The feasibility of sentinel lymph node biopsy in colorectal cancer staging

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The feasibility of sentinel lymph node biopsy in colorectal cancer staging

Edmund Leung, James Francombe, Simon Chew, Peter Douglas, and Graham Newstead

Abstract

Background: The usefulness of Sentinel Lymph Node (SLN) biopsy in colorectal cancer remains controversial. This study aims to determine the feasibility of SLN in colorectal cancer staging.

Methods: Forty-one patients underwent resection had their lymphatic drainage system mapped by Blue-dye injection into submucosa overlying tumour site intraoperatively. The blue-stained SLN is identified and sent to pathology separately. The SLN were stained with Haematoxylin & Eosin (H&E) and Immunohistochemical (IHC) technique. Regional nodes (NSLN) in the tumour specimen were examined by H&E.

Results: SLN was demonstrated in 38/41 patients (92.6%). 2 of the 3 cases were positive for their NSLN. 27/38 SLN had negative H&E staining (71.1%). The 27 H&E negative SLN, 1 SLN was positive with IHC. 7 cases were positive both in SLN and NSLN (sensitivity = 46.6%, positive predictive value = 63.6%), whereas 4 cases were positive in SLN but negative in NSLN. 19 patients shared negative SLN and NSLN staining (specificity = 82.6%, negative predictive value = 70.3%), whereas 8 cases were NSLN-positive but negative in SLN.

Conclusions: SLN biopsy is feasible, but should only be used as an adjuvant staging method. A positive SLN avoids examination of NSLN. A negative SLN does not exclude positive NSLN.

KEYWORDS: Sentinel Lymph Node, Haematoxylin staining, Colorectal Cancer, Immunohistochemistry, Histological staging
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RUNNING TITLE (40-character): Sentinel node biopsy in colorectal cancer

SYNOPSIS:
Sentinel lymph node biopsy is feasible in colorectal cancer staging. It is alone insufficient to accurately stage the disease and can be used as an adjuvant staging method.

KEYWORDS: Sentinel Lymph Node, Colorectal Cancer, Haemtoxylin staining, Immunohistochemistry, Histological staging

The study was approved by the Local Ethics Committee for Prince of Wales Hospital, Sydney.

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INTRODUCTION

Over the last few decades, the prognostic value of lymph node metastasis in colorectal cancer patients has been by Dukes, who included perirectal lymph node into his staging system [1]. Lymph node involvement decreases the 5 year survival rate by up to 30% [2].

On balance, the greater the number of examined lymph nodes, the higher the chance there is in detecting nodal metastasis [1,3]. Furthermore, nearly one-third of patients without lymph node involvement develop relapse due to occult nodal micrometastases, which are not usually detectable by routine histological examination of nodal basin [4].

Until recently, sentinel lymph node (SLN) biopsy has improved pathological staging of solid epithelial neoplasms: melanoma and breast cancer [5]. SLN is the first node that receives lymph from the primary tumour, which has the highest potential to contain tumour cells when present. Therefore, SLN histology is a good prognostic indicator of the regional lymph node status [6]. In breast cancer, SLN biopsy allows the pathologist to perform a focused analysis of one or only a few lymph nodes with immunohistochemistry (IHC). IHC provides a more accurate nodal staging compared to routine histopathological processing of the whole nodal basin [7].

In colorectal cancer patients, accurate pathological staging is the mainstay in the management of the whole disease process, with regards to adjuvant therapy. This study aims to determine the feasibility of SLN identification in colorectal cancer patients, and evaluates its accuracy with respect to staging lymph node basin.
MATERIALS AND METHODS

41 patients with colorectal cancer were entered prospectively in the study between January to December 2001. The study was conducted at the Colorectal unit of Prince of Wales Hospital, Sydney, Australia. All patients requiring elective colorectal cancer surgery were invited in the study. Exclusion criteria included patient refusal, palliative and emergency cases to relieve obstruction or divert a perforation.

The study protocol was approved by the local Ethics Committee of the Prince of Wales Hospital of Sydney, and all patients were fully informed before giving their written consent to the procedure.

All patients underwent clinical and radiological preoperative staging of the disease. Lymphatic mapping was performed by injecting 2 ml of vital blue dye intraoperatively subserosally at 4 sites close to the tumour site (Figure 1). Patients with low rectal cancer had dye injected into the submucosa beneath the tumour edge under the proctoscopic view, immediately prior to surgery. Leakage of blue dye into the lumen was avoided. After dye was infiltrated, bowel resections were performed as standard open procedure. The mesocolon was inspected to detect any blue-stained node. The identified node was then tagged with a silk stitch. The ex-vivo SLN were bisected and sent separately for pathological examination.

Once the specimens arrived in the laboratory, the histopathologist first confirmed the diagnosis of colorectal cancer by macroscopic inspection. Subsequently, the mesocolon was dissected to identify any potential lymph nodes. The SLN, which was submitted in a separate pot, was halved: one half of each SLN was examined by IHC of multiple 200-micrometre sections, and the other half was examined by standard haematoxylin-eosin (H&E) staining. The antibody used for
staining the SLN by IHC was anti-cytokeratin. All the remaining regional or non-SLNs were routinely examined by H&E staining.

RESULTS

All 41 patients had histological confirmation of invasive colorectal adenocarcinoma. SLN was demonstrated intra-operatively in 38 of 41 patients (92.6%). These 3 cases, which SLN were not identified: 2 of these 3 patients were positive for their regional NSLN. 27 of 38 SLN had negative H&E staining (71.1%). In these 27 H&E negative SLN, 1 SLN was found positive with IHC. 7 cases were positive both in SLN and NSLN (sensitivity = 46.6%, positive predictive value = 63.6%), whereas 4 cases were positive in SLN but negative in NSLN. 19 patients shared negative SLN and NSLN staining (specificity = 82.6%, negative predictive value = 70.3%), whereas 8 cases were positive in NSLN but negative in SLN. See Figure 2 and Table 1.

DISCUSSION

5 year survival rate of patients with curative colorectal cancer surgery is 50%. The International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT) B2 trial [8] concluded that chemotherapy is ineffective in improving survival rate in Dukes B cases, though it would benefit those 30% destined to relapse. Dukes C patients have a reduced 5 year survival rate by another 30%. Moreover, node positive patients require adjuvant chemotherapy after bowel resection. However, the extent of lymph node dissection in colorectal cancer surgery is still debatable. Radical
lymph node removal (at least 12 lymph nodes) has been suggested [9]. Herrara et al. [10] observed metastasis in 45% of lymph nodes measuring less than 5 mm.

Polymerase Chain reaction technique and Flow Cytometry analysis using monoclonal antibody, anti-cytokeratine, Cluster of Differentiation 44 variant 6 (CD44v6), Carcinoembryonic Antigen (CEA) and epithelial cellular adhesion molecule (EpCAM) antigen may improve sensitivity of pathological staging [11]. However, these techniques are time consuming, labour intensive and very expensive, should they be performed on every lymph node of the ex-vivo specimen. It is possible to consider a focused analysis using these techniques of one or only a few lymph nodes, which can reliably predict the nodal basin.

Morton et al [12] introduced the concept of staging melanoma using SLN, and the technique was subsequently applied to breast cancer surgery. In either case, radical lymph node dissection is planned based on the pathology result of the SLN.

As mentioned above, it is important to improve pathological staging of colorectal cancer in order to detect Dukes B patients bearing micrometastases in their lymph nodes. At present, Dukes B patients are given adjuvant treatment only within the purpose of clinical trials. Their efficacy is still undetermined. However, these Dukes B subsets with occult micrometastases have a higher risk of relapse and would benefit from adjuvant chemotherapy.

Saha et al. [13] reported controversial results that their SLN biopsy is highly accurate and feasible. They identified 99% of patients with a 91% sensitivity in 86 patients. There was 9% false negative rate, most likely due to skipped metastases as opposed to technical difficulties. This interesting data, regardless its reliability, is certainly an incentive to develop further work into the prognostic value of sentinel lymph node in colorectal cancer.
Our results showed feasibility of the technique in detecting SLN. IHC detected micrometastasis in 1 case out of 27 H&E negative SLN: an improved accuracy of 3.7%. This observation offers an insight that elective localisation of metastasis within SLN using more sensitive techniques can potentially upstage false node-negative patients. There is a clinical question as for management decision making and re-evaluation of adjuvant treatment in colorectal cancer patients.

CONCLUSION

SLN are easily identified using vital blue dye. IHC identified micrometastasis in 1 in 27 cases of H&E negative SLN. The preliminary results comparing SLN and Non SLN indicated that there is a risk of false negative findings and therefore further research is required to improve its sensitivity and specificity. The role of SLN mapping in colorectal cancer management is useful only as an adjuvant method of staging. It correlates poorly with the true nodal basin status with a high false negative rate. If SLN was identified positive, examination of nodal basin can be avoided. This has significant implications in terms of time and costs, especially IHC staining is labour intensive. Negative SLN does not exclude nodal metastasis, and therefore requires nodal basin examination.
Acknowledgement

Conflict of Interest:
NONE

Authors’ contributions:
EL wrote the manuscript and performed literature search
JF reviewed literature and revised the manuscript
SC, PD and GN carried out the practicals and collected the data

All authors have read and approved the manuscript.

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Abbreviations
SLN = sentinel lymph node
H&E = Haematoxylin&Eosin (H&E)
IHC = Immunohistochemical
NSLN = Non-sentinel lymph nodes or regional nodes
IMPACT = International Multicentre Pooled Analysis of B2 Colon Cancer Trials
CD44v6 = Cluster of Differentiation 44 variant 6
CEA = Carcinoembryonic Antigen
EpCAM = epithelial cellular adhesion molecule
REFERENCES:


FIGURE LEGEND

Figure 1. SENTINEL NODE WITH BLUE DYE STAINING

Figure 2. SLN DETECTION USING H&E STAINING

Table 1. PREDICTIVITY OF SLN HISTOLOGY
Figure 1.

![Image of surgical procedure]

Figure 2.

![Diagram showing lymph node status]
Table 1.

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<th>NSLN positive</th>
<th>NSLN negative</th>
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<tr>
<td>SLN Positive</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>SLN Negative</td>
<td>8</td>
<td>19</td>
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Sensitivity = 46.6%  (False negative rate = 53.3%)
Specificity = 82.6%
Positive Predictive Value = 53.3%
Negative Predictive Value = 70.3%