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Australia and New Zealand Horizon Scanning Network

**ANZHSN**

AN INITIATIVE OF THE NATIONAL, STATE AND  
TERRITORY GOVERNMENTS OF AUSTRALIA  
AND THE GOVERNMENT OF NEW ZEALAND

# **Horizon Scanning Technology Prioritising Summary**

## **Multi-catheter interstitial brachytherapy**

**October 2007  
(Updated November 2008)**



**ASERNIP/S**

**Australian  
Safety  
and Efficacy  
Register  
of New  
Interventional  
Procedures -  
Surgical**



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## 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; Goyal 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.

## **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 post-operative radiotherapy or accept mastectomy (Dirbas et al. 2004). Postoperative radiotherapy with reduced treatment periods, such as APBI, is a potential solution for these women.

## **DIFFUSION**

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

## **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.

## SAFETY AND EFFECTIVENESS ISSUES

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 ( $\geq 2$  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<sup>1</sup> fibrosis in eight patients (4%) and grade I<sup>2</sup>/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,  $\leq 3$  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

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<sup>1</sup> Grade II defined as moderate radiation effects.

<sup>2</sup> Grade I defined as mild radiation effects.

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).

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<sup>3</sup> and grade II<sup>4</sup> complications in brachytherapy patients, compared to the control group (22% versus 80%, P < 0.001). Grade III<sup>5</sup> 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).

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<sup>3</sup> Grade I complications were defined as mild, self-limited treatment toxicities, including skin erythema and desquamation, that required no specific treatment.

<sup>4</sup> Grade II complications were defined as moderate treatment toxicities that required non-surgical treatment.

<sup>5</sup> 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.

#### **COST IMPACT**

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

#### **ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS**

No issues were identified from the retrieved material.

#### **OTHER ISSUES**

No issues were identified from the retrieved material.

#### **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.

## **HEALTHPACT ACTION**

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

## **NUMBER OF STUDIES INCLUDED**

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

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#### **SEARCH CRITERIA TO BE USED**

Brachytherapy

Multi-catheter

Interstitial

APBI

Accelerated partial breast irradiation

# **PRIORITISING SUMMARY (2008 UPDATE)**

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**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).

Arthur et al (2008) did not report upon any adverse events during multicatheter brachytherapy.

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**

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