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Department of Health and Ageing



Horizon Scanning Technology Prioritising Summary Sentinel lymph node mapping for colorectal cancer

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



**Royal Australasian
College of Surgeons**

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Enquiries about the content of the report should be directed to:

HealthPACT Secretariat
Department of Health and Ageing
MDP 106
GPO Box 9848
Canberra ACT 2606
AUSTRALIA

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

PRIORITISING SUMMARY

REGISTER ID: S000031

NAME OF TECHNOLOGY: SENTINEL LYMPH NODE BIOPSY FOR
COLORECTAL CANCER

PURPOSE AND TARGET GROUP: TO DETECT NODAL METASTASES IN PATIENTS
SUFFERING FROM COLORECTAL CANCER

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- | | |
|---|---|
| <input checked="" type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input type="checkbox"/> Experimental | <input 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

- | | | |
|--|-------------|-----|
| <input type="checkbox"/> Yes | ARTG number | N/A |
| <input type="checkbox"/> No | | |
| <input checked="" type="checkbox"/> Not applicable | | |

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
France	✓		
Italy	✓		
Japan	✓		
Netherlands	✓		
United States	✓		

IMPACT SUMMARY:

Conventional histopathology techniques for examining lymph nodes in patients with colorectal cancer appear to be inadequate, with approximately 30% of node-negative patients dying as a result of recurrence or metastases. The use of sentinel node mapping to stage colorectal cancer may increase the detection of nodal metastases and lower recurrence rates, compared to conventional techniques. This prioritising summary examines whether current evidence supports the clinical application of sentinel node mapping in patients with colorectal cancer.

BACKGROUND

In patients with cancer, the sentinel lymph node (SLN) is commonly defined as the first lymph node that receives lymphatic drainage from the primary tumour (Chen et al. 2006). It is thought that the localisation, removal and histopathological analysis of SLNs can provide important staging and prognostic information on the spread of the primary tumour through the lymph system. SLN biopsy has already proven useful in patients with skin melanoma and breast cancer (Sticca 2006).

In colorectal cancer, lymph node status after tumour resection is one of the most important prognostic factors used to determine treatment. Patients with nodal disease are usually given adjuvant chemotherapy because this has been shown to reduce mortality and recurrence by up to 33% and 40%, but there is no definitive evidence of benefit in patients who are node-negative (Stage II¹) (Fricker 2006, de Haas et al. 2007). Approximately 20% to 30% of node-negative patients eventually die as a result of local tumour relapse or overwhelming metastatic disease (de Haas et al. 2007). While it is possible that a considerable number of these patients have occult nodal metastases that are not detected by conventional histopathological analysis, administering adjuvant chemotherapy to all Stage II patients is both unnecessary and costly (de Haas et al. 2007).

In conventional histopathological analysis, the nodes are bivalved, removed and then stained with hematoxylin-eosin (H&E) (Chen et al. 2006). Accurate cancer staging requires a detailed analysis of all lymph nodes recovered, but this is impractical, labour intensive, time consuming and expensive. In contrast, SLN mapping enables the use of more intensive 'ultrastaging' techniques, which require fewer nodes and are less costly. Ultrastaging utilises a combination of three techniques: serial sectioning, immunohistochemistry (IHC) and reverse-transcriptase polymerase chain reaction (RT-PCR) (Chen et al. 2006).

The procedure begins with the identification of the sentinel node, which typically involves injecting a tracer circumferentially around the tumour to map the lymphatic drainage pathway from the tumour. The most common mapping technique uses a combination of blue dye and radioisotope, although there are reports of excellent results with single modality techniques (Chen et al. 2006). In patient with colorectal cancer, the blue dye and/or radioisotope is injected into the subserosal surface of the bowel immediately adjacent to the base of the tumour. After several minutes, the mesentery is visually inspected to determine the location of sentinel nodes, which are characterised by the uptake of blue dye. If a radioisotope tracer was injected, a gamma counter is also used to pinpoint the nodes. All SLNs are marked with sutures or clips and are later removed and examined by a pathologist to determine if nodal metastasis is evident (Read et al. 2005).

CLINICAL NEED AND BURDEN OF DISEASE

Colorectal cancer is the second most common malignancy in developed countries, and is the second leading cause of cancer-related death worldwide (van Scheltinga et al. 2006). In 2003, 4,447 Australians died as a result of colorectal cancer (a rate of 22 per 100,000), making it the second most common cause of cancer mortality in the country (AIHW 2006). In 2001, a total

¹ **Stages of colorectal cancer:** *Stage 0* refers to a very early stage of colorectal cancer where the cancer cells are confined within the lining of the bowel; *Stage 1* indicates that the cancer has grown through the inner lining of the bowel but there is no cancer in lymph nodes; *Stage 2* indicates that the cancer has grown through the outer covering of the bowel/into tissues or organs next to bowel but there is no spread to the lymph nodes or another area of the body; *Stage 3* indicates the cancer has spread to the lymph nodes but not to other areas of the body; *Stage 4* indicates the cancer has spread to other parts of the body via the lymphatic system or bloodstream.

of 12,844 new colorectal cancer cases were identified; a substantial increase compared to 1991 when only 9,705 new cases were identified (AIHW 2006).

DIFFUSION

SLN sampling is routinely used in Australia for breast cancer and skin melanoma. However, at the time of writing there was no evidence that SLN sampling is being used for colorectal cancer.

COMPARATORS

The comparator of SLN mapping for colorectal cancer is conventional nodal staging, which involves resecting all regional lymph nodes and subjecting them to standard histopathological analysis.

SAFETY AND EFFECTIVENESS ISSUES

A systematic literature search conducted by de Haas et al. (2007) identified 17 case series studies on SLN mapping for colorectal cancer: 15 describing SLN mapping with blue dye alone and two describing SLN mapping with a combination of blue dye and radioisotope. Most of the included studies performed microscopic examination of SLNs using multisectioning, H&E-staining and/or immunohistochemical staining. Immunohistochemical staining was conducted with antibodies against cytokeratin (CK) and in one study against carcinoembryonic antigen (CEA).

Ten studies using blue dye alone reported identification rates from 90% to 100%, while the remaining five studies reported rates from 71% to 87%. In three studies that used a laparoscopic method, the identification rate was 100%. The reported accuracy ranged from 78% to 100%, although four studies did not have adequate data to determine the accuracy of SLN mapping. The false-negative rate (incorrectly classified as not having cancer cells present) varied substantially across the included studies, ranging from 0% to 54%. Possible upstaging percentages were between 3% and 20%, while the percentage for true upstaging (increase in patient's identified cancer stage e.g. from stage II to III) varied between 0% and 6% (five studies did not have sufficient data to recalculate the percentage of possible upstaging) (de Haas et al. 2007).

Of the two studies that used a combination of blue dye and radioisotope for SLN mapping, one employed an *ex vivo* technique². This achieved an identification rate of 88%, a sensitivity of 55% and a 45% false-negative rate. It is noteworthy that only 51% of blue nodes were radioactive, while 81% of radioactive nodes were dyed blue. The two remaining studies that utilised an *in vivo* technique achieved an identification rate of 98%. In one study utilising ultrastaging techniques, the researchers achieved a sensitivity rate of 83%, with a 17% false-negative rate. A true upstaging rate of 19% was revealed after IHC analysis of the SLNs. The use of radioisotope identified an additional 10 SLNs (5%), but only one of these SLNs would not have been identified with the use of blue dye alone. de Haas et al. (2007) stated that the addition of radioisotope tracer for SLN mapping did not provide any substantial improvement in identification rates, compared to blue dye alone.

Overall, the accuracy rates for SLN mapping ranged from 93% to 100%, with sensitivity rates of between 90% and 100% and true upstaging rates of 5% to 14%. However, the prognostic significance of IHC- and/or RT-PCR-detected micrometastases remains unclear. Only 25% (3/12 studies that reported on micrometastases) of the included studies reported that the

² The *ex vivo* technique involves the immediate subserosal injection of isosulfan blue dye around the tumour after the removal of the colectomy specimen. As with the *in vivo* technique, identified SLNs are marked with clips/sutures and are submitted for pathologic examination.

detection of micrometastases correlated with significantly worse survival rates (de Haas et al. 2007).

In one non-randomised comparative study, Saha et al. (2006) retrospectively reviewed 500 consecutive patients with colorectal cancer (418 colon, 92 rectal) who underwent SLN mapping with blue dye and pathological examination (Group A). Data from an additional 368 consecutive patients who underwent conventional surgery with pathological examination (no SLN mapping) (Group B) were retrospectively collected for comparison (it is unclear if the patients for each group were assessed over the same time period). For patients in Group A, SLN mapping was successful in 98% (489/500) of patients (99% for colon cancer; 91% for rectal cancer), while positive SLNs were detected in 45% (186/418) of patients with Stage I - Stage IV tumours. Skip metastases³ were detected in 10% of patients (11% for colon cancer; 7% for rectal cancer). Overall, positive nodes were detected in 50% of patients in Group A, with an overall accuracy of 96%, a sensitivity of 90% and a negative predictive value of 93%.

More positive nodes were detected in Group A patients (50%, 250/500 patients), compared to Group B (35%, 129/368 patients) ($P \leq 0.001$) (Saha et al. 2006). In patients with early (T1 to T2) colorectal cancer, 20% in Group A had positive nodes, compared to 10% in Group B ($P = 0.007$). For patients with advanced cancer (T3 to T4), these rates were 62% for Group A and 40% for Group B ($P < 0.0001$). These results indicate that the conventional lymph node examination may significantly understage patients with nodal metastases, compared to SLN mapping. In 153 patients from Group A who were followed for at least 2 years (median 5 years), the tumour recurrence rate was 7%, compared to 25% for 162 patients in Group B ($P = 0.001$). This significant difference between patient groups was evident for node-positive patients (11% in Group A, 37% in Group B; $P = 0.0004$) and node-negative patients (3% in Group A, 18% in Group B; $P = 0.0025$) (Saha et al. 2006).

³ Skip metastases: metastases found in non-sentinel lymph nodes in a patient whose sentinel lymph nodes were negative for metastases.

COST IMPACT

The cost-effectiveness of SLN mapping for colorectal cancer is not known. The cost of this technique will depend on the number of SLNs examined and the type of ultrastaging technique used in the histopathological examination (e.g. IHC staining is substantially cheaper than RT-PCR). The current lack of standardisation in SLN mapping methodology makes it difficult to calculate the cost of this technique for colorectal cancer.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified from the retrieved material.

OTHER ISSUES

For patients with breast cancer and melanoma, SLN mapping failures that occur due to inappropriate technique or inadequate pathological examination may result in undertreatment. However, in patients with colorectal cancer, SLN mapping does not preclude the excision of all regional lymph nodes because each lymph node is subjected to conventional pathological testing (while SLNs undergo more rigorous testing). Thus, patients with skip metastases will still receive the appropriate adjuvant chemotherapy and will not be undertreated, according to conventional standards (Saha et al. 2006).

RECOMMENDATION:

While the evidence for SLN mapping in patients with colorectal cancer suggests that it may potentially reduce the risk of understaging, compared to conventional techniques, it is still an experimental procedure. The large variation in results among studies reflects the lack of a standardised technique and a universal definition of which stained lymph node(s) should be considered SLNs. In addition, the true value of SLN mapping for improving nodal staging in colorectal cancer will only be demonstrated if it translates into improved survival for patients with accurately staged colon cancer. Based on the evidence currently available and the potential impact of this technique, this technique will be monitored for future studies.

SOURCES OF FURTHER INFORMATION:

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LIST OF STUDIES INCLUDED

Total number of studies	2
Pseudo-level I intervention evidence (systematic review of case series studies)	1
Level IV intervention evidence	1

SEARCH CRITERIA TO BE USED:

Sentinel lymph node biopsy*
Lymph node excision
Neoplasm staging
Colonic neoplasms
Colorectal cancer

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PRIORITISING SUMMARY UPDATE (2008)

REGISTER ID:	S000031
NAME OF TECHNOLOGY:	SENTINEL LYMPH NODE BIOPSY FOR COLORECTAL CANCER
PURPOSE AND TARGET GROUP:	TO DETECT NODAL METASTASES IN PATIENTS SUFFERING FROM COLORECTAL CANCER

A search of relevant databases was conducted in April 2008, following the recommendations in May 2007 that Sentinel lymph node (SLN) mapping for colorectal cancer be monitored for 12 months. A total of ten new studies were identified. The studies included one randomised controlled study and nine case series (including one case series in Russian). Four studies (one randomised controlled study and three case series) were selected for inclusion in this update (Stojadinovic et al. 2007; Kelder et al. 2007; Liberale et al. 2007; Bilchik et al. 2006) based on study quality and number of patients included.

2008 SAFETY AND EFFECTIVENESS ISSUES

Stojadinovic et al. (2007) conducted a randomised controlled study at five academic medical centers located in the United States, Israel and Serbia. One hundred and sixty two patients with stage I-III colon cancer with biopsy-proven, primary, non-metastatic colon carcinoma or colon tumours clinically consistent with cancer (pathology confirmed) were randomly assigned to standard complete surgical resection of the tumour bearing colon, with en bloc regional lymphadenectomy followed by either conventional histopathologic evaluation or sentinel lymph nod mapping, biopsy and ultra staging in conjunction with standard histopathologic evaluation. The control group consisted of 80 patients while the intervention group (SLN mapping) included 82 patients. The aim of the study was to determine the rate of upstaging of colon carcinoma lymph node metastasis with SLN mapping.

The mean number of nodes that were analysed per patient was 18.2 ± 0.9 (95% CI: 16.5 – 19.9). In the SLN group, SLN mapping identified a mean of 2.7 ± 0.3 (95% CI: 2.3 – 3.2) SLNs per patient. Stojadinovic et al. (2007), found considerable nodal upstaging with SLN ultra staging (control vs. SLN: 38.7% vs. 57.3%, $p = 0.019$). However, when SLNs with cell aggregates ≤ 0.2 mm in size were excluded, no statistically significant difference in node-positive between the control and SLN groups was observed (38.7% vs. 39.0%, $p = 0.97$). Additionally, a 10.7% (6/56) nodal upstaging was reported as a result of H&E stained step sections of SLNs among study arm patients who would have otherwise been staged node-negative (N0) by conventional pathologic assessment alone. In the SLN group, SLNs were successfully identified in 97.

The SLN was successfully identified in 67 patients (97%) with a mean number of SLNs per patient of 2.3. The two failed cases occurred in a patient with a carcinoma in the sigmoid colon surrounded by a concurrent diverticulitis and in a patient with extended lymph node metastases with angio-invasion at pathological examination. There were 27 node positive patients, of which in 24 the SLN was positive with either H&E or IHC staining (sensitivity of 89%). Excluding patients who had a positive SLN only after IHC staining, the sensitivity was reduced to 15 of 18 patients (83%). In nine of 27 patients with positive SLNs, metastases were detected only after IHC staining.

There were 49 node negative cases by H&E. With the use of IHC staining, the upstaging was 9/49 (18%). Negative results were seen in the SLN in 43 patients. Additionally, in 40 patients the non SLNs were also negative. This translated to a 93% negative predictive value and accuracy of 96%.

Liberale et al. (2007) investigated SLN mapping in 118 patients (59 males and 59 females, mean age 65 years). The blue dye injection technique was used and serial sections of the SLN's were analysed after hematoxylin-eosin staining.

At least one SLN was successfully detected in 112 patients, which the authors reported as a feasibility of 95%. In total, 2620 lymph nodes were dissected, including 217 SLNs. In 60 patients who underwent the in vivo technique, lymph node mapping demonstrated a particular lymphatic pattern in 7 patients (11.6%), which influenced intraoperative decision for the dissection procedure. In two of these patients, the SLN guided dissection demonstrated a positive specimen after histological analysis (one N1 and one N2). However at more than three years follow-up these patients are alive without recurrence. Prior to SLN analysis 84 patients (75%) were classified as pN0. Following analysis of the SLN, staging was pN1 for 14 patients (12.5%) and pN2 for 14 (12.5%). The false negative rate was determined to be 39% (for N+ patients) or 12% (for all patients including N0). In the 84 patients free of nodal involvement, SLN examination led to the upstaging of eight patients (9.5%).

Bilchik et al. (2006) conducted a multicentre trial of 132 patients (63 male, 69 female median age 74 years) with clinical stage I and II colorectal cancer. The trial included lymphatic mapping during standard oncologic resection. Hematoxylin-eosin staining was performed on all lymph nodes while immunohistochemistry was performed on lymph nodes negative by H&E staining.

In 127 cases, at least one stained sentinel node was identified by the surgeon compared to five cases by the pathologist. Sentinel node macrometastases were reported in 17 patients (12.9%), isolated tumour cell clusters ≤ 0.2 mm in the sentinel node were reported in 24 patients (20.1%) and micrometastases ≤ 2 mm in the sentinel node were reported in four patients (3.5%). In 87 patients (75.6%) there was no evidence of a tumour in the sentinel node. Seven patients with micrometastases or isolated tumour cells in a sentinel node had isolated tumour cells in non sentinel nodes. Upstaging occurred in 28 patients (23.6%). The sensitivity of lymphatic mapping of the sentinel node was reported at 88.2% and the false negative rate was reported at 7.4%. Finally, a significantly greater likelihood of tumour in sentinel nodes than non sentinel nodes was reported ($p = 0.001$).

2008 RECOMMENDATION

The evidence presented in the update suggests that sentinel lymph node mapping improves staging accuracy. However there is still a lack of comparative evidence available and the data regarding the most important outcome of sentinel lymph node mapping, whether sentinel lymph node mapping staging translates into improved survival for patients, is still lacking. Based on the lack of comparative studies and lack of patient survival data, it is recommended that sentinel lymph node mapping be archived.

TOTAL NUMBER OF INCLUDED STUDIES

Total number of studies	4
Level II intervention evidence	1
Level IV intervention evidence	3

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