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This brief was commissioned by Queensland Health, in its role as the Secretariat of the Health Policy Advisory Committee on Technology (HealthPACT). The production of this brief was overseen by HealthPACT. HealthPACT comprises representatives from health departments in all States and Territories, the Australian and New Zealand governments and MSAC. It is a sub-committee of the Australian Health Ministers’ Advisory Council (AHMAC), reporting to AHMAC’s Hospitals Principal Committee (HPC). AHMAC supports HealthPACT through funding.

This brief was prepared by Dr. Vicki Foerster and Robyn Lambert from the Australian Safety and Efficacy Register of New Interventions – Surgical.
Technology, Company and Licensing

Register ID WP162
Technology name Multi-catheter interstitial brachytherapy
Patient indication Women with early stage breast cancer undergoing adjunct breast conserving therapy

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

Clinical feedback indicates multi-catheter interstitial brachytherapy as treatment for patients who have had breast conserving surgery is currently being performed at several centres across Australia. Approximately 15 to 20 per cent of patients who have had breast conserving surgery are eligible for multi-catheter interstitial brachytherapy.

Australian Therapeutic Goods Administration approval

- Yes
- No
- Not applicable

ARTG number(s)*: 147701, 147702, 153895, 104341

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>Australia</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>European countries</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

*Searches of the ARTG found several listings for brachytherapy devices, only three of these reported that the intended use was interstitial brachytherapy treatment (ARTG 153895, 147701, 147702). ARTG 153895 is the brachytherapy applicator whilst ARTG 147701 and 147702 are the radionuclide sources. The applicator is reported to be for general use. According to RT Service Pty Ltd, breast treatments can be done with generic brachytherapy needles although specific breast applicators are available.

Clinical feedback indicates multi-catheter interstitial brachytherapy for patients who have had breast conserving surgery is well established in Europe and the United States in that patients do not need to be in trials to receive this treatment. There are also specific guidelines available in these countries defining patient eligibility for multi-catheter interstitial brachytherapy.
2013 Evidence and Policy

2013 Safety and effectiveness

Included in this update are three non-randomised comparative (Level III-2 Intervention evidence) studies of accelerated partial breast irradiation (APBI) performed via multi-catheter interstitial brachytherapy as a means of adjunct treatment to breast conserving therapy (BCT). In two of the studies, the clinical outcomes are compared to whole breast irradiation (WBI), which has been the traditional treatment, and in the third study, it is compared to MammoSite single-lumen brachytherapy (another type of APBI).

Shah et al (2011)\(^1\)

A prospective matched-pair study at a single institution in Michigan included 199 women with invasive early-stage breast cancer who received interstitial brachytherapy APBI from 1992 to 2001. Each woman was matched to a woman who had received WBI at the same institution between 1992 and 1996, with the pairs matched according to tumour size (±5 mm), nodal status (negative versus 1–3 positive), oestrogen receptor status (positive versus negative versus unknown), use of adjuvant hormonal therapy (yes versus no), and age (±10 years). The two groups were well balanced with respect to age, tumour size, receptor status, and tumour stage. However, patients in the APBI cohort received adjuvant hormonal therapy less frequently (p<0.001) and adjuvant chemotherapy more frequently (p<0.001). Also, the APBI patients were more likely to be node positive (p<0.001) and less likely to have negative margins (p=0.05), that is, they were at higher risk for disease recurrence.

Treatment techniques included a low-dose rate implant that delivered 50 Gy over 96 hours at 0.52 Gy/hr and a high-dose rate implant that delivered either 32 Gy in eight fractions or 34 Gy in 10 fractions twice-daily. Median follow-up was 10.7 years (range 0.1–16.9) for the interstitial APBI patients and 14.5 years (range 0.7–25.5) for the WBI patients (p<0.001).

Safety

There were no safety outcomes reported in this study.

Effectiveness

Results showed that clinical outcomes between the two groups were similar with the exception of distant metastases which occurred in a statistically significant greater proportion of patients in the WBI group (10.1%) compared with the APBI group (4.5%; p=0.05) (Table 1).
Ferraro et al (2012)²

At the Washington University School of Medicine in Saint Louis, Missouri, researchers retrospectively compared outcomes for 202 women who received APBI via multi-catheter interstitial brachytherapy from 2002 to 2007 to a control group of 94 women who were eligible for and offered APBI but chose WBI instead. APBI was delivered as 34 Gy in 10 fractions twice daily over 5 to 7 days, for all but two patients. WBI was prescribed as a 42.56-50.4 Gy dose in 1.8-2.66 Gy fractions with most patients receiving a 0.5 Gy boost in 200 cGy fractions to the whole breast followed by a 10 Gy boost to the tumour bed. Patients in each study arm were similar except that more Caucasian women chose APBI over WBI (84% versus 55%) compared to black women (15% vs 45%). In addition a significantly higher proportion of women in the WBI group had a tumour in the upper outer breast quadrant compared to those in the APBI group (68% versus 44%; p<0.001 for both comparisons). Median follow-up in both groups exceeded 60 months.

Safety

There were no safety outcomes reported in this study.

Effectiveness

Clinical outcomes are summarised in Table 2.

Table 1  Clinical outcomes for the paired analysis in Shah et al (2011)¹

<table>
<thead>
<tr>
<th></th>
<th>Local recurrence</th>
<th>Regional recurrence</th>
<th>Disease-free survival</th>
<th>Overall survival</th>
<th>Cause-specific survival</th>
<th>Distant metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>APBI group</td>
<td>5.0</td>
<td>1.1</td>
<td>91</td>
<td>71</td>
<td>95</td>
<td>4.5</td>
</tr>
<tr>
<td>WBI group</td>
<td>3.8</td>
<td>0</td>
<td>87</td>
<td>78</td>
<td>93</td>
<td>10.1</td>
</tr>
<tr>
<td>p value</td>
<td>0.40</td>
<td>0.15</td>
<td>0.30</td>
<td>0.06</td>
<td>0.28</td>
<td>0.05</td>
</tr>
</tbody>
</table>

APBI: accelerated partial breast irradiation; WBI: whole breast irradiation.

Table 2  Clinical outcomes for the comparative study by Ferraro et al (2011)²

<table>
<thead>
<tr>
<th></th>
<th>Local recurrence</th>
<th>Loco-regional (nodes)</th>
<th>Disease-free survival</th>
<th>Overall survival</th>
<th>Cause-specific survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>APBI group</td>
<td>3.0</td>
<td>4.3</td>
<td>94.3</td>
<td>91.9</td>
<td>99.4</td>
</tr>
<tr>
<td>WBI group</td>
<td>3.8</td>
<td>3.8</td>
<td>93.4</td>
<td>96.7</td>
<td>98.9</td>
</tr>
<tr>
<td>p value</td>
<td>0.71</td>
<td>0.90</td>
<td>0.87</td>
<td>0.11</td>
<td>0.95</td>
</tr>
</tbody>
</table>

APBI: accelerated partial breast irradiation; WBI: whole breast irradiation.

A number of patients in the APBI group had significant comorbidities and seven died as a result of those co-morbidities, this is reflected in the lower overall survival rate in the APBI group. Regional failure occurred in two patients at 55.0 months and 17.1 months in the APBI group; in one patient the recurrence was in a portion of the axilla which would have been
covered by WBI whilst in the other the recurrence developed outside of the area which would have been covered by WBI.

Wilder et al (2010)³

The prospective, non-randomised comparative study, conducted at a single institution in Irvine, California, examined the results of 173 patients with unifocal carcinoma of the breast treated with post-lumpectomy APBI using iridium-192 high-dose-rate brachytherapy between February 2003 and January 2009. Thirty-six patients were treated with multi-catheter brachytherapy and 137 patients were treated with a MammoSite single-lumen balloon catheter. Brachytherapy treatment protocol was as follows: a dose of 34 Gy was delivered in 10 fractions, 6 hourly, twice-daily, over 5 to 10 days. APBI treatments were generally started 28 days post-lumpectomy (median). Baseline patient characteristics were reported for each cohort and there were no notable differences with regards to age, tumour stage distribution, histology and hormone receptor status between the two cohorts. The median follow-up was 33 months.

Ipsilateral breast tumour recurrence was defined as a true recurrence/marginal miss if the recurrence occurred within or immediately adjacent to the primary tumour site and as an elsewhere failure if it occurred several centimetres from the primary site.

Safety

Complications are reported in Table 3

Table 3  Complications reported by Wilder et al (2010). There were no statistically significant differences in the incidence of complications between treatment groups ($p=0.10$).

<table>
<thead>
<tr>
<th></th>
<th>All expressed as number of patients experiencing event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seroma</td>
</tr>
<tr>
<td>Multi-catheter group</td>
<td>0</td>
</tr>
<tr>
<td>MammoSite group</td>
<td>16</td>
</tr>
</tbody>
</table>

Following the occurrence of four infections in the MammoSite treatment group, the authors stated that the length of the incisions around the MammoSite catheter were increased from 12 mm to 15 mm, after which, no further infections were reported. One patient with rib pain in the MammoSite group received a large radiation dose to that rib (150% of prescribed dosage).

Effectiveness

There were no cases of ipsilateral breast tumour recurrence in the multi-catheter treatment group compared with three ipsilateral recurrences (>

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Multi-catheter interstitial brachytherapy: Update May 2013 4
to 56 months follow-up in the MammoSite treatment group. Elsewhere failures occurred in the ipsilateral axillary nodes (n=1 at 19 months follow-up) and the lungs (n=2 at 34–51 months follow-up) in the multi-catheter treatment group. There was only one elsewhere failure in the MammoSite treatment group, in the brain at 40 months follow-up.

Ipsilateral breast tumour control at 3-years, including disease-free survival and overall survival, is reported in Table 4.

Table 4  Three year ipsilateral breast tumour control reported by Wilder et al (2010)

<table>
<thead>
<tr>
<th>All expressed as per cent of patients (Kaplan-Meier method)</th>
<th>3-year ipsilateral breast tumour control</th>
<th>3-year disease free survival</th>
<th>3-year overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-catheter group</td>
<td>100%</td>
<td>89% (95% CI 74-100)</td>
<td>100%</td>
</tr>
<tr>
<td>MammoSite group</td>
<td>100%</td>
<td>100%</td>
<td>99% (95% CI 97-100)</td>
</tr>
</tbody>
</table>

Note: no statistical comparisons were made.

Maximum radiation dose delivered to the skin did not differ significantly in patients treated with multi-catheter interstitial brachytherapy (mean 84 ± SD 17% of the prescribed dose) compared with MammoSite (mean 87 ± SD 30% of prescribed dose) (p=0.57). Similarly, the percentage of patients receiving skin doses more than 12.5 per cent of the prescribed dose was not significantly different between the treatment groups at zero per cent and 10 per cent, respectively (p=0.08).

Cosmetic results were measured using the Harvard Scale at three years follow-up (Table 5). There were no significant differences in regards to aesthetics following radiation using either modality (p=0.17). Cutaneous side-effects of treatment were erythema (83% multi-catheter, 92% MammoSite), hyperpigmentation (36% multi-catheter, 49% MammoSite) and telangiectasia (8% multi-catheter, 19% MammoSite).

Table 5  Cosmetic results at 3-years follow-up in Wilder et al (2010)

<table>
<thead>
<tr>
<th>All expressed as per cent of patients</th>
<th>Poor</th>
<th>Fair</th>
<th>Good</th>
<th>Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-catheter group</td>
<td>0</td>
<td>3</td>
<td>26</td>
<td>71</td>
</tr>
<tr>
<td>MammoSite group</td>
<td>2</td>
<td>6</td>
<td>32</td>
<td>60</td>
</tr>
</tbody>
</table>

2013 Economic evaluation

One multi-catheter interstitial brachytherapy catheter system which is known to be used in Australia is the Nucletron Oncosmart® Comfort Catheter. Pricing information for components of this system as well as approximate costs of after loaders and radioisotopes are provided in Table 6.4
One recent economic analysis compared the costs of various forms of radiotherapy after BCT. The United States-based study compared interstitial brachytherapy (as well as other forms of APBI) to WBI (various technologies).

### Table 6  Pricing information related to multi-catheter interstitial brachytherapy

<table>
<thead>
<tr>
<th>Component</th>
<th>Pricing</th>
<th>Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Catheters (Nucletron)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheters: CT/ MR OncoSmart®</td>
<td>$2,800</td>
<td>Single use. The set comprises of 3 sets of 6 sterile catheters.</td>
</tr>
<tr>
<td>Catheter Set (1 patient / 18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>channels)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT/ MR OncoSmart® Catheter Set</td>
<td>$4,660</td>
<td>Single use. The set comprises of 30 sterile catheters.</td>
</tr>
<tr>
<td>(1 patient / 30 channels)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Applicators (Nucletron)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast CT/ MR Template Set</td>
<td>$15,310</td>
<td>Not single use. All items are multiple use and have an approximate 3 year working lifespan.</td>
</tr>
<tr>
<td>OncoSmart® Flange Moulding Set</td>
<td>$9,850</td>
<td></td>
</tr>
<tr>
<td>CT Marker Set, 240 mm, Black</td>
<td>$3,490</td>
<td></td>
</tr>
<tr>
<td>(package of 18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>After loader</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete remote after loading</td>
<td>$400,000a</td>
<td>Once off purchase. Includes all necessary accessories and with full installation.</td>
</tr>
<tr>
<td>system</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachytherapy treatment planning</td>
<td>$200,000a</td>
<td>Once off purchase.</td>
</tr>
<tr>
<td>system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Four Ir-192 sources</td>
<td>$50,0009 per</td>
<td>Approximately four are required per annum.</td>
</tr>
<tr>
<td>annum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance</td>
<td>$60,0009 per</td>
<td>Includes maintenance of components and software upgrades.</td>
</tr>
<tr>
<td>annum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*approximate costs; *approximate usage is 12-15 catheters per patient

Shah et al (2013)5

The matched-pair analysis described in the safety and efficacy section above was used to develop economic analyses of multi-catheter APBI versus WBI. The analysis included five APBI technologies (interstitial catheters, 3D conformal radiation therapy APBI, APBI via intensity modulated radiotherapy [IMRT], single lumen applicator and multi-lumen applicator) and two WBI technologies (3D CRT WBI and IMRT WBI). Analyses included a cost minimisation analysis, incremental cost-effectiveness ratio (ICER) analysis and cost per quality-adjusted-life-year (QALY) analysis; only the data for multi-catheter versus the two types of WBI are shown here. When compared to WBI IMRT, all APBI techniques were cost-effective in the three analyses. Per 1,000 patients, the cost savings with interstitial catheter APBI versus WBI IMRT and WBI 3D-CRT were $9.7 million and $0.7 million, respectively. Some comparative cost calculations are shown in Table 7.
Table 7  Costs of selected radiotherapy modalities in Shah et al (2013)\textsuperscript{5}

<table>
<thead>
<tr>
<th>Modality</th>
<th>Calculated costs (US$) per patient</th>
<th>Reimbursement costs</th>
<th>Including non-medical costs (e.g., time, travel) and cost of recurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial APBI</td>
<td>11,765 13,710</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APBI 3D-CRT</td>
<td>6,578  8,522</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APBI SL</td>
<td>12,602 14,547</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APBI ML</td>
<td>16,439 18,384</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBI IMRT</td>
<td>20,637 23,797</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBI 3D-CRT</td>
<td>11,726 14,886</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


2013 Ongoing research

One long-term, multi-centre, randomised study is underway to compare APBI (interstitial brachytherapy) with WBI. There is also one long-term case series on interstitial brachytherapy.

- GEC-ESTRO APBI trial; NCT00402519: This large phase III European study enrolled 1300 women in five countries. Women aged 40+ years with low-risk stage 0-II invasive breast cancer (negative nodes, clear tumour margins) were stratified by centre, invasive versus non-invasive disease, and pre- versus post-menopausal status and then randomised to APBI brachytherapy or WBI. The primary outcome measure was local control. Recruitment started in 2004 and primary data collection was complete in late 2009; the study is to end in 2014. No publications were located.\textsuperscript{6}

- NCT01175694: This prospective phase II study started in 2010 and is due for completion in 2015. The study is currently recruiting patients. Women aged 50+ years with stage 0, I or II breast cancer and clear resection margins at least 2 mm in any direction are eligible. Women with prior malignancy (< 5 years to enrolment in the study) are not eligible. The aim of the study is to assess the role of a modified dose of pulsed-dose-rate (PDR) and high-dose-rate (HDR) brachytherapy alone as APBI in a defined low-risk group of invasive breast cancer or ductal carcinoma in situ. The primary outcome being investigated is local control rate (time frame 5 years). Secondary measures include acute and late side effects.\textsuperscript{7}

- Clinical feedback indicates that a case series study on multi-catheter interstitial brachytherapy for patients who have had breast conserving surgery is currently being conducted at St George public hospital in New South Wales. The study which commenced in September 2012 will run for three years and will enrol around 60 women. Outcomes being investigated include quality of life and cosmetic results.
2013 Other issues

There are a number of issues related to understanding the various forms of radiotherapy being used or piloted as adjuncts to BCT—these all affect decisions to be made when considering implementation of new treatment paradigms. For example:

- As is apparent from the studies and analyses described above, there are at least six forms of WBI and several forms of APBI with nuances based on differing dosage and timing regimens. A number of authors have sought to describe the many technologies now available. The evidence suggests that the safety and efficacy of one form of radiotherapy cannot be extrapolated to another, including forms of APBI, and neither can the economic comparisons. With respect to economic analyses, possibly each institution must perform its own economic assessment based on its traditional and planned radiotherapy modalities in order to determine the impact of switching from one therapy to another.

- Patient selection criteria have been developed by several expert bodies and physicians are encouraged to observe these criteria, that is, not to relax indications for treatment. The American Society for Radiation Oncology (ASTRO) published a consensus statement in 2009 that divides various patient risk factors (e.g., age, tumour size and stage, margins, and histology) into ‘suitable’, ‘cautionary’ and ‘unsuitable’. Likewise, the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group published patient selection criteria where three risk groups were identified (low-risk, intermediate-risk and high-risk) to assist physicians in determining when to offer APBI outside the context of a clinical trial. Practice guidelines for the use of high-dose brachytherapy were also made available by the American College of Radiology (ACR) and the American Society of Radiation Oncology (ASTRO) in cooperation with the American Brachytherapy Society (ABS). These guidelines found high-dose-rate brachytherapy to be an important modality in treating various malignancies due to its ability to deliver targeted treatment and spare surrounding tissue. In order to implement successful high-dose-rate brachytherapy programs, coordination of radiation oncologists and treatment planning staff is necessary, along with clearly defined quality assurance procedures.

Also of note is the Technology Evaluation Center (TEC) Assessment carried out by The Blue Cross Blue Shield Association on accelerated radiotherapy after breast-conserving surgery for early stage breast cancer. The objective of this assessment was to evaluate the outcomes of accelerated, hypofractionated WBI compared with APBI. The authors found the data available for APBI compared with WBI to be insufficient to draw conclusions about their relative effectiveness and that as such patients should be well-informed of these uncertainties before undergoing the procedure. The authors also
noted that each APBI technique (i.e. multi-catheter interstitial, single-lumen balloon, external beam etc.) should be considered on their own merits and that future studies should not only compare APBI with WBI, but various modalities of APBI with one another. The TEC Assessment recognised the large RCTs currently underway for this technology.

2013 Summary of findings

Evidence from three comparative studies (two comparing interstitial brachytherapy with WBI and one comparing interstitial brachytherapy with MammoSite single-lumen brachytherapy) supports the conclusions reached in the original 2007 version of this technology brief and the 2008 update, i.e., that patients with early-stage breast cancer who undergo APBI with multi-catheter interstitial brachytherapy post-BCT have similar rates of local tumour recurrence compared with those treated with WBI. These studies also demonstrate non-inferiority of APBI with respect to the other clinical outcomes measured including regional tumour recurrence, survival (disease-free, cause-specific and overall) and rate of distant metastases. Follow-up has extended to 12 years. Economic analyses show APBI with multi-catheter interstitial brachytherapy to be attractive although the analyses are complex as they generally compare multiple types of APBI and WBI therapies.

However, it is still not clear what group(s) of women will benefit from APBI with multi-catheter interstitial brachytherapy (versus WBI or alternative types of APBI). Large clinical trials are underway in several jurisdictions.

As was concluded in the original 2007 version of this technology brief, the uptake of this technology is likely to be rapid due to its much more convenient treatment schedule.

2013 HealthPACT assessment

Based on the relatively widespread use of multi-catheter interstitial brachytherapy for patients who have had breast conserving surgery in Australia, and the likelihood of its continued diffusion through clinical practice, it is recommended that no further research on behalf of HealthPACT is warranted at this time.

2013 Studies

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 III-2 studies 3
2013 References


Multi-catheter interstitial brachytherapy: 2007

2007 PRIORITISING SUMMARY

Register ID: S000066

Name of Technology: Multi-catheter interstitial brachytherapy

Purpose and Target Group: Early stage breast cancer in women

Stage of Development (In Australia):
- ☑ Investigational
- ☐ Yet to emerge
- ☐ Experimental
- ☐ Established
- ☐ Established but changed indication or modification of technique
- ☐ Nearly established
- ☐ Should be taken out of use

Australian Therapeutic Goods Administration Approval:
- ☑ Yes
- ☐ No
- ☑ Not applicable

ARTG number: N/A

International Utilisation

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>LEVEL OF USE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trials Underway or Completed</td>
</tr>
<tr>
<td>Austria</td>
<td>✓</td>
</tr>
<tr>
<td>Canada</td>
<td>✓</td>
</tr>
<tr>
<td>Germany</td>
<td>✓</td>
</tr>
<tr>
<td>Hungary</td>
<td>✓</td>
</tr>
<tr>
<td>Japan</td>
<td>✓</td>
</tr>
<tr>
<td>United States</td>
<td>✓</td>
</tr>
</tbody>
</table>

2007 Impact Summary

Accelerated partial breast irradiation using multi-catheter brachytherapy is an alternative to whole breast irradiation for women with early stage breast cancer who require breast conservation therapy. The technology is currently in the investigational stage in Australia.
2007 Background

Breast conservation therapy, consisting of breast conserving surgery (partial mastectomy or lumpectomy) followed by whole breast irradiation (WBI), is the standard of care for women with early stage breast cancer (stage 0, I and II) (Dirbas et al. 2004; Goya et al. 2007). Radiation therapy was incorporated into breast conservation therapy to reduce the risk of local tumour recurrence (Goyal et al. 2007). In WBI, radiation is delivered to the whole breast five days a week for approximately six to seven weeks (Arthur and Vicini 2005).

Breast conservation therapy has been shown to be as effective, in terms of local tumour control and survival, as radical or modified radical mastectomy in which the entire breast is removed (Fisher et al. 1985; Blichert-Toft et al. 1992). However, irradiation of the whole breast has been associated with a reduced quality of life because of the substantial disruption caused by the lengthy treatment process (Fearmonti et al. 2007). Furthermore, women who have received breast conservation therapy and experience cancer recurrence in the same (ipsilateral) breast must generally undergo mastectomy rather than repeat breast conservation therapy because it is considered unsafe to irradiate the whole breast more than once (Dirbas 2007).

In response to the difficulties presented by WBI, alternative methods of irradiating the breast, such as accelerated partial breast irradiation (APBI) have been developed. In APBI, radiation is only focused on the area of partial mastectomy (plus an additional margin of 1 cm to 2 cm), which has the greatest likelihood of tumour recurrence (Chronowski and Buchholz 2007; Fearmonti et al. 2007). This approach not only offers the patient increased convenience, but also decreases the amount of radiation delivered to the breast and surrounding vital structures (Fearmonti et al. 2007).

The most common method of delivering APBI is multi-catheter interstitial brachytherapy, which delivers a homogenous dose of radiation in a short space of time to the tumour bed (Goyal et al. 2007). Multi-catheter interstitial brachytherapy involves the temporary placement of 10 to 20 flexible catheters in the portion of the breast around the partial mastectomy cavity either intra-operatively or postoperatively (Fearmonti et al. 2007). High dose rate (HDR) radiation treatment is then administered in 30-minute sessions twice daily on an outpatient basis, with approximately 3.4 gray (Gy) being delivered per session over five days (total radiation 34 Gy). Low dose rate (LDR) treatment involves the delivery of approximately 45 Gy to the target area over five days on an inpatient basis (Fearmonti et al. 2007). This compares to approximately 50 Gy delivered to the whole breast during WBI (Dirbas et al. 2004).

Interstitial brachytherapy was originally used to provide a boost dose of radiation to the partial mastectomy cavity following breast conserving surgery and WBI (Frazier et al. 2001). The first studies reporting the use of interstitial brachytherapy as the sole radiation therapy in breast conservation therapy were conducted in the 1990s and reported high local tumour
recurrence rates (Chronowski and Buchholz 2007). Since that time, improvements in treatment planning and much stricter patient selection criteria have been incorporated with the aim of improving local control of tumour recurrence.

2007 Clinical Need and Burden of Disease

Breast cancer is the most common form of invasive cancer amongst Australian women (Paul et al. 1999). It is also the leading cause of cancer death in females. The incidence of breast cancer in Australia is on the rise, with new cases increasing from 5,318 in 1983 to 12,207 in 2002 (AIHW 2006). It is estimated that by 2011 the number of new diagnoses will reach 14,800 (AIHW 2006).

It is estimated that in the United States only one quarter of women eligible for breast conservation therapy actually receive it owing to the lengthy and inconvenient treatment process (Fearmonti et al. 2007). Many women who are unable to commit to several weeks of treatment due to family, work or transport issues may be forced to either decline postoperative radiotherapy or accept mastectomy (Dirbas et al. 2004). Postoperative radiotherapy with reduced treatment periods, such as APBI, is a potential solution for these women.

2007 Diffusion

Multi-catheter interstitial brachytherapy is currently in the investigational stage in Australia and around the world.

2007 Comparators

Breast conservation therapy using breast conserving surgery and WBI is the current standard of care for early stage breast cancer, and is the main comparator for multi-catheter brachytherapy.

However, three other forms of APBI also exist (Fearmonti et al. 2007).

- Intra-operative radiation therapy – this involves the delivery of the entire radiation dose in a single fraction while the patient is in the operating room.
- Three-dimensional conformal radiation therapy (3D-CRT) – this postoperative method delivers radiation to the lumpectomy cavity externally via custom-configured beams.
- Balloon-based intra-cavitary radiation therapy – this approach utilizes the MammoSite® Radiation Therapy System to deliver radiation to the lumpectomy cavity.

2007 Safety and Effectiveness

No randomised controlled trials of multi-catheter interstitial brachytherapy were found. Two non-randomised comparative studies were retrieved for inclusion in this summary. Both studies compared patients who underwent LDR and HDR brachytherapy with those undergoing WBI.
a) Safety

In one study conducted at the William Beaumont Hospital, women with early stage invasive breast cancer underwent interstitial brachytherapy as part of breast conservation therapy between 1993 and 2001 (Vicini et al. 2003). One hundred and fifty eight women with stage I/II breast cancer and gross total resection of the primary tumour were prospectively enrolled to undergo one of three brachytherapy protocols. An additional 41 women who did not meet all the eligibility criteria for minor reasons that were not likely to affect the recurrence rate were also included. The three protocols were: LDR brachytherapy delivering 50 Gy over 4 days at 0.52 Gy/hour (n = 120); HDR brachytherapy delivering 32 Gy in eight fractions (n = 71); and 34 Gy in 10 fractions (n = 8). All of the patients were 40 years of age or younger and had infiltrating ductal carcinomas smaller than 3.0 cm in diameter, as well as negative surgical margins (≥ 2 mm) and lymph nodes. Each of the 199 patients was matched with a patient who had received breast conservation therapy with WBI at the same institution between 1980 and 1997.

Although patients received three different brachytherapy protocols, complications were reported in a combined fashion (brachytherapy group). The complications reported during the median follow-up of 60 months included asymptomatic fat necrosis in eight patients (4%), grade II* fibrosis in eight patients (4%) and grade I †/II persistent oedema in 12 patients (6%). Safety outcomes were not reported for the control group (Vicini et al. 2003).

King et al. (2000) conducted a comparative study of interstitial brachytherapy in 50 women (n = 51 breast cancers) undergoing breast conservation therapy that included lumpectomy and axillary lymph node dissection. The study protocol mandated that only women who had opted to undergo breast conservation therapy and had intraductal or invasive tumours smaller than 4 cm (stages Tis, T1 and T2), negative inked surgical margins, ≤ 3 positive axillary nodes and no evidence of multi-centricity could enrol. An average of 15 catheters per patient were placed in a double plane fashion either intra-operatively (n = 23) or postoperatively (n = 28) under ultrasound guidance. The target breast treatment volume treated by interstitial brachytherapy was defined by a 2 cm to 3 cm perimeter beyond the lumpectomy cavity and covered approximately one-third to one-half of the breast. Alternating groups of 10 patients were treated with either LDR brachytherapy (45 Gy over four days; n = 25) or HDR brachytherapy (32 Gy over four days in twice daily fractions; n = 26). The charts of an additional 94 patients, who met the eligibility criteria but were treated with segmental mastectomy and WBI, were retrospectively reviewed as a control group (King et al. 2000).

* Grade II defined as moderate radiation effects.
† Grade I defined as mild radiation effects.
Although the brachytherapy patients received both LDR (n = 25) and HDR (n = 26), complications were reported in a combined fashion (brachytherapy group). The safety analysis revealed significantly fewer grade I‡ and grade II§ complications in brachytherapy patients, compared to the control group (22% versus 80%, P < 0.001). Grade III** complications requiring surgical intervention, on the other hand, were more common after brachytherapy than WBI (8% versus 5%), although the difference was not statistically significant. The grade III complications in the brachytherapy group included one surgical complication (wound haematoma), one infectious complication (infected seroma four months after completion of brachytherapy while receiving chemotherapy) and two cases of fat necrosis. The two patients with fat necrosis presented with skin discoloration and indurated, painful masses at the segmental mastectomy site, which required extensive surgery (King et al. 2000).

b) Effectiveness

Of the 199 patients assessed by Vicini et al. (2003), five had an ipsilateral breast tumour recurrence, which is equivalent to a five-year actuarial ipsilateral tumour recurrence rate of 1% (95% confidence interval 0% to 2.8%). Two of these recurrences were thought to be a regrowth of the primary tumour, while the remaining three were new cancers in the non-irradiated breast tissue. In 79 patients who were followed up for a minimum of five years, cosmetic results were rated as good or excellent by 99% (78/79 patients) and fair in the remaining patient. There was no statistically significant difference in the median time to local recurrence or five-year actuarial rates of ipsilateral breast tumour recurrence or regional failure between the brachytherapy and control group. In addition, there were no statistically significant differences between the groups with respect to five-year actuarial rates of distant metastases, disease-free survival, overall survival, or cause-specific survival (Vicini et al. 2003).

In the study by King et al. (2000), the mean tumour size was 1.4 cm (n=51), and 45% of the tumours were occult (King et al. 2000). A subset of the control group, matched for pathologic stage, tumour size and breast size to the interstitial brachytherapy patients, was used to compare cosmetic outcomes at a median follow-up of 20 months. Cosmetic outcomes were considered good to excellent in 75% of women who had received brachytherapy and 84% of control patients (P > 0.05). In the remaining patients, cosmetic outcomes were judged as fair, except for one control patient with a poor result (King et al. 2000).

‡ Grade I complications were defined as mild, self-limited treatment toxicities, including skin erythema and desquamation, that required no specific treatment.

§ Grade II complications were defined as moderate treatment toxicities that required non-surgical treatment.

** Grade III complications were defined as severe and required surgical intervention.
A comparative analysis of the two groups at a median of 74 months (control group) and 75 months (brachytherapy group) revealed one local failure and three regional nodal recurrences in the brachytherapy group (8% recurrence rate) and five local failures in the control group (5% recurrence rate; P > 0.05). While the difference in local failure and total recurrence rates between groups was not statistically significant, regional recurrences among brachytherapy patients were significantly lower compared to the control group (P = 0.04). At the last follow-up (time not stated), 88% of brachytherapy and 92% of control patients were disease free. Similar overall recurrence rates were achieved even though the brachytherapy patients were significantly older (63.0 years versus 56.9 years; P < 0.05) and had more invasive lesions (90% versus 64%; P < 0.005). However, the authors noted that the rate of regional lymph node failure in the brachytherapy group was higher compared to the 1% to 3% normally reported after breast conserving therapy with WBI, which suggests that women at higher risk of nodal involvement may be better suited for WBI.

2007 Cost Impact

The cost of APBI using multi-catheter brachytherapy is currently unknown.

2007 Ethical, Cultural or Religious Considerations

No issues were identified from the retrieved material.

2007 Other Issues

No issues were identified from the retrieved material.

2007 Summary of Findings

Evidence from two non-randomised comparative studies indicates that patients with early stage breast cancer who undergo breast conservation therapy with multi-catheter interstitial brachytherapy have similar rates of ipsilateral breast tumour recurrence compared to those treated with whole breast irradiation. However, further research is needed to determine which of the two treatment regimens, LDR or HDR, is the most effective. Studies with longer follow-up periods are also required to determine the long-term safety and effectiveness of the therapy. There is some suggestion that women at higher risk of nodal involvement may not be suitable candidates for the procedure, so further refinement of the patient selection criteria may be required. Furthermore, although not investigated in the studies presented, patient acceptance of this technology will substantially impact the uptake of this technology and should be considered in future studies.

If the technology proves to be as safe and effective as breast conserving surgery with WBI, the uptake of this technology is likely to be rapid because of its more convenient treatment schedule.
2007 HealthPACT Action

Based on the potential uptake and rapid diffusion of this technology, multi-catheter interstitial brachytherapy will be monitored for 12 months.

2007 Number of Studies included

Total number of studies: 2
Level III-2: 1
Level III-3 evidence: 1

2007 References


**2007 Sources of Further Information**


**Search Criteria to be Used**

- Brachytherapy
- Multi-catheter
- Interstitial
- APBI
- Accelerated partial breast irradiation
PRIORITISING SUMMARY (2008 UPDATE)

Name of Technology: Multi-catheter interstitial brachytherapy

Purpose and Target Group: Early stage breast cancer in women

2008 Safety and Effectiveness issues

A search of relevant databases, online journals and the Internet was conducted in October 2008, following the recommendation in October 2007 that multi-catheter interstitial brachytherapy be monitored for 12 months. A total of eight studies on the safety and effectiveness of this procedure were identified. Two larger case studies (n = 99 and n = 50) were selected for inclusion above other case series studies due to the number of procedures performed which offer insight to the efficacy and safety of multi-catheter interstitial brachytherapy.

Two randomised controlled trials were identified but were not included in the present update as the comparisons made and outcomes assessed were not appropriate.

Arthur and colleagues (2008) reported on the use of brachytherapy delivered with either a low or high dose rate in 100 enrolled patients. One patient who received a sentinel lymph node procedure rather than the required Level I/II axillary dissection was excluded from analysis. All patients had unicentric breast lesions that were stage T1 or T2 and pathologically identified as infiltrating nonglobular carcinoma that had been resected with a pathologically negative margin. Patients were excluded if they had evidence of extensive intraductal component, any lobular component, or history of a collagen vascular disease.

Patients were enrolled from 11 institutions between May 1997 and March 2000 and the majority were greater than 50 years old, with only 21% less than 50 years of age. Of the 99 patients 14% were premenopausal, 88% presented with tumour sizes less than or equal to 2cm and 80% were without evidence of axillary nodal disease.

Most patients received some adjuvant systemic treatment. Within the high dose group, 32 (49%) received tamoxifen, eight (12%) received chemotherapy and eight (12%) received both, while in the low dose group eight (24%) received tamoxifen, seven (21%) chemotherapy and seven (21%) received both.

Brachytherapy catheters were implanted either perioperatively or postoperatively and patients received either a low dose or high dose rate. Patients receiving high dose rate brachytherapy had a prescription dose of 3.4 Gy for 5 days and a total resultant dose of approximately 34 Gy over five treatment days. Patients receiving low dose brachytherapy was used were admitted to the hospital for 3.5-5 days, during which time 45 Gy was delivered.
Mathematical five year estimates for outcomes were provided, although the authors did not provide calculations. The five year estimates included 4% for local failures and 8% for mastectomy failure. Overall 87% of patients had mastectomy-free survival (88% high dose, 85% low dose rate) and overall 93% of all patients survived (92% high dose, 94% low dose rate).


Johansson et al (2008) reported on the outcomes after accelerated interstitial brachytherapy in 50 women with early T1 and T2 breast cancer. Patients were enrolled between December 1993 and March 2003 and a total of 51 treated breast cancers were assessed as one patient was included twice due to bilateral breast cancers.

Patients were included if they had unifocal invasive T1-T2 tumours irrespective of histopathology, N0-N1 (<4 involved lymph nodes), radical surgery with clear margins and no signs of multifocal invasive or in situ tumours.

Brachytherapy catheters were implanted perioperatively in 14 (28%) of cases and post-operatively in the remaining 37 (72%) of cases. Two patients received adjuvant chemotherapy before brachytherapy while four patients received adjuvant chemotherapy after brachytherapy, and ten patients received adjuvant hormonal treatment. All patients received antibiotics during the implant period and for the following five days.

All patients received a dose of 50 Gy, given in 12 pulses per day over 5 days where the dose per pulse was 0.833 Gy.

Clinical examinations occurred every three months during the first year and were followed by annual visits, while mammograms were obtained every 18 months. An evaluation of the cosmetic appearance was performed by the patient and an oncology nurse on all living patients at last follow up. The median follow up time was 86 months and there were no losses to follow up.

Three patients had an ipsilateral recurrence. One patient had a multicentric recurrence after 18 months and developed distal metastases in the pleura after 50 months, the second patient had a local recurrence at 24 months which was outside the treatment volume, and the third patient had a recurrence at 112 months located in another quadrant and with a different histopathology. The five- and the seven-year actuarial local control rates were 96%. Two patients (4%) had contralateral cancers. One patient developed cancer 12 years after previous irradiation of that breast, while the second patient developed cancer in a breast without previous cancer. Seven patients (14%) developed distant metastases, and two of these patients also had regional lymph node metastases. No isolated regional recurrence was reported. The actuarial disease free survival rates at five- and seven-years
were 88% and the actuarial overall survival rates were 88% at five years and 85% at seven years.

Side effects reported within three months were usually mild, including local radio-dermatitis in 20% of patients and infection in five patients, who then received a new antibiotic treatment. In the treatment volume, moderate fibrosis was reported in 18% of patients, while strong fibrosis was reported in 8%. Fat necrosis was reported in 10 patients (20%) of which six (12%) had symptoms and mammography findings while four (8%) had only mammography findings. One symptomatic patient developed chronic pain in the breast and received a mastectomy. This patient had a contralateral breast cancer and developed chronic pain in that breast after post-operative external irradiation. Two patients had fibrotic strings which required release by plastic surgery, while one patient underwent a reconstructive plastic surgery after resection of a central breast cancer and accelerated partial breast irradiation.

All living patients with preserved breasts assessed the cosmetic result at last follow up, which was scored as good or excellent in 51% of the patients. An oncology nurse scored the cosmetic result as good or excellent in 56% of the patients.

**2008 Summary of findings**

Evidence from one case series with five year follow up data indicated that although low dose rate appeared to result in more local failures than high dose rate, overall survival was higher in patients who had received low dose rate brachytherapy.

As no studies comparing multicatheter interstitial brachytherapy to another treatment were identified for this update, it is still unclear whether breast tumour recurrence is reduced compared to those treated with whole breast irradiation.

The side effects of the therapy, where reported, were usually mild.

One case series suggested that approximately only half of the cosmetic outcomes could be rated as good or excellent after brachytherapy, and there was no assessment of patient acceptance of the procedure.

Large randomised controlled trials comparing multicatheter interstitial brachytherapy to another treatment for breast cancer would add to the evidence base and allow further assessment of the effectiveness of this therapy.

**2008 HealthPACT Action**

Based on the lack of development in the last 12 months, multi-catheter interstitial brachytherapy will be archived.

**2008 Number of studies included**

Total number of studies 2
Level IV intervention evidence 2

2008 References


