Horizon scanning technology
prioritising summary

Total mesometrial resection for cervical cancer

November 2009
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The production of this Horizon scanning prioritising summary was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). 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.

This Horizon scanning prioritising summary was prepared by Mr Irving Lee from the Australian Safety and Efficacy Register of New Intervenational Procedures – Surgical (ASERNIP-S).
PRIORITISING SUMMARY

REGISTER ID  S000104

NAME OF TECHNOLOGY  TOTAL MESOMETRIAL RESECTION (TMMR)

PURPOSE AND TARGET GROUP  PATIENTS WITH EARLY STAGE CERVICAL CANCER

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

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☐ Yes
☐ No
☑ Not applicable

INTERNATIONAL UTILISATION

<table>
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<tr>
<th>COUNTRY</th>
<th>LEVEL OF USE</th>
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<tr>
<td></td>
<td>Trials Underway or Completed</td>
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<tr>
<td>Germany</td>
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IMPACT SUMMARY

TMMR is a modified surgical procedure that has been proposed as an alternative to total hysterectomy for early stage cervical cancer patients. Proponents suggest that it reduces patient morbidity, improves outcomes and can potentially eliminate the need for adjuvant radiotherapy.

BACKGROUND

Carcinoma of the uterine cervix continues to be a serious health issue worldwide despite the fact that its prevalence and incidence has steadily decreased in developed countries. Recently, the development and administration of human papilloma virus vaccines have had a major impact on further reducing the incidence of cervical cancer. However, it is important to note that it will take at least one to two decades before the impact of the vaccine becomes epidemiologically evident (Dornhöfer and Höckel 2008).
The current standard treatment protocol for cervical cancer involves staging, followed by stage-adjusted treatment with surgery and/or chemoradiation. Radical hysterectomy is the current gold-standard surgical treatment for cervical cancer, however it has been associated with relatively high morbidity, especially when performed in conjunction with chemoradiation. Refinements of hysterectomy with the use of minimal access techniques, robotics, nerve sparing and fertility sparing procedures could potentially decrease morbidity rates. However, one research group has pointed out that these refinements to radical hysterectomy all rely on historical foundations of surgical anatomy in the female pelvis and of local tumour spread that may be flawed. Dornhöfer and Höckel (2008) have stated that the standard surgical treatment for cervical cancer and recent advancements are all based on an uterocentric and ligament-focused view of surgical anatomy and the assumption of undirected intra- and transcervical tumour spread. The authors state that the uterocentric perspective is deceptive because it does not distinguish tissues integral to the uterovaginal tract from those that are only attached or connected to it. Furthermore, this ligament-focused view was described as misleading because prominent structures like the cardinal ligament and the posterior leaf of the vesicouterine ligament do not have any suspensory functions. In addition, the authors note that the sagittal pelvic curvature is not usually considered. As a direct result of the concept of undirected transcervical tumour spread, it is generally accepted that all paracervical tissues have to be resected in order to ensure the unrestricted radicality of hysterectomy (Höckel 2007, Dornhöfer and Höckel 2008).

Dornhöfer and Höckel (2008) suggest that local tumour spread is not random and is confined to a permissive compartment. This compartment can be morphologically delineated from the embryonic development of the organ. They propose that although tumour progression is usually random, the neoplasm actually respects the compartment borders for extended phases in its malignant progression (Höckel 2007). Therefore, surgical radicality can actually be reduced to sub- or intra-compartmental resection. Theoretically, this should allow for high local tumour control rates without the need for additional radiation therapy. Furthermore, this method of highly specific resection should substantially decrease the morbidity of the procedure relative to radical hysterectomy. TMMR is the translation of these insights into a new principle of surgical radicality for the treatment of cervical carcinoma of Federation of Gynaecology and Obstetrics (FIGO) stages IB, IIA and selected IIB. TMMR completely removes the Müllerian compartment except for the distal parts, where the resection is intracompartmental to preserve a functional vaginal vault (Höckel et al 2009).

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1 FIGO Staging, ovarian carcinoma: I Malignancy of one (Ia) or both (Ib) ovaries, without ascites; 5-year survival: 60%; II Malignancy of one (IIa) or both (IIb) ovaries, with pelvic extension and ascites; 5-year survival: 40%; III Malignancy involves one/both ovaries, intraperitoneal metastases outside pelvis and/or positive retroperitoneal lymph nodes; 5-year survival: 5%; IV Involvement of one/both ovaries with metastases and histologically confirmed extension to pleural cavity or liver; 5-year survival, 3%.
**CLINICAL NEED AND BURDEN OF DISEASE**

Worldwide, approximately 490,000 new cases of cervical cancer are diagnosed each year and it has been shown to be responsible for 270,000 deaths per year (Kamangar et al 2006). In Australia, there are approximately 700 new cases of cervical cancer each year and 200 women die from this disease annually. Cervical cancer is the second most common cancer in females and as a result of this many countries have instituted regular cervical screening programs to detect cervical abnormalities. Regular Pap tests save more than 1,200 Australian women each year from cervical cancer (Better Health Channel 2009). The Australian Institute of Health and Welfare reported that between 2007 and 2008, a total of 100 radical vaginal hysterectomies and 1023 radical abdominal hysterectomies were performed in the public health system (Australian Institute of Health and Welfare 2009).

**DIFFUSION**

The concept of TMMR was introduced in 1998 by Höckel et al (2009) and suggests a different approach to the surgical treatment of cervical cancer. To date, TMMR has been propagated and espoused by one institution and no other researchers have published additional studies on this procedure. Some have suggested that the anatomy and planes described by Höckel and colleagues are difficult to follow and that a high level of expertise is required in order to perform the procedure. Considering the level of experience and knowledge required for this procedure, it has only been performed at the University of Liepzig, Germany.

**COMPARATORS**

The key comparator to TMMR is the well-established radical hysterectomy procedure. Radical hysterectomy removes all the female reproductive organs including the ovaries, the fallopian tubes, the uterus, the cervix, and the upper part of the vagina. It includes removal of the pelvic lymph glands. This operation is generally performed for cervical cancer and for some ovarian cancers.

**SAFETY AND EFFECTIVENESS ISSUES**

*Study description*

Searches identified 3 published articles on the safety and efficacy of TMMR (Höckel et al 2003, Höckel et al 2005, Höckel et al 2009). Due to substantial patient overlap between these papers, the most recent and comprehensive article (Höckel et al 2009) was selected for inclusion in this summary.

The prospective case series study conducted by Hocket et al (2009) evaluated TMMR (without adjuvant radiation) for the treatment of cervical cancer in 212 consecutive patients from October 1999. All patients with FIGO stage IB1, IB2, IIA and selected IIB
cervical carcinoma were enrolled into this study after informed consent was obtained. Patients who had morbidity such as severe morbid obesity (BMI>35 until 2004; BMI>40 from 2005 onwards), that would have contributed to high surgical risks, were excluded from the study. In addition, patients with a tumour size >5cm received up to 6 courses of neoadjuvant chemotherapy, with 40 mg/m² cisplatin each week. Patients with FIGO stage IB and IIA were treated with TMMR irrespective of their response to neoadjuvant chemotherapy, due to the theoretical risk of compartamental transgression. For patients with IIB cervical cancer, those with tumour size >5cm were required to undergo neoadjuvant chemotherapy (only included if responsive), have no evidence of bladder or rectal involvement and no morbid obesity, in order to be included. After TMMR, patients were followed up at 3 month intervals for the first 2 years and 6 month intervals thereafter (Höckel et al 2009).

In addition to this, Höckel et al (2009) attempted to generate MRI-based pelvic relapse landscapes from patients who experienced pelvic failure after conventional radical hysterectomy. Retrospective analysis was performed on 2 groups of patients: 1) all patients with histologically proven pelvic recurrence selected for treatment with laterally extended endopelvic resection (LEER) from 2001 to 2007 and 2) all patients with histologically proven pelvic recurrences admitted for potential treatment from October 2001 to July 2003. T2-weighted MRI scans were used to delineate recurrences in the pelvis for each patient.

Safety and Effectiveness

Höckel et al (2009) reported that the surgical goal of resecting the Müllerian compartment was successful in all patients. In 5 patients who had FIGO stage IIB tumours, focal compartamental transgression was assumed during the operation which led to extended resection. The authors note that supracompartamental resection included parts of the bladder (3 patients), ureter (1 patient) and mesorectum (2 patients). Oophorectomy was performed in 160 patients. At a median of 41 months (range: 5-110 months), 35% (75/212) of patients had grade 1 complications and 9% (20/212) had grade 2 complications (complications graded according to the Franco-Italian glossary) (Table 1). No grade 3 or 4 complications were observed. Median blood loss was not reported, however 42% (88/212) of patients received an intraoperative transfusion.

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<th>Grade 1</th>
<th>Grade 2</th>
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<tr>
<td>Gastrointestinal*</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Urinary†</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Vascular‡</td>
<td>43</td>
<td>12</td>
</tr>
<tr>
<td>Cutaneous§</td>
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</tr>
<tr>
<td>Peripheral nerves¶</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Total complications</td>
<td>75</td>
<td>24</td>
</tr>
</tbody>
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*Small bowel obstruction; † residual urine, urinary incontinence, hydronephrosis; ‡ lymphoedema, lymphocyst, thromboembolism, § wound dehiscence; ¶ femoral nerve neuropathy.
Disease recurrence in the pelvis only was observed in 1.4% (3/212) of patients, all of which underwent successful secondary treatment. Meanwhile, 1.1% (2/212) had pelvic and distant disease and 2.4% (5/212) had distant metastases at the time of relapse diagnosis. The mortality rate for cervical cancer in this patient group was 2.4% (5/212), all of which had systemic disease. An additional patient died from metastatic secondary cancer, leading to an overall mortality rate of 2.8% (6/212). Kaplan-Meier estimates of 5-year disease free and overall survival was 94% (95% CI: 90-98) and 96% (95% CI: 93-99), respectively. When the analysis was limited to patients with FIGO stage IB-IIA tumours (n=159), disease-free and overall survival rates were 98% (95% CI: 96-100) and 98% (95% CI: 96-100), respectively. Meanwhile, patients with node-positive disease (n=44) achieved 5-year overall and disease-free survival rates of 91% (95% CI: 81-100) and 81% (95% CI: 67-94), respectively.

The examination of relapse landscapes obtained from MRI scans of 2 retrospective patient cohorts indicated that pelvic relapse landscapes have a characteristic pattern. The data indicates that the peak zones for recurrence probability cover the area of the ligamentous mesometrium adjacent to the mesorectum, from the central lower to the peripheral upper parts. The authors state that this transversally curved dorsally directed pattern demonstrated by the relapse landscapes are not explained by current concepts of surgical anatomy and tumour spread of cervical cancer. However, Höckel and colleagues suggest that this can be understood from the conceptual and practical differences between TMMR and radical hysterectomy (Höckel et al 2009).

**COST IMPACT**

There are no cost-effectiveness studies on TMMR to date. The most recent study states that the median operation time was 7.1 hours (range: 5.1-11.6 hours) with median hospital stay of 12 days (5-24 days) (Höckel et al 2009). The operative time for TMMR suggests that it is a substantially longer procedure relative to open radical hysterectomy, contributing to increased overall cost. If TMMR is effective, cost savings can be realised from improved long-term patient outcomes and eliminating the need for adjuvant radiotherapy. However, no firm conclusions can be elucidated at this time due to the paucity of comparative studies.

**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 one long-running prospective case series study suggests that TMMR is feasible and has the potential to achieve impressive overall and disease-free survival
rates. However, there is little data on the claimed benefits of reduced patient morbidity. Considering the fact that all of the available evidence has been generated by the same institution, there is some concern that the apparent success of this procedure may not be reproducible in other institutions.

It is important to note that accepting close resection margins on the basis of tumour spread being confined to the Müllerian compartment is a concept that goes against the basic principles of oncological surgery. It remains to be shown if the wider medical community is ready to adopt or test this new procedure.

**RECOMMENDATION**
The evidence suggests that TMMR is a promising procedure. However, as the best available evidence to date is limited to a single prospective case series study, the effectiveness of TMMR remains unclear. Comparative studies are required in order to determine the procedure’s true effectiveness relative to radical hysterectomy. Based on the limited evidence available and the possibility that new studies may not be published in the near future, further assessment of this procedure by HealthPACT is not necessary at this time.

**NUMBER OF STUDIES INCLUDED**
Total number of studies 1
Level IV intervention evidence 1

**REFERENCES**


**SEARCH CRITERIA TO BE USED**

Total mesometrial resection, TMMR, Uterine Cervical Neoplasms/surgery*. 