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Lymph node staging in colon cancer

Kelder, Wendy

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Chapter 5

The sentinel node procedure in colon carcinoma: a multi-centre study in the Netherlands

Wendy Kelder^{1,2}, Andries E. Braat^{3,6}, Arend Karrenbeld⁴, Joris A.K. Grond⁵, Johannes E. De Vries³, J. Wolter A. Oosterhuis³, Peter C. Baas¹, John T.M. Plukker²

¹Department of Surgery, Martini Hospital, Groningen, The Netherlands

²Department of Surgery, University Medical Centre, Groningen, The Netherlands

³Department of Surgery, Isala Klinieken, Zwolle, The Netherlands

⁴Department of Pathology, University Medical Centre Groningen, The Netherlands

⁵Department of Pathology, Laboratory of Public Health, Leeuwarden, The Netherlands

⁶Department of Surgery, University Medical Centre Leiden, The Netherlands

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Abstract

Background: Lymph node status is the most important predictive factor in colorectal carcinoma. Recurrences occur in 20% of the patients without lymph node metastases. The sentinel lymph node (SLN) biopsy is a tool to facilitate identification of micro-metastatic disease and aberrant lymphatic drainage. We studied the feasibility of in vivo SLN detection in a multi-centre setting and evaluated nodal microstaging using immunohistochemistry (IHC).

Patients and Methods: Subserosal injection with Patent Blue dye was used in the SLN procedure in 69 patients operated for localized colon cancer in 6 Dutch hospitals. Each SLN was examined with routine haematoxylin-eosin (H&E) staining. In tumor-negative SLN's we performed CK7/8 or 18 IHC.

Results: The procedure was successful in 67 of 69 patients (97%). The SLN was negative in 43 patients. In 3 cases it was false negative, resulting in a negative predictive value of 93% and an accuracy of 96%. In 24 of 27 patients with lymph node metastases in a successful SLN procedure, the SLN was positive (sensitivity 89%). In 15 patients the SLN was the only positive node (21%). In 9 patients we only found micrometastases or isolated tumor cells, resulting in 18% upstaging. Aberrant lymphatic drainage was seen in 3 patients (4%).

Conclusion: The SLN procedure in localized colon carcinoma is reliable in a multi-centre setting. It is helpful to identify patients who would be classified as stage II with conventional staging (18%) and who might benefit from adjuvant treatment.

Introduction

Survival in patients with colon carcinoma is strongly correlated with lymph node status: the 5-year disease-free survival rate is 70-80% for patients with lymph node negative disease (stage I/II), but only 45-50 % for those with node positive disease (stage III).¹ The presence of lymph node metastases indicates the use of adjuvant chemotherapy in these patients, which increases the 5-year survival rate with about 10%.² Despite the favorable prognosis of patients with localized colon carcinoma without regional lymph node metastasis, 20-30% of these patients will develop recurrent disease after apparently curative resection.³ It is possible that in this group of patients small lymph node metastases have been missed, resulting in understaging. This may be due to an inadequate surgical lymphadenectomy or insufficient pathological examination.⁴ According to international guidelines meticulous pathological examination of at least 12 lymph nodes is warranted for adequate staging of patients with colon carcinoma.⁵ However, several studies showed that the minimal number of lymph nodes necessary for correct staging varied considerably from 6 to 18 to as many as possible in the study of Goldstein et al.^{4,6-9} In addition, in depth pathological examination of lymph nodes by immunohistochemical staining for cytokeratin or reverse transcriptase-polymerase chain reaction (RT-PCR) may reveal micrometastases that could have been missed by routine haematoxylin & eosin (H&E) examination. Several authors have reported a decreased survival rate when micrometastases are detected in colon carcinoma.^{10,11 12,13} The possible benefit of adjuvant therapy in this group of patients is not clear yet. These (ultra)staging techniques are time consuming, labour intensive and costly. For optimal staging, in depth examination of only the SLN could be helpful. In colon carcinoma the SLN's are defined as the first one to four blue-stained nodes with the most direct lymph drainage from the primary tumour. They have the greatest potential to harbour metastatic disease when present, enabling focused examination with multilevel microsectioning of the SLN's to provide a more efficient and cost-effective detection of micrometastases. In addition, patterns of aberrant lymphatic drainage can be visualized with SLN mapping, which may lead to a more extended resection. Several studies have reported varying results of the SLN procedure in colon carcinoma.¹⁴⁻²⁰ This study presents the results of the SLN procedure in six Dutch hospitals. The primary aim of this study is to test the accuracy and sensitivity of the SLN procedure in a multi-center setting. Furthermore, we looked at upstaging and possible aberrant lymphatic drainage.

Patients and Methods

Patients

Only patients with histological proven primary colon carcinoma were included in the study. Patients with distant metastases or gross lymph node involvement as shown by pre-operative examinations or palpation during surgery were excluded.

Surgical procedure

This study was performed between May 2002 and May 2005 in five teaching hospitals and one university hospital. All procedures were supervised by one of the coordinating surgeons (JTMP, AEB). The procedure was only performed when one of the study coordinators was available for supervision (JTMP, AEB,WK). The study was approved by the local scientific ethics committee and all patients had given informed consent. Patients with rectal cancer were excluded from the study.

SLN mapping was carried out through an open procedure by injection of 1-3 ml Patent Blue with a tuberculin syringe and 29 gauge needle subserosally in 4 quadrants around the tumor. The subserosal injection was carried out prior to vascular ligation. Within 5 to 10 minutes after the blue dye injection, the SLN could be identified by following the blue stained lymphatic vessels leading to the blue stained SLN. These lymph nodes were tagged with a long suture. SLN's were defined as the first one to four blue-stained lymph nodes seen within the regional basin. After marking of the SLN's, routine resection was performed. If the SLN was found outside the normal lymphatic basin, we performed an extended resection.

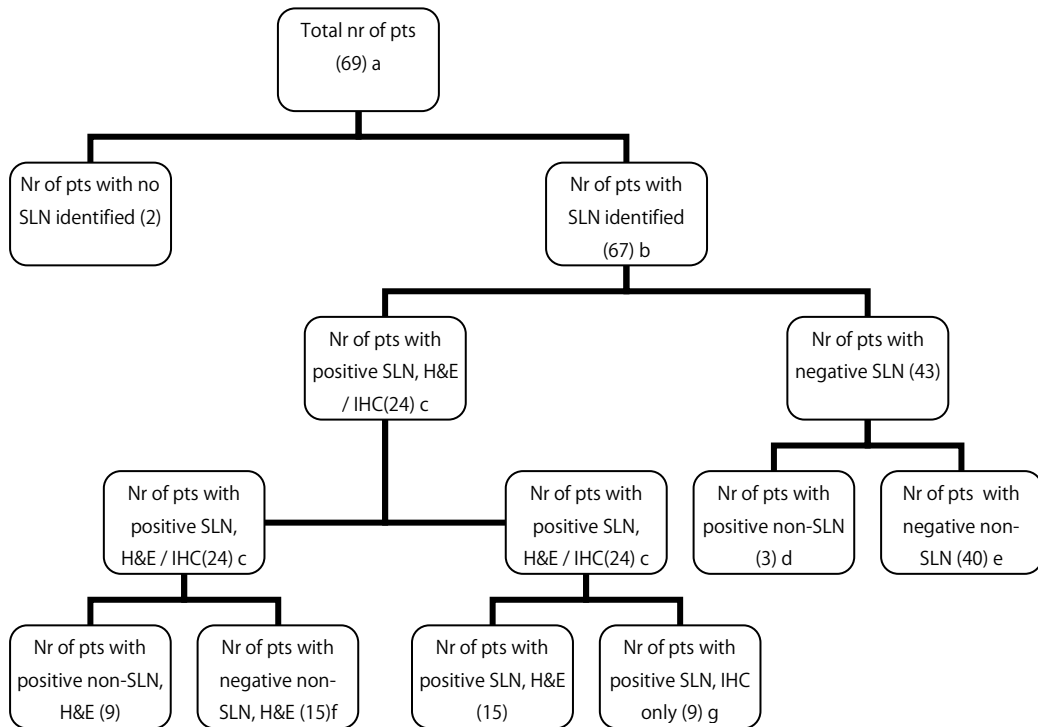
Pathology

The tumor and all lymph nodes were examined according to standard guidelines.⁵ If the SLN's were negative after routine haematoxylin-eosin (H&E) staining, they were sectioned at 150 µm intervals and examined at 3 levels with H&E as well as immunohistochemistry on cytokeratins (CK7/8 or 18). Metastases between 0,2 mm and 2 mm were referred to as micrometastases. Metastases smaller than 0,2 mm were referred to as isolated tumor cells.⁵ Upstaging was defined as the presence of micrometastases or isolated tumor cells after immunohistochemistry in patients with a negative lymph node status after H&E.

Definitions

See Figure 1. Identification rate is the number of patients with one or more SLN's identified (b) / the total number of procedures (a) x 100%. Negative SLN's were false-negative if one of the other regional lymph nodes (non-SLN's) were tumor-positive (d). The accuracy of the SLN procedure suggests a conformity of the SLN status and the regional nodal status i.e. the total number of patients with a positive SLN (c) + the number of patients with a true negative SLN (e) / the number of patients with an identified SLN (b) x 100%. Sensitivity is the number of patients with a positive SLN (c) / The total number of node positive patients (c+d) x 100%. Upstaging is the number of patients with positive SLN's by IHC (g) / the number of patients who were node negative by H&E examination (e+g) x 100%.

Fig. 1 Flowchart. *SLN*/Sentinel lymph node; *pts* Patients



Results

The SLN procedure was performed in 69 patients. Tumor characteristics are shown in table 1. Figure 1 shows the total number of patients and SLN results. At pathological examination a mean of 11 nodes per specimen was found; per hospital this varied between 9 and 17 (9,10,12,14,17,17 respectively). The mean number of SLNs was 2,3 per patient. The SLN was identified in 67/69 patients (97%). One of the two failed procedures was in a patient with a carcinoma in the sigmoid colon surrounded by a concurrent diverticulitis. The other patient had extended lymph node metastases with angio-invasion at pathological examination. In 28 patients lymph node metastases were identified at the pathological examination, this includes the one case where the SLN procedure failed due to extensive lymph node metastases (28/69=41%). This one case with lymph node metastases and a failed procedure was excluded from further statistical analysis on the SN procedure, leaving 27 node positive patients in the final analysis. In 24 patients the SLN was positive, either with H&E staining or with IHC, resulting in a sensitivity of (24/27) 89% in the group of 67 patients with a successful SLN procedure. If we leave out the patients who had a positive sentinel node only after IHC, the sensitivity is 15/18= 83%. In 15 of 24 SLN positive patients, the SLN was the only involved lymph node (63%). In 9/27 lymph node positive patients metastases were found only after IHC. In 4 patients these were micrometastases, whereas in five cases isolated tumor cells were found. So without IHC the number of node positive cases would have been 27 minus 9 is 18. This corresponds to a total of 49 node negative cases by H&E in the group with a successful SLN procedure. With IHC the upstaging is 9/49 is 18% . The SLN was negative in 43 patients. In 40 patients the non-SLN's were also negative. This results in a negative predictive value of 93% (40/43). One of the three patients with a false-negative SLN had lymph node metastases with extra-nodal growth in the non-SLN. In another patient a small tumor deposit was found in the mesocolon right next to the primary tumor. This was classified as N1 according to the AJCC classification, although it is unclear whether this is a true lymph node metastasis or some kind of 'in transit' metastasis. The last patient with a positive non-SLN showed micrometastases at H&E examination in a small peritumoral lymph node. Aberrant lymphatic drainage was seen in three patients (4%). In two cases the SLN was found on the left side of the middle colic artery in patients with a tumor in the ascending colon. In both cases an extended right hemicolectomy was performed. The third patient had a tumor near the rectosigmoid junction with a high para-aortal SLN. Therefore we performed an extended left sided resection en-bloc with a partial para-aortal dissection. None of these lymph nodes contained metastases. All other SLNs were found in the mesocolon in close proximity to the tumor. In these cases, the central

lymph node as identified by the pathologist was always a non-SLN. The accuracy of the SLN procedure in this study was 96%, as the pathological status of the SLN corresponds with the definitive lymph node status in 64 of the 67 patients.

Table 1. Tumor characteristics

Tumor location	
Right colon	35
Left colon	2
Sigmoid colon	32
T-stage	
1	1
2	14
3	48
4	6
Mean nr of lymph nodes	11
Mean nr of SLN	2,3

Table 2. Results of multi-center studies of the SLN procedure in colon cancer

Study	Nr of patients	Nr of centers	Identification rate	Accuracy	Sensitivity	Upstaging
Bilchik ¹⁵	40	3	100%	100%	100%	10%
Saha ¹⁸	131	3	99%	97%	92%	16%
Bertagnolli ¹⁴	72	13	92%	81%	42%	0%
Read ²¹	38	2	79%	76%	25%	3%
Kelder/Braat	69	6	97%	96%	89%	13 or 18%

Discussion

With an identification rate of 97%, accuracy of 96%, sensitivity of 89% and negative predictive value of 93%, this study shows that it is possible to perform the SLN procedure properly in patients with localized colon carcinoma in a multi-center setting. Other multi-center studies showed varying results of this technique (table 2).¹⁴⁻²¹ Our results correlate with those from other larger studies which show accuracy and sensitivity rates of 95-98% and 89-93% respectively.^{15,18-20} Most smaller studies show worse results with low accuracy and success rates and corresponding low sensitivity rates and negative predictive values.^{14,17,21} In one study the time between injection of the blue dye and identifying the SLN was too long, leading to a larger number of SLN's.¹⁷ It is very likely that not all of these blue nodes were true SLN's. In the study by Bertagnolli et al 79 patients were operated on by 25 different surgeons in 13 different hospitals.¹⁴ A mean of three procedures per surgeon seems insufficient to adequately learn this technique. It is known that the learning curve of the SLN in colon carcinoma stabilizes after about five procedures.²⁰ To minimize technical failures, the procedure in our study was performed by a few surgeons under direct supervision of one of the two surgeons coordinating this study (AEB, JTMP). Apart from too few procedures, the worse results in some studies might be explained by inclusion of patients with advanced disease. Some studies included patients with clinically apparent stage III or stage IV disease.²¹ Widespread lymph node metastases could result in obstruction of lymphatic channels, and lymphatic drainage is bypassed to other (non-sentinel) lymph nodes. This phenomenon is called skip-metastasis. It was noted in one of the patients with a false-negative SLN in our study who had advanced lymphatic metastases with extranodal growth. Patient selection is therefore important for a reliable SLN procedure in colon carcinoma. In fact, the SLN procedure is not useful in patients with clinically apparent stage III or stage IV disease as false-negativity rates will be higher. Moreover, in these patients metastases will be easily found at routine pathological examination and the SLN procedure will not have any additional value. The SLN procedure could be useful in those patients with (micro)metastases that would not be identified with routine pathological examination. Furthermore, the failed procedure in one of our patients with concurrent diverticulitis, also suggests the importance of an undisturbed lymphatic drainage for a successful SLN procedure.

We saw aberrant lymphatic drainage in three patients (4%). This percentage correlates with the literature.^{15,18,20} In this study, none of these aberrant SLN's showed metastases. However, potentially these aberrant SLN's are the only lymph nodes containing metastasis, as shown in a previous study.²² In an experimental situation it seems justified to perform an extended

resection in these cases. Further study should be performed to justify an extended resection in the daily practice.

Literature not clearly indicates how many nodes should be examined to accurately predict lymph node status.^{6-8,23,24} One study showed that a colon specimen usually contains about 50 lymph nodes, and that more than 70% of the lymph nodes containing metastases are smaller than 5 mm.⁹ It is also known that the prognosis in node negative patients with colon carcinoma is better when more lymph nodes have been examined.²⁴ Taking this into account, the pathologist takes only a sample of the lymphatic basin of a resected colon specimen, even when international guidelines are followed which state that at least 12 lymph nodes are needed for adequate staging.⁵ The mean number of 11 lymph nodes in our study is not enough to predict lymph node status according to the international guideline. This fact could theoretically lower the chance to detect metastases in non-SLN and thus could lower the false negative rate. However, we did not find any differences in false negative rates between the two hospitals with a mean number of 9 and 10 examined nodes (40 cases) and the hospitals with more than 12 examined nodes (29 cases). With regard to upstaging, most studies show an upstaging of 10-16%.^{15,18-20} However, they calculated upstaging by dividing the number of IHC positive patients by the total number of patients (figure 1: g/a, 9/69, 13% in our group). We think it is better to consider upstaging solely in the H&E node negative group, as this is the group to be upstaged by IHC. Using this method we find 18% upstaging in our series. In addition to this true upstaging, patients with a SLN as the only site of metastases could have been 'possibly upstaged' as conventional pathological dissection of the mesentery might have missed this lymph node. The SLN procedure with patent blue might be able to improve adequacy of the lymph node examination by selecting the right lymph nodes, even small nodes <5mm, to be examined in depth by the pathologist. We found the SLN to be the single lymph node with metastasis in 15 (21%) of the patients (figure 1: f). 'Possible upstaging' might play a role here, but we cannot prove this.

As we believe that even isolated tumor cells are important for staging we assigned patients with micrometastases or isolated tumor cells to the group of node positive patients. It must be remarked however, that these cases were also used for the calculation of upstaging. Our idea of the biological importance of micrometastases and isolated tumor cells is based on a recent meta-analysis which showed that micrometastases detected retrospectively by RT-PCR correlated better with overall survival than IHC and carried significant prognostic value.¹² Regarding the detection of micrometastases, two studies showed a high reliability

of the SLN concept to predict micrometastases and/or isolated tumor cells also in non-SLN's. Therefore, it seems sufficient to perform IHC only on the SLN, while examining the non-SLN with H&E ^{25 26} Prospective studies are needed to evaluate the potential benefit of systemic chemotherapy in patients with these micrometastases. A reliable SLN procedure might facilitate this intensive pathological examination by allowing focused examination of only the SLN and thereby aid in a better patient selection for adjuvant therapy in the future.

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