Health Policy Advisory Committee on Technology

Technology Brief

Margin Probe® to assess surgical margins during lumpectomy for breast cancer

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HealthPACT
emerging health technology
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This brief was prepared by Dr. Vicki Foerster, Dr. Merric Edgar-Hughes, Deanne Forel and Stef Gurgacz for the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).
Technology, Company and Licensing

Register ID WP 141

Technology name MarginProbe® to assess surgical margins during lumpectomy for breast cancer

Patient indication Use of the device is indicated for a patient with breast cancer undergoing lumpectomy during breast conservation surgery.

Description of the technology

The goal of breast conservation surgery (BCS) for breast cancer is the complete removal of the tumour with clear specimen margins, since failure to obtain clear margins is a leading risk factor for local recurrence; however, since microscopic involvement is not readily assessable intra-operatively, finding tumour cells close to or at the margin of a lumpectomy specimen on histology exam (often not reported until days later) is fairly common.¹

Reoperation for positive margins may be needed in 30 to 50 per cent of cases and is associated with patient anxiety and discomfort, increased costs and poorer cosmetic outcomes. MarginProbe® is designed to detect malignant cells at or near a tissue margin. (Note that an issue recently profiled is the lack of consensus on the optimal distance between the tumour and surgical margin, which varies from 1 mm to 5 mm.) The technology is applied to a lumpectomy specimen immediately upon excision, that is, when a surgeon is deciding about immediate additional tissue removal.²,³

The device employs radiofrequency (RF) spectroscopy to differentiate between healthy and cancerous tissue. These tissues differ in a number of ways, such as polarisation of cell membranes, volume of the nucleus, speed of copying of DNA, growth of new blood vessels, and the level of connectivity between one cell and another. The technology subjects the tissue to an electric field and then measures tissue response to that field, yielding an electromagnetic ‘signature’ that uses a proprietary algorithm to differentiate between healthy and cancerous tissue. The result is displayed on a console screen.⁴

The MarginProbe System® consists of a console and an attached sterile, disposable hand-piece (Figure 1). Measurement is performed by applying the probe tip to a point on the resected lumpectomy specimen; detection depth is 1 mm. Each assessed point is visited for several seconds and the total procedure, assessing multiple spots, takes less than five minutes.²
Company or developer
Dune Medical Devices, Inc., a private company based in Israel, Switzerland and the United States of America.

Reason for assessment
An innovative device with the potential to determine the presence of malignant cells at or near the margins of the excised lumpectomy specimen in ‘real time’ during breast conservation surgery.

Stage of development in Australia
- Yet to emerge
- Experimental
- Investigational
- Nearly established
- Established
- Established but changed indication or modification of technique
- Should be taken out of use

Licensing, reimbursement and other approval
MarginProbe® received CE Mark approval in Europe in 2006 and has been available there since 2008. The device system received US Food and Drug Administration (FDA) Premarket Approval (PMA) in January 2013, following the recommendation of a June 2012 FDA advisory panel.5
Australian Therapeutic Goods Administration approval
☐ Yes  ARTG number(s)
☒ No  
☐ Not applicable

Technology type  Device

Technology use  Diagnostic

Disease indication and setting

Disease description and associated mortality and morbidity

Breast cancer is the most common cancer in Australian women (including Aboriginal and Torres Strait Islander women), accounting for 28 per cent of all new cancers in women in 2008. That year there were 13,567 new cases of breast cancer in women (and 113 new cases in men). Average age at diagnosis was 60 years. The risk of being diagnosed with breast cancer increases with age. Breast cancer survival rates are increasing: between 1982 to 1987 and 2006 to 2010, five-year relative survival from breast cancer increased from 72 per cent to 89 per cent. Ten-year relative survival is 83 per cent.6

Breast cancer is the second leading cause of cancer-related death in Australian women, accounting for 15.5 per cent of all cancer deaths in women in 2007. In that year there were 2,706 deaths from breast cancer. It is the leading cancer cause of burden of disease in Australian women, estimated to account for 61,300 disability-adjusted life years in 2012: 40,800 years lost due to premature death and 20,500 years of healthy life lost due to disease, disability or injury.7

For most patients with early stage breast cancer, the first phase of treatment is surgical intervention, particularly BCS (lumpectomy plus radiation therapy). BCS is now the preferred method of treatment for eligible patients and 60 to 75 per cent of women with breast cancer choose BCS.8 BCS has been shown to be as effective as mastectomy in eligible patients; however, a cornerstone of the equivalence is the achievement of cancer-clear surgical margins.4

Number of patients

The incidence of breast cancer in Australia is increasing: new cases increased from 5,310 in 1982 to 13,567 in 2008, and 17,210 new cases per year are estimated by 2020. Between 1982 and 1995, the age-standardised incidence rate of breast cancer in women in Australia increased from 81 to 116 per 100,000 women, although it has remained stable since then — in 2008, the age-standardised incidence breast cancer rate was 115.4 per 100,000 women.7 The Breast Cancer Network of Australia estimated that 14,610 women would be diagnosed with breast cancer in 2012.9 Australian clinical guidelines (2001) suggest that, preoperatively, BCS may be suitable for 70 per cent of cancers detected through
mammography, and 50 per cent of clinically detected cancers (although this information may now be out of date).10

Speciality Surgery

Technology setting Specialist hospital / general hospital

Impact

Alternative and/or complementary technology

MarginProbe® is an additional step which occurs after excision of the main lumpectomy specimen, as an adjunct to – not a replacement for – standard of care. It allows intraoperative assessment of a specimen boundary so a surgeon can immediately assess whether additional tissue should be removed. No other standard of care procedures following surgery, including the histology exam, are affected by use of the device.11

Current technology

Current standard of care activities for determining the state of specimen margins include palpation; specimen imaging (e.g. plain film X-ray for micro-calcifications, ultrasound, ultrasound-guided cryoprobe-assisted localisation); and intraoperative gross and/or microscopic pathology assessment (e.g. frozen section analysis, imprint cytology).2,3 New technologies are also being explored including PET, radio-guided occult lesion localisation and near-infrared fluorescence optical imaging.3

Diffusion of technology in Australia

Not as yet

International utilisation

<table>
<thead>
<tr>
<th>Country</th>
<th>Trials underway or completed</th>
<th>Limited use</th>
<th>Widely diffused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

Cost infrastructure and economic consequences

The evidence shows that the use of MarginProbe® significantly reduces the need for a number of women to undergo further surgeries to remove malignant tissue that was undetected at the time of the initial procedure. This suggests cost savings (balanced in part by the cost of purchasing and operating the device, plus disposables).
Ethical, cultural or religious considerations

No specific considerations were identified.

Evidence and Policy

Safety and effectiveness

Evidence comes from two multicentre randomised controlled trials (RCTs) (level II diagnostic accuracy studies), the first conducted in Israel and the second slightly later in the US and Israel. In addition, a study comparing device readings with histology findings is described (level III-1 diagnostic accuracy study).

Allweis et al

An industry-funded, two-arm, prospective RCT at 11 sites in Israel (35 surgeons, November 2006 to November 2007) was designed to study use of MarginProbe® in BCS intraoperative margin assessment. Included patients (n=300) were scheduled to undergo BCS for treatment of invasive and/or pre-invasive breast cancer. Exclusion criteria were neoadjuvant chemotherapy and prior surgical procedures or implants in the affected breast.

Patients were randomised to either the device group or the control group in the operating room (OR) once excision and suture orientation of the main lumpectomy specimen were complete to ensure uniformity of the initial specimen excision in both study arms. The groups were equal, with 41 per cent of specimens ultimately showing tumour within 1 mm of a margin. In the device group, the probe was applied to the excised lumpectomy specimen at five to eight areas of each of six margins (medial, lateral, superior, inferior, deep and anterior). Results were displayed on the console screen, grouped by margin (a short blue bar indicated a negative reading, while a long red bar indicated a positive reading). A margin was considered positive if one or more device readings were indicated as positive.

The patients were all women (mean age 60 years, mean lesion size 18 mm). In both study arms the surgeons used standard intraoperative margin assessment at their discretion and performed re-excision of cavity margins as deemed necessary. Intraoperative modalities included palpation, specimen imaging and intraoperative pathological assessment (gross and microscopic). The latter two were performed after MarginProbe® application by a professional blinded to the patient’s randomisation arm away from the OR.

Reoperations were performed according to institutional treatment protocols and patient preferences. Patient follow-up extended to six months. The main study outcome (in addition to safety) was device effectiveness in increasing the likelihood of a correct intraoperative surgical reaction (ISR) during lumpectomy, compared to patients in the control group. Additional outcomes were reoperation rates, excised tissue volume and cosmetic results.
Safety

No safety issues or adverse events were reported.

Effectiveness

Effectiveness was based on comparisons with final histology data. The ability to correctly and intraoperatively identify all involved margins and re-excite them was defined as correct ISR. Study arms were compared for correct ISR, re-excision rates, reoperation rates, volume of tissue excised and long-term cosmetic outcome (Table 1).

Table 1 Results for Allweis et al Randomised Controlled Trial

<table>
<thead>
<tr>
<th></th>
<th>Surgery using MarginProbe® group</th>
<th>Surgery without MarginProbe® (control) group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>143</td>
<td>150</td>
<td>-</td>
</tr>
<tr>
<td>Correct ISR rate (%)</td>
<td>60 (35/58)</td>
<td>41 (25/61)</td>
<td>0.044</td>
</tr>
<tr>
<td>Re-excision rate (%)</td>
<td>5.6 (8/143)</td>
<td>12.7 (19/150)</td>
<td>0.0027</td>
</tr>
<tr>
<td>Reoperation rate (including mastectomy)</td>
<td>12.6 (18/143)</td>
<td>18.6 (28/150)</td>
<td>NS (0.098)</td>
</tr>
<tr>
<td>Excised tissue volume, mean (cm³)</td>
<td>107</td>
<td>94</td>
<td>NS (0.066)</td>
</tr>
<tr>
<td>Good or excellent long-term cosmetic outcome (%)</td>
<td>71</td>
<td>69</td>
<td>NS (1.0)</td>
</tr>
</tbody>
</table>

ISR = intraoperative surgical reaction, NS = not significant

Results showed that correct ISR rate was significantly higher in the device arm than the control arm at 60 per cent versus 41 per cent (p=0.044). Re-excision (repeat lumpectomy) rate was reduced by 56 per cent (6% vs 13%, respectively; p=0.0027). There were no differences in reoperation rates, excised tissue volume or good/excellent cosmetic outcome.

A sub-analysis was performed for patients with non-palpable lesions (57 per cent in each group). Findings were similar for the group as a whole with, for the device group, significantly higher rates of correct ISR (69% vs 39%, p=0.024); a 52 per cent decrease in re-excision rates (p=0.039); and non-significant differences in excised tissue volume or good/excellent cosmetic outcome. However, for this group the rate of reoperation was significantly lower (10% vs 21% [53% decrease], p=0.024).

An additional analysis was performed. In the base case, the threshold of positivity was defined as tumour within 1 mm of margin edge. When this threshold was raised to 2 mm, 3 mm and 5 mm, correct ISR rates decreased in both arms; however, the benefit of the device over the control was maintained.

The study authors concluded that:

The device is safe and effective in increasing the ability of the surgeon to detect positive margins and to react correctly during the primary procedure. The device thus contributes to a significant 56% reduction in reoperation rates for BCS.
NCT00749931; pivotal study for the FDA\textsuperscript{11, 13}

An industry-funded, two-arm (standard of care alone versus device + standard of care) prospective RCT at three sites in Israel and 18 in the US enrolled 664 women (of 721 screened) starting in October 2008. Patient mean age was 60 years and 85 per cent were white. This study has not been published and the information was accessed from the FDA-required manufacturer’s submission.

The study design was similar to that of Allweis et al\textsuperscript{2}, with patients randomised post-lumpectomy in the OR. However, in this study, standard of care to detect residual tumour included palpation and specimen imaging but did not include other methods of intraoperative pathological specimen assessment (e.g. frozen section or gross assessment by sectioning).

The primary outcome was effectiveness of the device in increasing the likelihood of a complete surgical resection during lumpectomy, defined as all positive margins on the main specimen were addressed intra-operatively. The FDA requested two additional primary endpoints:

- Normalised total tissue volume: This was defined as the percentage of total tissue volume excised during lumpectomy and any subsequent re-excision procedures (excluding mastectomies) normalised to patient baseline bra cup size. This explored the potential effect of device false positive indications on the cosmetic outcome.
- Non-randomness test of the device: This outcome evaluates the association between the margin level device output (positive margin or negative margin) and the histology results (positive or negative) of the main specimen.

Ten additional endpoints were tracked, including re-excision procedure rate, which was 28 per cent lower in the device group (34 events per 100 patients [55/163]) versus the control group (47 events per 100 patients [69/147]), RR=0.719, \(p=0.0414\).

\textit{Safety}

Adverse events were rare and were distributed across study groups. Only one, a wound infection five weeks post-lumpectomy, was deemed possibly related to the device (although it was noted that the device does not touch the patient, but only the excised specimen). The conclusion was that ‘use of the MarginProbe\textsuperscript* System device was safe and was not associated with increased risk over control’.

\textit{Effectiveness}

Results are provided here for the three primary outcomes:

- Complete surgical resection: three times greater in the device group versus the control group (72\% vs 22\%, \(p<0.0001\)).
• Normalised total tissue volume (looking for non-inferiority): 15 per cent versus 13 per cent.
• Non-randomness test: Analysis showed that there was significant association between device readings and histology results (p<0.0001), demonstrating that the device readings were not random.

Extensive analysis of the many endpoints was carried out by the manufacturer to respond to concerns posed by the FDA. The efficacy conclusion was supportive of MarginProbe:

Collectively, the diagnostic endpoints demonstrated that the overall ability to detect cancer at the margin of the excised specimen is improved with use of the device as an adjunct to SOC [standard of care]. This improvement in detection is not associated with a clinically meaningful adverse effect of device false positive outputs based on the findings with respect to tissue volume.

Pappo et al\textsuperscript{12}
In 2006–2007, researchers in Israel tested the diagnostic performance of MarginProbe\textsuperscript{®} by applying the device to freshly excised lumpectomy and mastectomy specimens (n=753 from 76 patients) and comparing the results with histology findings. Of the tissue samples, 165 were malignant and 588 were non-malignant. Medical staff members were blinded to device output. Data were analysed for the full dataset and also for relatively homogeneous samples (most common with small cancers):
• Full dataset: sensitivity 0.70 (95% CI [0.63, 0.77]), specificity 0.70 (95% CI [0.67, 0.74])
• Homogeneous samples: sensitivity 1.00 (95% CI [0.85, 1.00]), specificity 0.87 (95% CI [0.83, 0.90]).

Device sensitivity was estimated to change from 56 per cent to 97 per cent as the cancer feature size increased from 0.7 mm to 6.6 mm. The detection rates of samples containing ductal carcinoma in situ clusters, a more challenging intraoperative tissue assessment target, were not different from rates of samples containing invasive ductal carcinoma.

Economic evaluation
Information provided by Dune Medical Devices, Inc.\textsuperscript{14} regarding the US market indicated that the console, which does the analysis of the signals, is priced at approximately A$23,700 (US$24,995). The sterile, single-use probe, which is an ancillary device to the console, is priced at approximately A$944 (US$995). The company added that they believe that the cost per-patient of A$944, after the purchase of the console, is significantly less than the cost of repeat surgery.

No other economic analysis was identified, although in Germany a fee code has been assigned for MarginProbe\textsuperscript{®} use. This is seen as a:
... first step in securing reimbursement for new medical technologies from the German Ministry of Health and [it] will facilitate determination of cost effectiveness and cost benefit of the MarginProbe System.\textsuperscript{15}

**Ongoing research**

No additional studies were located at ClinicalTrials.gov, nor referred to in the existing studies or manufacturer information.

**Other issues**

The manufacturer’s website refers to potential MarginProbe\textsuperscript{®} use for patients undergoing radical prostatectomy for prostate cancer, as well as applications in solid tumours such as sentinel nodes, and liver, kidney, oesophagus, basal and squamous cell carcinomas.\textsuperscript{4}

It has been suggested that similar results, to those obtained by using MarginProbe\textsuperscript{®} can be obtained using standard portable ultrasound equipment.\textsuperscript{16}

**Summary of findings**

MarginProbe\textsuperscript{®} was developed as a non-invasive device that uses RF spectroscopy to differentiate between malignant and normal cells in excised breast tissue. The objective is for a surgeon to determine whether surgical margins are clear while still in the OR. This can have major implications with respect to the need for repeat surgery. Evidence came from two large RCTs, namely, an early trial performed in Israel (n=300) and a subsequent trial in the US and Israel for submission to the FDA (n=664). Both compared findings obtained with MarginProbe\textsuperscript{®} to those of ‘reference standard’ final histology results and found significantly increased rates of clear margins in the device group versus the control group. Re-excision (repeat lumpectomy) rate was significantly reduced in both studies, by 56 per cent in the first and 28 per cent in the second. In both studies, excised tissue volume and long-term cosmetic results were not significantly different between groups. Safety issues were not identified. The device received CE mark approval in 2006 and has been in limited use in Europe since 2008; FDA approval was granted on 2 January 2013. Pricing information on the equipment is available but additional economic information is not yet available, although this may be forthcoming from Germany where a reimbursement fee has been established.

**HealthPACT assessment**

Despite promising results in regards to a reduction in the need for repeat lumpectomy compared with the control group, the costs associated with the use of the MarginProbe\textsuperscript{®} remain high and additive to the existing costs regarding post-operative biopsy. On this basis, adoption of this technology is unlikely to take place at this time; however, if the cost of MarginProbe\textsuperscript{®} was to reduce significantly and/or it is found that its use can reduce or eliminate the need for routine postoperative biopsy, there may be potential for uptake by the public health system. Consequently, this technology will be archived.
Number of studies included

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

| Total number of studies | 3 |
| Total number of Level II diagnostic accuracy studies | 2 |
| Total number of Level III-1 diagnostic accuracy studies | 1 |

References


Dune Medical Devices, Inc. ASERNIP-S | Request for Permission & Information | MarginProbe® System. Email to Hoggan, B. 16 Jan 2013 [cited 17 Jan 2013]


Walsh, D. MBBS FRACS (Surgeon). ASERNIP-S | Request for Clinical Review | MarginProbe. Email to Edgar-Hughes, M. 14 Jan 2013 [cited 17 Jan 2013]

Search criteria to be used (MeSH terms)

Mesh: breast neoplasms; Radio Frequency Identification Device

Other: MarginProbe, margin, spectroscopy; suggest using: margin AND breast neoplasms AND spectroscopy