Sentinel Lymph Node Staging in Colon Cancer. Experience in 250 Cases

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Abstract: *Background*: The level of lymph node involvement is the most important factor in staging colorectal cancer without metastasis. Sentinel lymph node mapping identifies the node(s) that most accurately reflect the lymph node status of patients and intensive techniques that improve staging can be focused on these nodes. *Objective*: The aim of this study was to assess the efficacy of *ex vivo* sentinel lymph node mapping in the staging of colon cancer. *Design*: The selection of the cohorts was carried out on a prospective basis from September 2009 to April 2013, including all cases with no randomisation. *Settings*: Patients from the Alava University Hospital health region (Alava–Basque Country) in Spain. *Patients*: Study of 250 patients diagnosed prior to surgery with colon cancer without distant metastasis. A comparative study was also performed based on a control group of 170 patients staged with conventional techniques, involving a single slice and haematoxylin-eosin staining, from June 2006 to February 2009. *Interventions*: In these patients, we used *ex vivo* sentinel lymph node mapping with methylene blue, studying the sentinel nodes with multiple slices and immunohistochemical techniques as well as haematoxylin-eosin staining. *Main outcome measures*: The main outcome variable was change in staging after the Sentinel lymph node mapping. *Results*: The Sentinel lymph node identification rate was 98%, with 3.7% of false negatives. Upstaging occurred in 11% of cases compared to the group studied using conventional techniques. *Limitations*: The patients are not randomly selected and are compared with a retrospective series. *Conclusions*: *Ex vivo* Sentinel lymph node mapping with methylene blue accurately reflects the lymph node status of patients with colon cancer. This approach upstages patients classified as stages I and II by conventional techniques to stage III, indicating chemotherapy that may improve their prognosis.

Keywords: Sentinel lymph node, *ex vivo* technique, methylene blue, colon cancer, upstaging.

INTRODUCTION

Tumour staging, including an adequate evaluation of lymph node metastasis, is the most important prognosis factor in colorectal cancer (CRC). Specifically, patients have different survival rates depending on the TNM stage, early stages (I and II) being associated with 5-year survival rates of 82% to 93%, while the presence of lymph node metastases (stage III) decreases the rate to 59% [1].

Fifty percent of patients with CRC are diagnosed in early stages of the disease, with no lymph node metastasis, and are treated surgically with the intent to cure. However, around 20-30% of patients die in within 5 years of diagnosis [2]. This high percentage may be explained in part by incorrect staging, due to not performing a sufficiently thorough lymph node examination. We should, however, recognise that the survival of patients with lymph node involvement treated with chemotherapy has improved and mortality has decreased more than 30% [3].

The American Joint Committee for Cancer (AJCC) recommends analysing at least 12 lymph nodes to achieve accurate staging [2]. To improve the staging of patients with CRC, it has been proposed that intensive techniques should be used for assessing lymph nodes. This is not, however, realistic for all lymph nodes, given the high use of resources associated with carrying out such analysis.

The concept of the sentinel lymph node (SLN) is based on the idea that there is an orderly progression of tumour cells, from the primary tumour to the first lymph node involved, through the lymphatic system. Thus, the SLN has the highest risk of metastasis and, accordingly, is the node that may best reflect the lymph node status of patients. Once SLNs are identified, analysis with intensive techniques can be focused on a single node, allowing better use of resources. The main aim of this study was to assess the efficacy of *ex vivo* SLN mapping with dyes in the staging of colon cancer.

MATERIALS AND METHODS

This was a single-centre cross-sectional study to assess the efficacy of SLN mapping in the staging of colon cancer. A total of 250 patients from the Txagorrixu hospital health region (Alava) were included in the study. The selection of the cohorts was carried out on a prospective basis from September 2009 to

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April 2013, including all cases with no randomisation. The diagnosis was based on colonoscopy, abdominal CT and thorax radiography findings. The SLN mapping was carried out by 6 surgeons, with previous experience of this technique in colon cancer, each surgeon having performed the mapping in at least 10 previous cases. The inclusion criteria were to have been diagnosed with colon cancer, due to undergo elective curative surgery, and being at least 18 years of age. Cases of rectum cancer, at stage IV, or requiring emergency or palliative surgery were excluded.

Additionally, we carried out a comparative study with a control sample in which we had performed the conventional histopathological analysis (single slice and haematoxylin-eosin staining). This group was composed of 170 consecutive patients who underwent surgery from February 2009 backwards until June 2006. Patients underwent surgery by the same surgeons and complied with the same inclusion criteria as for the SLN study. The histopathological analysis was not, however, carried out by the same pathologists as those who studied the SLN group. The information required on this group of patients was obtained by reviewing their medical records.

The main outcome variable was change in staging after the SLN mapping. Secondary variables included the age and sex of the patient, tumour site and T and N stages, total number of lymph nodes and SLNs and total number of lymph nodes involved (as assessed by the conventional or SLN techniques), as well as the level of involvement.

All the procedures complied with the principles of the Declaration of Helsinki adopted in 1964, and last amended in Seoul in 2008, and the study was approved by the Clinical Research Ethics Committee of Txagorritxu Hospital.

Identification of the SLN

SLNs were identified *ex vivo*, after resection of the specimen. Our procedure is to inject around the tumour and the subserosal layer, 1-2ml of methylene blue, depending on the size of the tumour. The site is then gently massaged for 5-10 minutes, to improve the spreading of the dye through the lymphatic vessels to the lymph nodes. The mesocolon is then dissected close to the tumour following the path of the dye. We consider as SLNs the first 1 to 4 blue-dyed lymph nodes, and also any clearly and directly receiving drainage from a blue-dyed lymphatic vessel, even when dye has not reached the node itself [4].

Intensive Study of the SLNs

Before taking photographs, we prepared 2-mm slices of the SLNs, though those less than 5 mm in diameter were sliced only once. After fixation in 4% buffered formaldehyde solution for 24 hours, we cut six 4-µm slices. Samples were then examined with haematoxylin-eosin staining and by immunohistochemical analysis using cytokeratin immunostaining (CAM 5.2), three slices being analysed by each technique.

Interpretation of the Histopathological Findings

According to the AJCC system [5], the type of lymph node involvement was classified as *metastasis* when greater than 2 mm in diameter, *micrometastasis* when between 0.2 mm and 2 mm, and *isolated tumour cells (ITCs)* when there were *single tumour cells or small cell clusters* not greater than 0.2 mm. The presence of metastasis or micrometastasis affected the staging being considered pN1 and pN1mi, respectively. On the other hand, lesions less than or equal to 0.2 mm did not change the staging, being considered as pN0(i+). We note that the remaining lymph nodes were analysed in the conventional way with a single slice and using haematoxylin-eosin.

Statistical Analysis

The quantitative and qualitative data were expressed as means and standard deviations, and frequencies and percentages, respectively. The similarity of the groups was investigated using the Student's t and the chi square tests, the latter also being used to compare percentages of lymph nodes found to be involved and rates of upstaging. Further, we assessed the validity of the diagnostic test by calculating the sensitivity and specificity, along with the corresponding confidence intervals, with respect to the gold standard (conventional lymph node staging). The level of statistical significance was set at 0.05.

RESULTS

Group Staged by SLN Technique

SLN identification was achieved in 245 (98%) of 250 patients, with an error in the technique of 2%. Subsequently, analysis of the SLNs detected involvement in 76 (31%) of these 245 patients, as reported in Table **1**. Overall, the SLN technique correctly predicted lymph node status in 236 out of 245 cases, so that test accuracy was 93.06%, sensitivity was 88.3% and specificity was 95.24% (Table **1**).

Table 1: Group Studied with SLN Technique. Analysis of Test Validity

	Patients N +	Patients N -	Total
Sentinel lymph node +	68	8	76
Sentinel lymph node -	9	160	169
Total	77	168	245

Analysis of SLNs detected lymph node metastasis in 31 of the 40 patients found to have lymph node metastasis in the conventional staging (lymph nodes +) (Table **2**). In 9 of the 245 cases no metastasis was found in the SLN but at least one other lymph node was involved. Therefore, overall, the rate of false negatives was 3.67%.

Further, the SLN technique identified lymph node involvement in 46 (22.44%) of the 205 patients with no lymph node metastasis in the conventional staging (lymph nodes -) (Table **2**). The detailed analysis of the SLNs in these 46 patients, detected metastasis in 25 cases, micrometastasis in 13 and 8 patients with ITCs. Thus, the rate of upstaging using the SLN techniques in this group was 22.44%.

Comparison of SLN Group and Control Group

In the *control group*, staged by the conventional procedure, we detected lymph node metastasis in 33 (19.4%) of 170 patients (Table **3**), while in the *SLN group* we detected lymph node involvement in 77 (30.4%) of the 250 patients. That is, with the SLN technique we found 11% more patients with lymph node involvement, the difference being statistically significant. This corresponds to the overall rate of upstaging using the SLN technique (11%). Table **3** shows that in the SLN group, the SLN technique used on its own detected lymph node involvement in 76 (31%) of the 250 patients. This is 11% higher rate than among patients in the control group (19,4%).

DISCUSSION

Lymph node involvement is the single most important prognostic factor in CRC. Various studies [6-9] have demonstrated that survival is higher when more lymph nodes are analysed, especially when the results are negative. Accurate staging of CRC requires the identification of at least 12 lymph nodes: a smaller number may lead to downstage and poorer prognosis since the patient would not be given suitable adjuvant treatment.

In the surgical specimen, the number of lymph nodes in which involvement is detected depends on many factors, including the limitations of histopathological analysis. Specifically, as well as the intrinsic difficulty of the procedure, it is estimated that around 70% of the lymph nodes involved are smaller than 5 mm, so tend not to be detected [10]. Further, studying only one slice allows the analysis of only 1% of the lymph node tissue, so that small subcapsular tumour lesions may not be detected [11].

Table 2: Group Studied with SLN Technique. Histopathological Staging of Lymph Nodes Analysed by Technique: Conventional or Intensive (Sentinel Lymph Node Mapping)

		Non sentinel lymph nodes (Conventional technique)		Total
		+ lymph nodes	- lymph nodes	
Sentinel lymph node (SNL) mapping	+ SLNs	31	46	77
	- SLNs	9	159	168
Total		40	205	245

Table 3: Comparison of Lymph Node Involvement Detected by Type of Pathological Analysis in the Two Groups (Control Group and SLN Group)

	Histopathological techniques	Patients with lymph node involvement	Percentage	Level of significance
Control group (n=170)	Conventional	33	19.4%	$p < 0.05$ (11 %)
Sentinel lymph node group (n=250)	Combined	77	30.4%	
	Sentinel lymph node	76 68	31% 27.8%	(11.6%)* (8.4%)

*included isolated tumour cells

SLN mapping identifies one or a small number of lymph nodes that can provide a reliable assessment of the overall lymph node status of a patient and, as this means studying a smaller number of nodes, the use of intensive techniques does not lead to a high use of resources. Several studies [4, 11-14] report rates of upstaging of 10-20% with the use of immunohisto-chemistry and RT-PCR techniques. Taking multiple slices increases the stage by up to 9% [15].

The use of radioisotopes is the norm in breast cancer and melanoma. The use of dyes has, however, been described as a good alternative [16]. From our point of view, the dye technique is easier to perform since it does not require the involvement of nuclear medicine and digestive system specialists. Further, it avoids the risks associated with colonoscopy required for the injection of a radiotracer. For this reason, and given the lack of studies confirming that radioactive tracers achieve better results, we believe that the use of dyes such as methylene blue is the most suitable approach for analysing SLNs in cases of CRC.

Aberrant lymphatic drainage and better lymphatic circulation when the specimen has not been resected are the reasons in favour of the *in vivo* technique. The former concern relates to the fact that there may be metastasis outside the limits of the standard lymph node resection. The rate of aberrant drainage is, however, relatively low, between 2-8%, and many researchers fail to detect any cases [17, 18]. With regards to lymphatic drainage in the specimen removed, the experience in breast cancer and melanoma help to confirm that gently massaging the injection site is effective at stimulating flow of the dye through the lymphatic system [19]. Further, surgical resection interrupts the neurological mechanism that regulates the constriction of the lymphatic vessels, facilitating lymphatic drainage [20].

In 2001, Wong *et al.* [21] published the first large series of patients staged using *ex vivo* SLN mapping. The results achieved in that study, and in others published more recently, are similar to those obtained using the *in vivo technique* [20-22]. Arguments in favour of the *ex vivo* SLN technique include the fact that it avoids the risk of perforation and spread of tumour cells due to tumour manipulation inside the patient and avoids anaphylactic reactions to contrast media, while it does not require modification of the surgical technique and can be carried out by a surgeon other than the one involved in the intervention, allowing a shorter learning curve. In our opinion, however, the main advantage is that it is easier to perform, which is particularly important in larger tumours and those located in the rectum and in cases requiring laparoscopic surgery. In relation to this, some groups who usually use the *in vivo* technique, also perform *ex vivo* techniques in the aforementioned types of cases [23,24].

SLN identification rates range from 58% to 100%, most authors [20-26] reporting values of over 95%, while the rate of false negatives is between 0 and 10%. These results mainly depend on the experience of the team carrying out the technique, as well as on the quantity of dye injected [13]. The type of technique, whether *in vivo* or *ex vivo,* using radioactive tracers or dyes, does not, however, seem to influence these rates [20, 27]. In breast cancer, the recommended validation parameters should be a SLN identification rate at least 95% and rate of false negatives no more that 5% [28]. The learning curve for the SLN technique in CRC is unknown but seems to be shorter than in breast cancer, requiring 5 to 10 cases per surgeon [29,30]. Our study has been performed by surgeons with previous experience of at least 10 cases. We achieved a SLN identification rate of 98% and a rate of false negatives close to 3.7%.

The rate of ***upstaging*** in our study was 11% when comparing with the control group staged only by conventional techniques. The value is comparable to those published by more experienced groups [11-14, 26]. Conventional histopathological analysis detected a similar percentage of patients with lymph node involvement in the two groups. Given this, the rate of upstaging in the SLN group can be attributed to the SLN technique. We note that the objective of the SLN mapping is not to modify surgery avoiding lymphadenectomy. Further, it was possible to identify the cases responsible for the rate of false negatives by means of the conventional analysis. That is, in the combined histopathological analysis the SLN technique results in upstaging and the conventional approach identifies false negatives.

Finally, due to the implication on survival of the micrometastasis is unknown we should wait for results of long term studies in this patients.

CONCLUSIONS

We conclude that *ex vivo* SLN mapping performed using methylene blue does enable a correct assessment to be made of the lymph node status of patients with colon cancer. The SLN technique results

in upstaging, moving patients that with the conventional techniques are classified as stage 0, I or II, to stage III, and this justifies giving them chemotherapy that may improve their prognosis.

CONTRIBUTION OF THE AUTHORS

The following authors made substantial contributions to:

- The conception, design, and implementation of the study and the collection of data: J.D. Sardon, J. Errasti, E. Campo, B. Cermeño, J. A. Romeo, L. Fernandez, J. Saenz de Ugarte, M. Cuadra, A. Maqueda, B. Atares.

- The drafting of the manuscript: J.D. Sardon.

- Critical revision of the manuscript: J.D. Sardon, J. Errasti, E. Campo, B. Cermeño, J. A. Romeo, L. Fernandez, J. Saenz de Ugarte, M. Cuadra, A. Maqueda, B. Atares.

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