and radiotherapy contribute to loco-regional control and have decreased the therapeutic value of axillary surgery. Furthermore, its staging role is declining with decisions for adjuvant therapies often based on primary tumor characteristics and various biomarkers of clinical utility. Rates of axillary recurrence for SLN biopsy negative and selected SLN biopsy positive cases are very low (5,6). So why perform SLN biopsy if there is no survival benefit from ALND, regional recurrence rates are low and results of axillary surgery infrequently select patients for adjuvant treatments? (7). There is a finite rate of lymphoedema from SLN biopsy (approximately 5% at 5 years) that has relevance to prolonged survivorship. Two ongoing trials are exploring the feasibility of omission of surgical staging of the axilla in some breast conserving surgery patients who are clinically node negative with favorable primary tumor characteristics (8,9). Eligible patients will be randomized to SLN biopsy or no axillary surgery and preliminary analysis suggests that non-inferiority will be upheld for the observation arm. Imaging of axillary nodes using MRI with newer contrast agents (iron nanoparticles) may increase negative and positive predictive values but functional imaging with FDG-PET seems unlikely to reach levels of sensitivity which will stratify axillary tumour burden and aid initial management of early breast cancer patients (10). Axillary node clearance still forms a fundamental operation in breast cancer, with no progress being made in lymphoedema prevention. Techniques to allow visualisation and protection of lymphatics, possibly using nanotechnology may warrant investigation. Sentinel node mapping is the basis of histological axillary staging. Radioisotope has resource and safety implications, however newer magnetic-based techniques are limited by the inability to use metallic surgical tools. Nanotechnology

may offer further options for sentinel node identification and potentially even local delivery of treatment.

Innovations in Reconstructive Breast Surgery

Breast reconstructive surgery is by nature personalised by the surgeon to the patient with the aim of achieving a result that is both technically satisfactory and more importantly meets patient expectations. Implant based breast reconstruction has far higher infection and implant loss rates than other surgical devices. This is largely because of the compromised skin perfusion following mastectomy. Intra-operative techniques to assess vascularity, for example using near-infra-red spectroscopy and quantum dot nanoparticles, would allow intervention at an early stage, with directed skin resection.

Acellular dermal matrices

The use of acellular dermal matrices (ADM) has revolutionised implant based breast reconstruction since its first use in 2005. A great deal of literature is available, involving over 7000 ADM-based reconstructions [44]. Their use has become an attractive, but expensive option. The matrixes can be subdivided into human derived, which are not available in the UK, or xenografts such as porcine. ADMs have recently become significantly more user friendly, with shaped, perforated (to reduce seroma) and bilateral versions [45].

Traditionally ADMs have been used for lower pole coverage, however there is a body of growing literature for its use in pre-pectoral implant based reconstruction where the ADM covers the entire implant. This has the advantage of leaving the pectoralis muscle undisturbed, reducing breast animation and reduced post-operative pain [46].

Synthetic meshes

These are mass-synthesized polymers, which maybe multifilament (Polyglyctain 910, Vicryl) or monofilament (Poly-4-hydroxybutyrate, P4HB). These are far more cost effective than ADMs. The TiLOOP Bra, pfm medical) is a permanent mesh which has shown to have a major complication rate of 13.4% [47]. The Polyglyctain is an absorbable mesh which has shown to have a low infection rate (2.7%) [48].

Studies of ADMs and meshes tend to be small and non-randomised, however the ibra study which is soon to be reported aims to compare different implant based reconstruction methods in a prospective cohort study [49].

Tissue Engineering

The premise behind the technology is the use of an absorbable biologic matrix that is then impregnated with autografted lipocytes from the patient's abdomen or other fatty area. This may be used to fill a defect after breast conservation or whole breast reconstruction. Microtubular structures throughout the matrix provides influx of blood and bionutrients to potentially increase lipocyte viability compared with that of fat grafting alone. Currently the only trials are in animal models, however tissue engineering has recently received National Institute of Health funding with the aim of a clinical trial in due course. Researchers at Queensland University of Technology in Brisbane, Australia, are concurrently working on bioabsorbable 3D printed scaffolds based on MRI reconstruction of the contralateral breast that dissolves over a 2-3 year period as the fatty breast tissue regenerated[50]. At the University of Texas Scientists are working with TeVido BioDevices toward developing 3D bioprinted breast implants for nipple areola complex reconstruction and bespoke volumetric replacement of lumpectomy defects[51]

ICG Angiography

SPY Elite is an intraoperative fluorescence imaging system and it enables surgeons to assess skin perfusion during surgery. It is particularly useful for mastectomy flap assessment during breast reconstruction and has been demonstrated to significantly reduce skin necrosis rates following immediate breast reconstruction.[52]

Volumetric Analysis

Measuring breast volume has been a challenge for breast and plastic surgeons for decades. Methods to do this have ranged from Archimede's principle of water displacement, anthropomorphic methods, thermoplastic/plastic casting to magnetic resonance imaging, computer tomography and three-dimensional surface imaging (3D-SI).[53] 3D-SI has been used to take 3D images of the torso. From this the breast volume is

calculated by interpolating the chest wall and measuring the volume within the mound of the breast. Plastic surgeons have been using this technology to simulate how a patient may appear after an augmentation or breast reduction. It remains to be seen whether this tool is useful to help plan oncological and oncoplastic breast procedures.[54]

Innovations in Follow-up & Survivorship

Issues around survivorship will become increasingly important in breast cancer as so many women survive for so long with the consequences of their treatment. Each new treatment will bring unknown and potential permanent changes which have the potential to impact on people's lives. Personalised medicine and de-escalation of treatment have the potential to increase individual anxiety and fear of cancer recurrence, and work will need to be done to find ways to educate people about risks and risk perception.

Techniques to reduce arm lymphoedema

Lymphovenous Anastomosis (LVAs)

Lymphovenous anastomosis (LVA) aims to overcome obstructions in the lymphatic system caused by axillary dissection by diverting lymph into the venous system proximal to the areas of obstruction. A suitable lymphatic channel must be identified using a distally injected dye (e.g. patent blue) and/or indocyanine green lymphography. Next, a suitable vein of compatible size, location and minimal backflow must be identified for anastomosis. There is no consensus on the optimal timing, number and location of the anastomoses.

Lymph Node Transfer

Vascularized Lymph Node Transfer (VLNT) is the transplantation of vascularized lymph nodes to a lymphoedematous area. There remain many unanswered questions with regards to mechanism of action, donor site selection, recipient site selection, and postoperative care. There is no accepted mechanism by which VLNT improves lymphedema, it is hypothesised that the VLNT functions as a sponge or pump to take

the lymph via the nodes into the venous circulation through naturally occurring lymphovenous connections in the transplanted tissues [58].

Virtual Clinics

The combination of wearable technology, virtual reality, body computing, artificial intelligence and mobile apps has brought about unprecedented advances in technology making the future of breast clinics technology driven. Virtual Care Clinics being established by the University of Southern California have demonstrated the success of hologram house calls. By beaming real-time holograms, clinicians can take a medical history, diagnose a problem and discuss the treatment options with the patients without ever leaving their office. This virtual clinician has the ability to recognise emotion and show empathy through facial expressions, gestures and voice. In the immediate future, this technology may have a huge impact on the management of patients receiving adjuvant treatment for breast cancer. A study of more than 900 patients demonstrated that over 18 months after the diagnosis, an average patient requires 67 appointments in 44 days and spends 3.6 hours in clinics per month and was admitted for 1.9 days.[i] Evidence suggests that during chemotherapy and radiotherapy, 28% of patients require appointments to treat side effects. In 43% of patients these appointments had an impact on their professional life and 77% of patients needed to arrange a caregiver to accompany them. [ii] Virtual Care Breast Clinics have the potential to significantly reduce some of these clinic visits saving patients and their carers the stress and difficulties of unnecessary hospital visit. Future use of this technology can reduce cost and increase clinician productivity.

Virtual Care Breast Clinics have the capacity to transform the symptomatic breast clinic. By using ultrasound related technology, it is possible to create a sensation of temperature and touch. Therefore, intelligent robotic medium and virtual reality techniques can be used to virtually assess abnormalities of breast tissue, that have traditionally been diagnosed by inspection and palpation. By combining the executive function of the human brain with a near complete interaction with the virtual environment, it is potentially possible to perform a remote full clinical breast (digital) examination. For the diagnosis of breast cancer, the advent of portable ultrasound machines connected to smartphone devices have a huge potential for the future. These

portable ultrasound devices have a semiconductor chip which creates sound waves and relay the images to the smart phone. The image can be adjusted and manipulated remotely to gain a better view of the tissue. These devices are relatively affordable, however, their reliability in the remote setting remains to be established.

Virtual Breast Care Clinics have the potential to provide a convenient, effective, affordable, personalised and safe breast care to patients universally. Virtual Breast Care Clinics have got potential for strong consumer appeal. The transformation brought by these technologies can help breast clinicians to become more efficient, and improved patient experience. Virtual Care Breast Clinics can provide opportunity to bridge the gap in specialist service and conduct virtual multidisciplinary team meetings. While Virtual Care Breast Clinics can provide immediacy of consultation and convenience, such clinics may be impersonal and may have a negative impact on rapport development and the doctor-patient relationship.

Delivery of Virtual Clinical Care in the digital healthcare system would require immense infrastructure investment. Surgical teams will need access to efficient and reliable digital platforms and must be trained to be proficient in the use of these technologies. Patient confidentiality and protection of digital data will impose ethical and regulatory challenges, that will need to be addressed as a part of infrastructure development for Virtual Care Breast Clinics.

Breast Cancer Surgical Research

The future for breast cancer treatment is likely to include a wide variety of changes which will result in an increased use of technology, increased use of targeted personalised treatment plans (due to increased understanding of the human genome and cancer biology) and an increase in individual treatment choices. It is important to consider that these changes will take place in a culture which continues to have a limited understanding of the biological mechanisms which drive cancer development and so the gap in understanding between the general public and experts in cancer care will potentially widen. Current Western culture conceptualises and understands cancer in a way that still incorporates language about ‘fighting’ and ‘battling’ and so de-escalation of cancer treatment is unlikely to meet patient expectations. Traditional treatment for cancer has, for so long, been focused on eliminating tumours and potential tumours by surgery, that many women are looking to increase the amount of

surgery that they have in order to minimise their risk of cancer, even at the expense of other poor long term outcomes.

Concurrently, expectations around the way that women look and perceive their own bodies continue to idealise particular notions of the body ideal, particularly in relation to the breast and any future treatment will need to be able to incorporate these ideals into delivery. Consequences of breast surgery on sexuality are also an issue with respect both to the appearance and sensations of the affected breast. While patient choices increase, patient expectations are also increasing. The potential for advanced technologies to improve cosmetic outcomes is great. Future possibilities include the potential to reduce over treatment by large excisions and to perform surgery which leaves good cosmetic outcomes have the potential to more closely match patient expectations with less impact on body image and sexuality.

The consequence of this for the future of breast cancer surgery is that there will be a need to increase service delivery around patient education and supporting patient decision-making. Confidence in health professionals varies over time and the use of new techniques and materials (such as implants and meshes) raises concerns in those who may be the recipients. Health professionals will need increased skills to explain technological advances and support shared decision-making. There will be a need for tools to be developed and tested which will support complex decision making. Clinical teams may have to restructure service delivery to enable these changes to take place.

Finally, if this gap between health experts and the public is to be decreased then clinicians may need to spend much more time in public education and influencing public opinion by engaging widely in public and social media spaces.

REFERENCES

SURGICAL TREATMENT

1. Wong S, De Los Santos J, Basik M. Eliminating Surgery in Early-Stage Breast Cancer: Pipe-Dream or Worthy Consideration in Selected Patients? Current breast cancer reports. 2017;9:148-55.
2. Peek MC, Ahmed M, Napoli A, Usiskin S, Baker R, Douek M. Minimally invasive ablative techniques in the treatment of breast cancer: a systematic review and meta-analysis. International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group. 2016:1-12.
3. Ito T, Oura S, Nagamine S, Takahashi M, Yamamoto N, Yamamichi N, et al. Radiofrequency Ablation of Breast Cancer: A Retrospective Study. Clinical breast cancer. 2017.
4. Peek MC, Ahmed M, Napoli A, ten Haken B, McWilliams S, Usiskin SI, et al. Systematic review of high-intensity focused ultrasound ablation in the treatment of breast cancer. Br J Surg. 2015;102(8):873-82; discussion 82.
5. Simmons RM, Ballman KV, Cox C, Carp N, Sabol J, Hwang RF, et al. A Phase II Trial Exploring the Success of Cryoablation Therapy in the Treatment of Invasive Breast Carcinoma: Results from ACOSOG (Alliance) Z1072. Ann Surg Oncol. 2016;23(8):2438-45.
6. McArthur HL, Diab A, Page DB, Yuan J, Solomon SB, Sacchini V, et al. A Pilot Study of Preoperative Single-Dose Ipilimumab and/or Cryoablation in Women with Early-Stage Breast Cancer with Comprehensive Immune Profiling. Clinical cancer research : an official journal of the American Association for Cancer Research. 2016;22(23):5729-37.
7. Mauri G, Sconfienza LM, Pescatori LC, Fedeli MP, Ali M, Di Leo G, et al. Technical success, technique efficacy and complications of minimally-invasive imaging-guided percutaneous ablation procedures of breast cancer: A systematic review and meta-analysis. European radiology. 2017;27(8):3199-210.
8. Peek MCL, Douek M. Ablative techniques for the treatment of benign and malignant breast tumours. Journal of therapeutic ultrasound. 2017;5:18.

NON-OPERATIVE TREATMENTS

1. Kuerer HM, Rauch GM, Krishnamurthy S, Adrada BE, Caudle AS, DeSnyder SM, 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.
2. Kuerer HM, Vrancken Peeters M, Rea DW, Basik M, De Los Santos J, Heil J. Nonoperative Management for Invasive Breast Cancer After Neoadjuvant Systemic Therapy: Conceptual Basis and Fundamental International Feasibility Clinical Trials. Ann Surg Oncol. 2017;24(10):2855-62.
3. Wong S, De Los Santos J, Basik M. Eliminating Surgery in Early-Stage Breast Cancer: Pipe-Dream or Worthy Consideration in Selected Patients? Current breast cancer reports. 2017;9:148-55.
4. 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.
5. Grimm LJ, Ryser MD, Partridge AH, Thompson AM, Thomas JS, Wesseling J, et al. Surgical Upstaging Rates for Vacuum Assisted Biopsy Proven DCIS: Implications for Active Surveillance Trials. Ann Surg Oncol. 2017;24(12):3534-40.
6. Francis A, Thomas J, Fallowfield L, Wallis M, Bartlett JM, Brookes C, et al. Addressing overtreatment of screen detected DCIS; the LORIS trial. European journal of cancer (Oxford, England : 1990). 2015;51(16):2296-303.

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1) Krag D, Anderson SJ, Julian TB, et al. Sentinel lymph node resection compared with conventional axillary lymph node dissection in clinically node negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol* 2010; **11:** 927 – 933

2) Ballardini B, Santoro L, Sangalli C, et al. The indocyanine green method is equivalent to the Tc-labelled radiotracer method for identifying the sentinel lymph node in breast cancer: A concordance and validation study. *Eur J Surg Oncol* 2013; **39:** 1332 – 1336

3) Douek M, Monneypenny I, Kothari, et al. on behalf of the SentiMAG Trialists Group. Sentinel node biopsy using a magnetic tracer versus standard technique: the SentiMAG multicentre trial. Ann Surg Oncol 2013: published online Dec10 DOI: 10.1245/s10434-013-3379-6

4) Benson JR. Evaluation of the clinical utility of the ICG fluorescence method in comparison to the radioisotope method for sentinel lymph node biopsy in breast cancer (commentary). Ann Surg Oncol 2015; DOI 10.1245/s10434-015-4801-z

5) van der Ploeg IMC, Nieweg OE, van Rijk MC et al. Axillary recurrence after a tumour negative sentinel lymph node biopsy in breast cancer patients: a systematic review and meta-analysis of the literature. *Eur J Surg Oncol* 2008; **34:** 1277 – 1284

6) Guiliano AE, Ballman KV, McCall L, et al. Effect of axillary dissection versus no axillary dissection on 10 year overall survival among women with invasive breast cancer and sentinel node metastases. The ACOSOG Z0011 (ALLIANCE) Randomised Clinical Trial. JAMA 2017; 318 (10): 918 - 926

7) Gentilini O, Veronesi U. Staging the axilla in early breast cancer: will imaging replace surgery? JAMA Oncol 2015; 1(8): 1031 -32

8) 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 versus Observation after axillary UltrasouND. Breast 2012; 12: 678 – 81

9) Comparison of axillary sentinel lymph node biopsy versus no axillary surgery (INSEMA) ClinicalTrials.gov [NCT02466737]

10) El Hage Chehade H, Headon H, Kasem A, Mokbel K. Refining the performance of sentinel lymph node biopsy post-neoadjuvant chemotherapy in patients with pathologically proven pre-treatment node positive breast cancer: an update for clinical practice. ANTICANCER RESEARCH 2016; 36: 1461 – 72

INNOVATIONS CHAPTER (DANIEL, ED, RACHEL)

1. Omer RK, Sorensen KM, Neumayer LA, Factor RE, Doyle TE. High-frequency ultrasound for evaluating margins during breast conservation surgery: Results from a 17-patient pilot study. *The Journal of the Acoustical Society of America.* 2015;138(3):1746-1746.
2. Tang R, Coopey SB, Buckley JM, et al. A pilot study evaluating shaved cavity margins with micro-computed tomography: a novel method for predicting lumpectomy margin status intraoperatively. *The breast journal.* 2013;19(5):485-489.
3. Papa M, Allweis T, Karni T, et al. An intraoperative MRI system for margin assessment in breast conserving surgery: Initial results from a novel technique. *Journal of surgical oncology.* 2016;114(1):22-26.
4. Mohs AM, Mancini MC, Singhal S, et al. Hand-held spectroscopic device for in vivo and intraoperative tumor detection: contrast enhancement, detection sensitivity, and tissue penetration. *Analytical chemistry.* 2010;82(21):9058-9065.
5. Keller MD, Vargis E, de Matos Granja N, et al. Development of a spatially offset Raman spectroscopy probe for breast tumor surgical margin evaluation. *Journal of biomedical optics.* 2011;16(7):077006.
6. Zysk AM, Chen K, Gabrielson E, et al. Intraoperative Assessment of Final Margins with a Handheld Optical Imaging Probe During Breast-Conserving Surgery May Reduce the Reoperation Rate: Results of a Multicenter Study. *Annals of surgical oncology.* 2015;22(10):3356-3362.
7. Erickson-Bhatt SJ, Nolan RM, Shemonski ND, et al. Real-time Imaging of the Resection Bed Using a Handheld Probe to Reduce Incidence of Microscopic Positive Margins in Cancer Surgery. *Cancer research.* 2015;75(18):3706-3712.
8. Chang PT, Leff DR, Shousha S, et al. Imaging breast cancer morphology using probe-based confocal laser endomicroscopy: towards a real-time intraoperative imaging tool for cavity scanning. *Breast cancer research and treatment.* 2015;153(2):299-310.
9. Brachtel EF, Johnson NB, Huck AE, et al. Spectrally encoded confocal microscopy for diagnosing breast cancer in excision and margin specimens. *Laboratory investigation; a journal of technical methods and pathology.* 2016;96(4):459-467.

10. Tummers QR, Verbeek FP, Schaafsma BE, et al. Real-time intraoperative detection of breast cancer using near-infrared fluorescence imaging and Methylene Blue. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology.* 2014;40(7):850-858.
11. Nyirenda N, Farkas DL, Ramanujan VK. Preclinical evaluation of nuclear morphometry and tissue topology for breast carcinoma detection and margin assessment. *Breast cancer research and treatment.* 2011;126(2):345-354.
12. Grootendorst MR, Cariati M, Pinder SE, et al. Intraoperative Assessment of Tumor Resection Margins in Breast-Conserving Surgery Using 18F-FDG Cerenkov Luminescence Imaging: A First-in-Human Feasibility Study. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine.* 2017;58(6):891-898.
13. Thill M, Dittmer C, Baumann K, Friedrichs K, Blohmer JU. MarginProbe(R)--final results of the German post-market study in breast conserving surgery of ductal carcinoma in situ. *Breast.* 2014;23(1):94-96.
14. Schnabel F, Boolbol SK, Gittleman M, et al. A randomized prospective study of lumpectomy margin assessment with use of MarginProbe in patients with nonpalpable breast malignancies. *Annals of surgical oncology.* 2014;21(5):1589-1595.
15. Dixon JM, Renshaw L, Young O, et al. Intra-operative assessment of excised breast tumour margins using ClearEdge imaging device. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology.* 2016.
16. 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 research : BCR.* 2017;19:59.
17. Zhang J, Rector J, Lin JQ, et al. Nondestructive tissue analysis for ex vivo and in vivo cancer diagnosis using a handheld mass spectrometry system. *Science translational medicine.* 2017;9(406).
18. Volders JH, Haloua MH, Krekel NM, et al. Intraoperative ultrasound guidance in breast-conserving surgery shows superiority in oncological outcome, long-term cosmetic and patient-reported outcomes: Final outcomes of a randomized controlled trial (COBALT). *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology.* 2017;43(4):649-657.
19. Cox CE, Russell S, Prowler V, et al. A Prospective, Single Arm, Multi-site, Clinical Evaluation of a Nonradioactive Surgical Guidance Technology for the Location of Nonpalpable Breast Lesions during Excision. *Annals of surgical oncology.* 2016;23(10):3168-3174.
20. Jeffries DO, Dossett LA, Jorns JM. Localization for Breast Surgery: The Next Generation. *Archives of pathology & laboratory medicine.* 2017;141(10):1324-1329.
21. Schermers B, van der Hage JA, Loo CE, et al. Feasibility of magnetic marker localisation for non-palpable breast cancer. *Breast.* 2017;33:50-56.
22. Dauphine C, Reicher JJ, Reicher MA, Gondusky C, Khalkhali I, Kim M. A Prospective Clinical Study to Evaluate the Safety and Performance of Wireless Localization of Nonpalpable Breast Lesions Using Radiofrequency Identification Technology. *American Journal of Roentgenology.* 2015;204(6):W720-W723.
23. Ungi T, Gauvin G, Lasso A, et al. Navigated breast tumor excision using electromagnetically tracked ultrasound and surgical instruments. *IEEE transactions on bio-medical engineering.* 2015.
24. Janssen N, Eppenga R, Peeters MV, et al. Real-time wireless tumor tracking during breast conserving surgery. *Int J Comput Assist Radiol Surg.* 2017.
25. Peek MCL, Douek M. Ablative techniques for the treatment of benign and malignant breast tumours. *J Ther Ultrasound.* 2017;5:18.
26. Peek MC, Ahmed M, Scudder J, et al. High intensity focused ultrasound in the treatment of breast fibroadenomata: results of the HIFU-F trial. *Int J Hyperthermia.* 2016;32(8):881-888.
27. Kovatcheva R, Zaletel K, Vlahov J, Stoinov J. Long-term efficacy of ultrasound-guided high-intensity focused ultrasound treatment of breast fibroadenoma. *J Ther Ultrasound.* 2017;5:1.
28. Peek MC, Ahmed M, Napoli A, et al. Systematic review of high-intensity focused ultrasound ablation in the treatment of breast cancer. *The British journal of surgery.* 2015;102(8):873-882; discussion 882.
29. Simmons RM, Ballman KV, Cox C, et al. A Phase II Trial Exploring the Success of Cryoablation Therapy in the Treatment of Invasive Breast Carcinoma: Results from ACOSOG (Alliance) Z1072. *Annals of surgical oncology.* 2016;23(8):2438-2445.

30. Lai LM, Hall-Craggs MA, Mumtaz H, et al. Interstitial laser photocoagulation for fibroadenomas of the breast. *The Breast.* 1999;8(2):89-94.
31. van Esser S, Stapper G, van Diest PJ, et al. Ultrasound-guided laser-induced thermal therapy for small palpable invasive breast carcinomas: a feasibility study. *Annals of surgical oncology.* 2009;16(8):2259-2263.
32. Kinoshita T, Iwamoto E, Tsuda H, Seki K. Radiofrequency ablation as local therapy for early breast carcinomas. *Breast cancer.* 2011;18(1):10-17.
33. Manenti G, Scarano AL, Pistolese CA, et al. Subclinical Breast Cancer: Minimally Invasive Approaches. Our Experience with Percutaneous Radiofrequency Ablation vs. Cryotherapy. *Breast Care (Basel).* 2013;8(5):356-360.
34. Ito T, Oura S, Nagamine S, et al. Radiofrequency Ablation of Breast Cancer: A Retrospective Study. *Clinical breast cancer.* 2017.
35. Zhang W, Li JM, He W, et al. Ultrasound-guided percutaneous microwave ablation for benign breast lesions: evaluated by contrast-enhanced ultrasound combined with magnetic resonance imaging. *J Thorac Dis.* 2017;9(11):4767-4773.
36. Yu J, Chen BH, Zhang J, et al. Ultrasound guided percutaneous microwave ablation of benign breast lesions. *Oncotarget.* 2017;8(45):79376-79386.
37. Zhou W, Zha X, Liu X, et al. US-guided percutaneous microwave coagulation of small breast cancers: a clinical study. *Radiology.* 2012;263(2):364-373.
38. Bennett IC. The Changing Role of Vacuum-assisted Biopsy of the Breast: A New Prototype of Minimally Invasive Breast Surgery. *Clinical breast cancer.* 2017;17(5):323-325.
39. Strachan C, Horgan K, Millican-Slater RA, Shaaban AM, Sharma N. Outcome of a new patient pathway for managing B3 breast lesions by vacuum-assisted biopsy: time to change current UK practice? *Journal of clinical pathology.* 2016;69(3):248-254.
40. 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 research and treatment.* 2016;159(2):203-213.
41. Whitworth PW, Simpson JF, Poller WR, et al. Definitive diagnosis for high-risk breast lesions without open surgical excision: the Intact Percutaneous Excision Trial (IPET). *Annals of surgical oncology.* 2011;18(11):3047-3052.
42. Razek NA, Eshak SE, el Ghazaly H, Omar OS, Yousef OZ, Shaalan M. Percutaneous breast lesion excision system (BLES): A new tool for complete closed excision of high risk lesions (Egyptian experience). *The Egyptian Journal of Radiology and Nuclear Medicine.* 2013;44(2):383-389.
43. Niinikoski L, Hukkinen K, Leidenius MHK, Stahls A, Meretoja TJ. Breast Lesion Excision System in the diagnosis and treatment of intraductal papillomas - A feasibility study. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology.* 2018;44(1):59-66.
44. Eichler C, Schulz C, Vogt N, Warm M. The Use of Acellular Dermal Matrices (ADM) in Breast Reconstruction: A Review. *Surg Technol Int.* 2017;31:53-60.
45. Kim JYS, Mlodinow AS. What's New in Acellular Dermal Matrix and Soft-Tissue Support for Prosthetic Breast Reconstruction. *Plast Reconstr Surg.* 2017;140(5S Advances in Breast Reconstruction):30s-43s.
46. Wazir U, Mokbel K. The evolving role of pre-pectoral ADM-assisted implant-based immediate breast reconstruction following skin-sparing mastectomy. *Am J Surg.* 2018.
47. Dieterich M, Paepke S, Zwiefel K, et al. Implant-based breast reconstruction using a titanium-coated polypropylene mesh (TiLOOP Bra): a multicenter study of 231 cases. *Plast Reconstr Surg.* 2013;132(1):8e-19e.
48. Meyer Ganz O, Tobalem M, Perneger T, et al. Risks and benefits of using an absorbable mesh in one-stage immediate breast reconstruction: a comparative study. *Plast Reconstr Surg.* 2015;135(3):498e-507e.
49. Potter S, Conroy EJ, Williamson PR, et al. The iBRA (implant breast reconstruction evaluation) study: protocol for a prospective multi-centre cohort study to inform the feasibility, design and conduct of a pragmatic randomised clinical trial comparing new techniques of implant-based breast reconstruction. *Pilot Feasibility Stud.* 2016;2:41.
50. https://www.theaustralian.com.au/news/health-science/absolutely-biofabulous-bioprinting-to-regrow-damaged-body-parts/news-story/e937047876da7539424cee00e6a5d556?sv=e211c7cd03a4fe58bb6d06ba590aec78. In.
51. **3-D Tissue Printing Will Help Women with Breast Cancer** http://engineering.utep.edu/announcement062713.htm. In.

52. Sood M, Glat P. Potential of the SPY intraoperative perfusion assessment system to reduce ischemic complications in immediate postmastectomy breast reconstruction. *Annals of surgical innovation and research.* 2013;7(1):9.
53. Choppin SB, Wheat JS, Gee M, Goyal A. The accuracy of breast volume measurement methods: A systematic review. *Breast.* 2016;28:121-129.
54. 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):331-342.
55. Tsujimoto M, Nakabayashi K, Yoshidome K, et al. One-step nucleic acid amplification for intraoperative detection of lymph node metastasis in breast cancer patients. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2007;13(16):4807-4816.
56. Tiernan JP, Verghese ET, Nair A, et al. Systematic review and meta-analysis of cytokeratin 19-based one-step nucleic acid amplification versus histopathology for sentinel lymph node assessment in breast cancer. *Br J Surg.* 2014;101(4):298-306.
57. Ahmed M, Rubio IT, Kovacs T, Klimberg VS, Douek M. Systematic review of axillary reverse mapping in breast cancer. *Br J Surg.* 2016;103(3):170-178.
58. Allen RJ, Jr., Cheng MH. Lymphedema surgery: Patient selection and an overview of surgical techniques. *J Surg Oncol.* 2016;113(8):923-931.
59. Soybir G, Fukuma E. Endoscopy Assisted Oncoplastic Breast Surgery (EAOBS). *J Breast Health.* 2015;11(2):52-58.
60. Leff DR, Vashisht R, Yongue G, Keshtgar M, Yang GZ, Darzi A. Endoscopic breast surgery: where are we now and what might the future hold for video-assisted breast surgery? *Breast cancer research and treatment.* 2011;125(3):607-625.
61. Kitamura K, Ishida M, Inoue H, Kinoshita J, Hashizume M, Sugimachi K. Early results of an endoscope-assisted subcutaneous mastectomy and reconstruction for breast cancer. *Surgery.* 2002;131(1):S324-S329.
62. Clemens MW, Kronowitz S, Selber JC. Robotic-assisted latissimus dorsi harvest in delayed-immediate breast reconstruction. *Seminars in plastic surgery.* 2014;28(1):20-25.
63. Selber JC, Baumann DP, Holsinger CF. Robotic harvest of the latissimus dorsi muscle: laboratory and clinical experience. *Journal of reconstructive microsurgery.* 2012;28(7):457-464.
64. Toesca A, Peradze N, Manconi A, et al. Robotic nipple-sparing mastectomy for the treatment of breast cancer: Feasibility and safety study. *Breast.* 2017;31:51-56.
65. Ruidiaz ME, Messmer D, Atmodjo DY, et al. Comparative healing of human cutaneous surgical incisions created by the PEAK PlasmaBlade, conventional electrosurgery, and a standard scalpel. *Plastic and reconstructive surgery.* 2011;128(1):104-111.
66. MacDonald JD, Bowers CA, Chin SS, Burns G. Comparison of the effects of surgical dissection devices on the rabbit liver. *Surgery today.* 2014;44(6):1116-1122.
67. van Bastelaar J, van Roozendaal L, Granzier R, Beets G, Vissers Y. A systematic review of flap fixation techniques in reducing seroma formation and its sequelae after mastectomy. *Breast cancer research and treatment.* 2017.
68. Thekkinkattil DK, Hussain T, Mahapatra TK, McManus PL, Kneeshaw PJ. Feasibility of use of a barbed suture (v-loc 180) for quilting the donor site in latissimus dorsi myocutaneous flap breast reconstruction. *Archives of plastic surgery.* 2013;40(2):117-122.
69. Cortez R, Lazcano E, Miller T, et al. Barbed sutures and wound complications in plastic surgery: an analysis of outcomes. *Aesthet Surg J.* 2015;35(2):178-188.
70. van Bastelaar J, Theunissen LLB, Snoeijs MGJ, Beets GL, Vissers YLJ. Flap Fixation Using Tissue Glue or Sutures Appears to Reduce Seroma Aspiration After Mastectomy for Breast Cancer. *Clinical breast cancer.* 2017;17(4):316-321.
71. Eichler C, Fischer P, Sauerwald A, Dahdouh F, Warm M. Flap adhesion and effect on postoperative complication rates using Tissuglu(R) in mastectomy patients. *Breast cancer.* 2016;23(3):486-490.
72. Tang R, Coopey SB, Specht MC, et al. Lumpectomy specimen margins are not reliable in predicting residual disease in breast conserving surgery. *American journal of surgery.* 2015;210(1):93-98.
73. St John ER, Scott AJ, Irvine TE, Pakzad F, Leff DR, Layer GT. Completion of hand-written surgical consent forms is frequently suboptimal and could be improved by using electronically generated, procedure-specific forms. *The Surgeon.* 2017;15(4):190-195.
74. Patel TA, Puppala M, Ogunti RO, et al. Correlating mammographic and pathologic findings in clinical decision support using natural language processing and data mining methods. *Cancer.* 2017;123(1):114-121.

75. Bartlett RD, Radenkovic D, Mitrasinovic S, et al. A pilot study to assess the utility of a freely downloadable mobile application simulator for undergraduate clinical skills training: a single-blinded, randomised controlled trial. *BMC Med Educ.* 2017;17(1):247.
76. Kowalewski KF, Hendrie JD, Schmidt MW, et al. Validation of the mobile serious game application Touch Surgery for cognitive training and assessment of laparoscopic cholecystectomy. *Surgical endoscopy.* 2017;31(10):4058-4066.