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Factors Influencing the Success of In Vivo Sentinel Lymph Node Procedure in Colon Cancer Patients

Swiss Prospective, Multicenter Study Sentinel Lymph Node Procedure in Colon Cancer

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Abstract
Background The sentinel lymph node (SLN) procedure has the potential to provide relevant improvement in nodal staging in colon cancer patients. However, there remains room for improvement for SLN identification and sensitivity. Therefore, the objective of the present investigation was to analyze factors influencing the success of the SLN procedure in colon cancer patients.
Methods One hundred seventy-four consecutive colon cancer patients were prospectively enrolled in this multicenter study and underwent in vivo SLN procedure with isosulfan blue 1 % followed by open standard oncologic colon resection. Several patient-, tumor-, and procedure-related factors possibly influencing the SLN identification and sensitivity were analyzed.
Results Sentinel lymph node identification rate and accuracy were 89.1 and 83.9 %, respectively. Successful identification of SLN was significantly associated with the intraoperative visualization of blue lymphatic vessels ($p < 0.001$) and with female gender ($p = 0.024$). True positive SLN results were significantly associated with higher numbers of SLN ($p = 0.026$) and with pN2 stage ($p = 0.004$). There was a trend toward better sensitivity in patients with lower body mass index (BMI) ($p = 0.050$).
Conclusions The success of the SLN procedure in colon cancer patients depends on both procedure-related factors (intraoperative visualization of blue lymphatic vessels, high number of SLN identified) and patient factors (gender, BMI). While patient factors can not be influenced, intraoperative visualization of blue lymphatics and identification of high numbers of SLN are key for a successful SLN procedure.

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Introduction

The sentinel lymph node (SLN) procedure has the potential to provide relevant improvement in nodal staging in colon cancer patients. Several multicenter studies, including our own, have shown that in-depth and focused analysis of SLN reveals small nodal tumor infiltrates in about 15 % of patients that were diagnosed node-negative in the initial routine hematoxylin & eosin (H&E) analysis [1–7]. While these findings are promising, there is still room for improvement regarding overall SLN identification rate and sensitivity. However, it remains unclear whether these results are influenced by patient-, tumor-, or procedure-related factors. Therefore, the objective of this study was to analyze factors influencing the SLN identification rate and sensitivity in patients with resectable colon cancer.

Patients and methods

The "Swiss Prospective, Multicenter Study Sentinel Lymph Node Procedure in Colon Cancer" (www. clinicaltrials.gov: NCT00826579) enrolled 174 patients with biopsy-proven, resectable colon cancer (stage I–III according to the American Joint Cancer Commission [AJCC], 6th Edition) from May 2000 through December 2006. The study was approved by all ethical committees of the participating centers, and it was conducted in compliance with the Declaration of Helsinki. All patients gave written informed consent. All patients underwent open surgery with an in vivo SLN procedure with isosulfan blue 1 % (without radioisotopes) according to a standardized protocol as previously described [8]. Three levels of each SLN were stained with H&E and immunostained with the pancytokeratin marker AE1/AE3 if H&E was negative. Results regarding technical details, identification rate, accuracy, and upstaging rate have been reported elsewhere [6].

Factors influencing the success of the procedure

Our prospectively collected database was queried to evaluate the importance of the following factors possibly influencing the SLN identification and accuracy: gender, localization of the primary tumor, previous abdominal surgery, intraoperative visualization of blue lymphatic vessels, presence of lymphovascular invasion, T stage, N stage, nodal status in H&E, grading, AJCC stage, age, body weight, height, body mass index (BMI), volume of dye injected, tumor size, number of SLN identified, total number of lymph nodes analyzed, number of positive lymph nodes in H&E.

Statistical analysis

Categorical variables were analyzed with the Fisher's exact test. For continuous variables, Student's *t*-test was used. Statistical analyses were performed with SPSS 13.0 for Macintosh (SPSS Inc., Chicago, IL). A p value <0.05 was considered to be significant. All p values were two-sided. Accuracy was defined as (true positive + true negative)/all patients with SLN identification; sensitivity was defined as true positive/(true positive + false negative).

Results

Overall, 174 patients were enrolled in the study. The median age was 73.7 years (range: 27.3–93.0 years); 54.6 % of the patients were men. The SLN identification rate was 89.1 % (155/174 patients; Fig. 1), the accuracy was 83.9 % (130/155 patients), and the sensitivity of the procedure was 55.4 % (31/56 patients). Of 104 stage I and II patients, 16 (15.4 %) were upstaged after identification of small nodal tumor infiltrates in the SLN [6].

Factors influencing the success of the procedure

Numerous factors from our prospective database were assessed to determine whether they influence the SLN identification rate and sensitivity. Successful identification of SLN was significantly associated with the intraoperative visualization of blue lymphatic vessels ($p < 0.001$) and with female gender ($p = 0.024$; Table 1). True positive SLN results were significantly associated with higher numbers of SLN ($p = 0.026$) and with pN2 stage ($p = 0.004$; Table 1). There was a trend toward better sensitivity in patients with lower BMI ($p = 0.050$).

Discussion

The present study—one of the first in the literature—provides evidence that the success of the in vivo sentinel lymph node procedure in colon cancer patients is influenced by both procedure-related and patient-related factors. Sentinel lymph node identification significantly depended

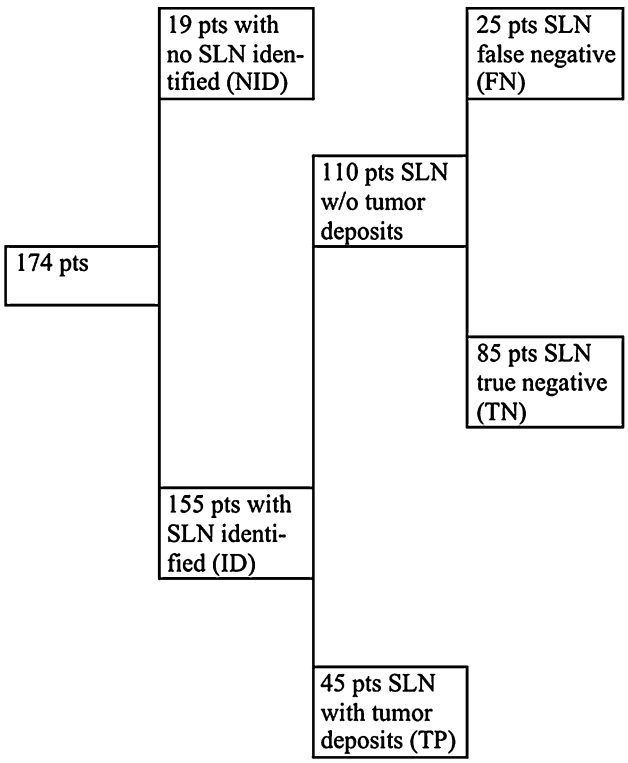

Fig. 1 Comparative groups. *FN* false negative group, *ID* identification group, *NID* non-identification group, *pts* patients, *SLN* sentinel lymph node, *TN* true negative group, *TP* true positive group, *w/o* without

Table 1 Analysis of influencing factors

Parameter	Sentinel lymph node					Sentinel lymph node				
	Identified ($n = 155$)		Not identified ($n = 19$)			True positive ($n = 45$)		False negative ($n = 25$)		
	n	%	*n*	%	*P* value	*n*	%	*n*	%	*P* value
Gender					0.024					0.098
Male	80	51.6	15	78.9		29	64.4	11	44.0	
Female	75	48.4	4	21.1		16	35.6	14	56.0	
Localization of primary tumor					0.949					0.375
Right colon	67	43.2	8	42.1		14	31.1	12	48.0	
Left colon	28	18.1	3	15.8		12	26.7	5	20.0	
Sigmoid colon	60	38.7	8	42.1		19	42.2	8	32.0	
Previous abdominal surgery					0.884					0.591
No	87	56.1	11	57.9		24	53.3	15	60.0	
Yes	68	43.9	8	42.1		21	46.7	10	40.0	
Blue lymphatics identified intraoperatively					<0.001					0.803
No	14	9.7	10	52.6		3	7.0	2	8.7	
Yes	130	90.3	9	47.4		40	93.0	21	91.3	
Lymphovascular invasion					0.618					
L0	123	79.4	16	84.2		28	62.2	16	64.0	
L1	32	20.6	3	15.8		17	37.1	9	36.0	
T stage					0.714					0.713
pT1	11	7.1	1	5.3		1	2.2	0	0.0	
pT2	23	14.8	3	15.8		3	6.7	2	8.0	
pT3	99	63.9	14	73.7		32	71.1	20	80.0	
pT4	22	14.2	1	5.3		9	20.0	3	12.0	
N stage					0.834					0.004
pN0	99	63.9	11	57.9		0	0.0	0	0.0	
pN1	38	24.5	5	26.3		16	51.6	22	88.0	
pN2	18	11.6	3	15.8		15	48.4	3	12.0	
Nodal status in H&E					0.610					
Negative	99	63.9	11	57.9		0	0.0	0	0.0	
Positive	56	36.1	8	42.1		45	100.0	25	100.0	
Grading					0.106					0.937
G1	0	0.0	0	0.0		0	0.0	0	0.0	
G2	112	72.3	17	89.5		32	71.1	18	72.0	
G3	43	27.7	2	10.5		13	28.9	7	28.0	
Stage					0.870					n/a
I	29	18.7	3	15.8		1	2.2	0	0.0	
II	70	45.2	8	42.1		13	28.9	0	0.0	
III	56	36.1	8	42.1		31	68.9	25	100.0	

Parameter	Median	Range	Median	Range	*P* value	Median	Range	Median	Range	*P* value
Age (years)	73.7	27.3–92.4	76.4	57.3–93.0	0.198	74.3	47.6–88.2	70.5	47.4–92.4	0.270
Body weight (kg)	73.6	39.2–130	82.0	52.0–106	0.167	72.0	45.0–100	70.0	57.0–128	0.176
Height (cm)	168	145–189	170	155–194	0.126	169.5	152–185	167	150–186	0.527
BMI (kg/cm^2)	25.6	15.9–44.3	25.8	21.6–37.6	0.671	24.2	15.9–33.1	25.4	20.5–44.3	0.050
Volume of dye (ml)	2.0	0.2–10.0	2.0	1.0–10.0	0.436	2.0	0.3–10.0	2.0	1.0–6.0	0.515
Tumor size (cm)	4.1	1.5–16.0	3.7	1.0–8.5	0.101	4.0	1.5–9.5	4.5	2.5–8.0	0.456
Total no. of SLN identified	3	1–20	0	0–0	n/a	3	1–20	2	1–10	0.026
Total no. of LN analyzed	24	5–62	16	7–67	0.091	23	12–62	29	11–54	0.598

Table 1 continued

Parameter	Median	Range	Median	Range	*P* value	Median	Range	Median	Range	*P* value
No. of positive LN in H&E	0	0–17	0	0–19	0.298	0	0–17	2	0–9	0.564

BMI body mass index, *H&E* hematoxylin and eosin staining, *LN* lymph nodes, *n/a* not applicable

on the intraoperative visualization of blue-stained lymphatic vessels. This finding is quite intuitive, as the surgeon often has to follow the blue-stained lymphatics to identify the SLN. However, blue lymphatics are not always easily discerned, particularly in a fatty mesentery. This problem might be overcome with a second, submucosal blue dye injection ex vivo and careful dissection of the mesentery [9], or by using newer lymphatic tracers that can be visualized with near-infrared fluorescence light [10]. Moreover, in the present study, patients with true positive SLN results had significantly more SLN identified than patients with false negative results, underlining the importance of carefully looking for and identifying several SLN during the procedure. In fact, two thirds of the patients with false negative results had fewer than four SLN identified intraoperatively (data not shown). In this respect, it is noteworthy that the median number of SLN in colon cancer patients is usually higher than that, for instance, in breast cancer [6, 11]. It is important that all patients underwent open colon cancer resection. Therefore, our results cannot necessarily be generalized to patients undergoing laparoscopic procedures. Additionally, even though the SLN procedure leads to a better staging in colon cancer patients (upstaging rate 15.4 %) [6, 12], due to the high false negative rate the nodal staging must not solely rely on the SLN results.

It must be emphasized that several tumor-related factors, like localization of the primary tumor, tumor size, pT-stage, and lymphovascular invasion, did not influence either the SLN identification rate or the sensitivity. Therefore, the SLN procedure seems to be applicable irrespective of tumor stage and size. This is in line with findings from a recent meta-analysis in which no differences in sensitivity were found for different T-stages [5]. In the present investigation, however, pN2 patients showed significantly more true positive SLN results than pN1 patients. Obviously, the likelihood of identifying a positive SLN increases with the number of positive nodes.

Patient-related factors might also play an important role. For example, patients with lower BMI showed a statistical trend toward true positive results ($p = 0.050$). Moreover, successful identification of SLN was significantly associated with female gender ($p = 0.024$). Other patient-related factors, however, did not influence the success of the SLN procedure. Finally, the success of the procedure was not influenced by a history of previous abdominal surgery either, indicating that the SLN procedure might safely be performed after previous abdominal surgery.

Only two other multicenter studies have investigated factors affecting the success of the SLN procedure: Bembenek et al. [1] found a significantly better identification rate and—in line with our results—sensitivity with lower BMI, an improved identification rate with lymphovascular invasion, and—similar to our results—an improved sensitivity with increasing numbers of involved lymph nodes. In the study by Nissan et al. [13] identification of ≥ 3 SLN was an independent predictor of a true positive SLN result, also is in line with our findings, whereas tumor-replaced lymph nodes were predictive of false negative SLN results.

Interestingly, patients with SLN identification showed a trend toward a higher number of analyzed and reported lymph nodes than patients without SLN identification (median 24 versus 16; $p = 0.091$). By successfully performing the SLN procedure, the pathologist's attention to nodal staging is increased, thus spurring him or her to find more lymph nodes, which is among the positive "side effects" of the SLN procedure.

In summary, the success of the SLN procedure in colon cancer patients depends on both procedure-related and patient-related factors. While the latter cannot be influenced, intraoperative visualization of blue lymphatics and identification of high numbers of SLN are key for a successful SLN procedure.

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