



Australian Government
Department of Health and Ageing



Australia and New Zealand Horizon Scanning Network

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TERRITORY GOVERNMENTS OF AUSTRALIA
AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology

Prioritising Summary

Vaginal brachytherapy for treatment of women with high-intermediate risk of endometrial cancer

November 2010



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ISBN

Publications Approval Number:

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The production of this Horizon scanning prioritising summary was overseen by the Health Policy Advisory Committee on Technology (HealthPACT). HealthPACT comprises representatives from departments in all states and territories, the Australia and New Zealand governments; and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

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PRIORITISING SUMMARY

REGISTER ID: 000499

NAME OF TECHNOLOGY: VAGINAL BRACHYTHERAPY

PURPOSE AND TARGET GROUP: TREATMENT OF WOMEN WITH HIGH-INTERMEDIATE RISK ENDOMETRIAL CANCER

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- | | |
|---|--|
| <input type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input type="checkbox"/> Experimental | <input checked="" type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- Yes
- No
- Not applicable

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
USA			✓
UK			✓
Netherlands			✓
Australia		✓	

IMPACT SUMMARY:

Various companies provide multi-component vaginal cylinder systems for intracavitary vaginal brachytherapy (VBT). In many cases, VBT is administered as an adjunctive treatment following surgical resection of endometrial cancer. The focus of this summary is on newly emerged literature that investigates whether brachytherapy provides an equally effective post-operative treatment alternative to pelvic external beam radiotherapy (EBRT) with lower toxicity outcomes for women affected by high-

intermediate¹ endometrial cancer. The technology is currently available through tertiary hospitals with developed radiation oncology facilities.

BACKGROUND

Endometrial cancers are a group of malignancies arising from the endometrium, or lining of the uterus, and comprise the majority of uterine cancers (CCV 2010). For this reason, uterine cancers as a whole are sometimes referred to interchangeably as endometrial cancers. The majority of endometrial cancers are adenocarcinomas, while less common types include adenosquamous carcinoma, papillary serous carcinoma and clear cell carcinoma. Endometrial carcinoma is the most common gynaecological cancer affecting women in Australia. Most women affected (75% of cases) are post-menopausal, while only three per cent of women who develop endometrial cancer are under 40 years of age (Kong et al 2008). Other risk factors include being overweight, hypertension, diabetes mellitus, nulliparity, late menopause, tamoxifen therapy for breast cancer, oestrogen replacement therapy without progesterone, and family history. The most common symptom of endometrial cancers is post-menopausal vaginal bleeding or unusual bleeding patterns among women who are pre-menopausal.

The majority of women with endometrial cancer present with FIGO¹ stage I disease (Shepherd 1989) and have good prognosis with overall survival approaching 90 per cent. With the exception of women with locally advanced or metastatic disease, the standard of treatment is complete abdominal hysterectomy with bilateral salpingo-oophorectomy (surgical removal of the fallopian tubes and ovaries). The decision to give adjuvant treatments such as VBT depends on patient risk profiles as defined by age, histological grade (tumour differentiation) and presence/extent of myometrial invasion (Kong et al 2008).

Following hysterectomy, VBT is in most cases delivered via multi-component cylinder systems to the upper vagina, the most frequent site of recurrence. The vaginal cylinder comprises a smooth plastic casing which houses the radiation source. During the VBT procedure, the physician inserts the cylinder and secures it in the vaginal vault with gauze packing. A CT is performed to indicate the position of the cylinder in relation to the surrounding anatomical structures and a treatment is guided by computerised planning, thereby ensuring the prescribed radiation dosage treats the appropriate risk areas while sparing proximal healthy tissues from excess radiation. The radioactive source is introduced by way of a custom wire and moves within the cylinder resting at different points for a prescribed time until the treatment concludes. The time for which the cylinder remains within the patient varies according to dosage rates, but total preparation and treatment can be expected to take two hours for a first

¹As defined by the International Federation of Gynaecology and Obstetrics (FIGO) (Shepherd 1989). The FIGO uses both surgical and pathological staging which are further subdivided into histological grade of tumour.

session and one hour for subsequent sessions (ACC 2010; SPHCS 2010; SBUMC 2007).

CLINICAL NEED AND BURDEN OF DISEASE

Endometrial cancers account for the majority of all uterine cancer which is the most common gynaecological cancer affecting Australian women (CCV 2010).

Consequently, data for uterine cancers overall provides a reasonable estimate of the burden of disease attributable to endometrial cancer alone for which data is scarce. The most recent year for which incidence rates for uterine cancers are available from the AIHW is 2005. For that year there were 8.6 per 100,000 women² with incident uterine cancer and of these cases more than half of these were in the age range of 50-69 years (AIHW 2010a; AIHW 2008). For the year 2007-08, there were 3,817 public hospital separations due to malignant neoplasms of the uterus (AIHW 2010c). No mortality data was identified during the literature search conducted for this summary.

New Zealand data on uterine cancer is available until the year 2007. For that year there were 19.9 uterine cancer registrations per 100,000 women and the mortality rate was 4.7 deaths per 100,000 women (MoH 2010).

It is important to note that while these rates provide an overall measure of the incidence and mortality, they do not provide a measure of premature death or disability due to uterine cancer given data in the form of PYLL (person-years of life lost) or DALYs (disability-adjusted life years) are lacking.

DIFFUSION

During the year 2007-2008, there were 744 intracavitary brachytherapy procedures performed in all hospitals across Australia, and of these procedures 211 were high dose rate intravaginal brachytherapy (AIHW 2010b). Given there were 3,817 separations for uterine cancer during the same year, and 30 per cent of women with early disease carry high-intermediate risk profiles, the number of VBT procedures performed appears low compared with the number of women who may benefit from this procedure.

COMPARATORS

Common adjuvant therapies following surgery for endometrial cancer include EBRT, chemotherapy and hormonal therapy. Given this summary is concerned primarily with the comparison between VBT and EBRT, chemotherapy and hormonal therapy are not further considered. It is thought that while EBRT and VBT may be equally effective in the prevention of cancer recurrence and survival outcomes, adverse effects from toxicity are considered to be much lower from VBT.

² Age standardised to the 2001 Australian population.

SAFETY AND EFFECTIVENESS ISSUES

An open-label, non-inferiority trial randomised 427 high-intermediate risk³ patients with endometrial carcinoma to receive VBT (n=213) or pelvic EBRT (n=214) (Nout et al 2010) (level II intervention evidence). Patients were recruited from 19 Dutch radiation oncology centres. Investigators were blinded to treatment assignment and the primary outcome was vaginal recurrence. The predefined non-inferiority margin was an absolute difference of six per cent in vaginal recurrence. Secondary outcomes were pelvic recurrence, distant metastases, overall and disease-specific survival, treatment related toxic effects.

Pelvic EBRT dosage was 46 Gy⁴, delivered in 2 Gy fractions five times per week in accordance with International Commission on Radiation Unit and Measurements (ICRU-50) standards. Brachytherapy was delivered by vaginal cylinder following low and high dose rate regimes with equivalent doses in the range of 45-50 Gy to the vaginal mucosa. Participating centres were required to use the same treatment schedule for the period of the trial following ICRU-38 criteria. Patients were assessed by a radiation oncologist 2-4 weeks after radiotherapy was completed and followed up alternately by a gynaecologist and radiation oncologist for a median of 45 (range 18-78) months. Yearly chest radiograph, blood count and chemistry tests were obtained. Vaginal and pelvic recurrences required histological confirmation, and patients who recurred were screened for distant metastasis. Acute and late toxicity were assessed using the scale of the European Organisation for Research and Treatment of Cancer and Radiation Therapy Oncology Group (EORTC-RTOG).

Oncological and survival outcomes of the study are summarised in Table 1. At median follow-up, there were four vaginal recurrences after EBRT and three after VBT with estimated 5-year vaginal recurrence rates of 1.6 (95% CI [0.5, 4.9]) and 1.8 (95% CI [0.6, 5.9]) per cent, respectively (p=0.74). The hazard ratio for vaginal recurrence after VBT, taking EBRT as the reference point, was 0.78 (95% CI [0.17, 3.49]), which excludes the pre-specified non-inferiority margin of six per cent.

A total of 55 patients died – 26 after EBRT and 29 after VBT. Of the 26 EBRT patients who died, 16 (62%) died from concurrent disease and ten (38%) from endometrial cancer. Of the 29 VBT patients who died, 14 (48%) died from concurrent disease 15 (52%) from endometrial cancer. Five-year overall and disease-free survival were 84.8 (95% CI [79.3, 90.3]) and 82.7 (95% CI [76.9, 88.6]) per cent, respectively, for VBT. For EBRT overall and disease-free survival were 79.6 (95% CI [71.2, 88.0]) and 78.1 (95% [69.7, 86.5]) per cent, respectively. Neither of these comparisons between VBT and EBRT showed a significant difference.

³ High-intermediate risk women were defined using FIGO criteria and were eligible under two alternative profiles: (1) age >60 years and stage 1C grade 1 or 2 disease, or stage 1B grade 3 disease; and (2) stage 2A disease, any age (apart from grade 3 with greater than 50% myometrial invasion).

⁴ Gy=Gray the standard unit of absorbed radiation dose of ionizing radiation.

Table 1 Recurrence and survival (all patients), after median follow-up of 45 months

	Events/total, n	Estimated 5-year, % (95%CI)	Hazard ratio (95% CI)	p-value
Vaginal recurrence				
EBRT	4	1.6 [0.5,4.9]	1.0	0.74
VBT	3	1.8 [0.6, 5.9]	0.78 [0.17,3.49]	
Pelvic recurrence				
EBRT	1	0.5 [0.1,3.4]	1.0	0.02
VBT	8	3.8 [1.9,7.5]	8.29 [1.04,66.4]	
Distant metastasis				
EBRT	13	5.7 [3.3,9.9]	1.0	0.46
VBT	16	8.3 [5.1,13.4]	1.32 [0.63,2.74]	
Disease-free survival				
EBRT	31	78.1 [69.7,86.5]	1.0	0.74
VBT	32	82.7 [76.9,88.6]	1.09 [0.66,1.78]	
Overall survival				
EBRT	26	79.6 [71.2,88.0]	1.0	0.57
VBT	29	84.8 [79.3,90.3]	1.17 [0.69,1.98]	

Acute and long-term toxicity outcomes were worse overall for EBRT patients than VBT patients. Grade 1 and 2 gastrointestinal toxicity (EORTC-RTOG) increased significantly after treatment with EBRT compared with VBT, 53.8 (112/208) vs. 12.6 (27/215) per cent, respectively. This difference decreased with further follow-up and no difference was observed between the two groups after 24 months. Late grade 3 gastrointestinal toxicity was reported in four (2%) patients who received EBRT and in one (<1%) who received VBT. In these five cases, surgery was required for bowel obstruction due to adhesions or fibrosis. From six months onwards, grade 1 and 2 atrophy of the vaginal mucosa increased, and significantly more EBRT patients experienced grade 2 atrophy compared with VBT patients. Grade 3 atrophy was reported in one (<1%) EBRT patient and four (2%) VBT patients. No treatment related deaths occurred (Nout et al 2010).

One retrospective cohort study of 499 women with endometrial carcinoma was identified for inclusion in this summary (Byrd et al 2008) (level III-2 intervention evidence). However, only 30 patients in total received VBT alone following hysterectomy while 224 patients underwent EBRT alone or in combination with VBT, and 121 underwent surgery alone (no radiotherapy) for their endometrial cancer. The results showed that there was no difference between patients who underwent surgery alone and those who underwent adjuvant radiotherapy in any form (p=0.115). Toxicity was poorly reported and not stratified by patient treatment group. Given this lack of comparison for toxicity outcomes, and the small number of patients treated with adjuvant VBT alone, this study does not provide conclusions as to whether VBT results in fewer acute and long term toxic effects.

COST IMPACT

Brachytherapy for intravaginal treatment alone is listed on the MBS under item numbers 15311 and 15312 for which fees are \$314.95 and \$312.65, respectively, and numbers 15315 and 15316, both with a fee of \$618.30 (DoHA 2010).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

No issues were identified/raised in the sources examined.

SUMMARY OF FINDINGS

The included evidence for the safety and effectiveness contained one high-level study (Nout et al 2010) which indicated VBT has similar oncological and survival outcomes, but lower toxic effects when compared to EBRT. Thus VBT potentially offers improved quality of life for endometrial cancer patients. Importantly, one included study (Byrd et al 2008) reported outcomes and cited further sources which suggest that the benefit of post-operative radiotherapy remains uncertain. Although EBRT and VBT provide similar improvement in vaginal recurrence, it is not clear that this outcome translates to overall or disease-free survival exceeding surgery alone. If radiotherapy is to be performed at all, the indication at present is that prophylactic VBT should be sufficient to reduce the majority of vaginal recurrence following total abdominal hysterectomy with bilateral salpingo-oophorectomy while resulting in fewer toxic effects than EBRT.

HEALTHPACT ASSESSMENT:

As vaginal brachytherapy is already an established technology in Australia, no further evaluation on behalf of HealthPACT is warranted.

NUMBER OF INCLUDED STUDIES

Total number of studies	2
Level II intervention evidence	1
Level III-2 intervention evidence	1

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SEARCH CRITERIA TO BE USED:

Brachytherapy, vagina*
External beam radiotherapy/EBRT
Radiotherapy/radiation therapy
Endometrial cancer