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Intraoperative Sentinel Lymph Node Mapping in Patients with Colorectal Cancer

Krasimir Ivanov, Nikola Kolev and Anton Tonev
Medical University "Prof. Dr. Paraskev Stoyanov"
Bulgaria

1. Introduction

The sentinel lymph node (SLN) is defined as the first lymph node/nodes receiving direct drainage from the tumor and consequently possessing the greatest metastatic potential. (Nieweg OE. et al., 2001; Tanis PJ. Et al, 2002; Saha S et al, 2004; Bilchik A et al., 2001; Wood Th. F. et al, 2001; Bertagnolli M. et al, 2001; Dahl K. Et al, 2005; Feig BW et al, 2001; Patten LC et al, 2001) Sentinel lymph node mapping in colorectal cancer (CRC) is related to two questions that are important for the surgeon:

1. Is the extending of the lymph dissection necessary in certain patients and which are these patients?
2. Is the staging of the disease correct?

Additional questions that may be answered in the future are:

1. Can the volume of the visceral resection and lymph dissection be decreased (economy resections) in the aspect of implantation of laparoscopic surgery or local tumor excision – endoscopic or transanal?
2. Can the method help in deciding for sphincter preservation and nerve preservation in rectal surgery?
3. What is the impact on survival rates?
4. Is PET-CT a comparable method?
5. Will sentinel lymph node mapping have clinical application?

To answer these questions well-designed trials are needed.

The most important factor affecting the outcomes of the surgical treatment and the survival rate is the presence of metastases. (Bertoglio S et. Al, 2004; Wood Th. F. et al, 2001; Bertagnolli M. et al, 2001; Saha S. et al, 2000; Paramo JC. Et al, 2001; Trocha SD. et al, 2003; Wood TF et al, 2001) The presence of lymph metastases places the patients from first and second stage into third stage and significantly deteriorates the prognosis and the survival rate. (Bilchik AJ et al., 2002; Philips RKS. et al., 1984; O'Connell MJ. et al., 1997; Saha S. et al., 2000) The atypical lymph-drainage occurs in about 8-14% of the patients. (Saha S. et al., 2001; Saha S. et al., 2001; Wood TF et al, 2001; Kitagawa Y. et al., 2002; Bilchik AJ et al., 2001) The failure to detect the atypical drainage is one of the reasons for recurrences due to incorrect staging and adjuvant therapy. (Bilchik AJ et al., 2001; Paramo JC. et al., 2001; Martinez SR et al., 2005) It results from specific anatomical features of the lymph flow. The atypical lymph metastases are observed in terms of the localization level of the metastatic lymph nodes (jumping or "skip" metastases and also in affecting the atypical lymph basin

(aberrant lymph drainage) for the given localization of the primary tumor. (Kitagawa Y. et al., 2000; Bilchik AJ et al., 2002; Wood TF et al., 2002)

In CRC the resection volume and the lymph dissection are determined by the tumor localization and they have been standardized to a great extent. (Schlag PM et al., 2004) The metastatic lymph nodes in the presence of aberrant lymph drainage can be found beyond the lines of the standard lymph dissection. In these cases the radicality of the surgery requires extension of the lines of lymph dissection. (Paramo JC et al., 2001; Tsioulis G. et al., 2002; Kitajima M. et al., 2004) It is important to apply a method for lymph metastases detection. The possibilities of the intraoperative examination and palpation as well as the existing methods for imaging diagnostics of the lymph basin in CRC are not sufficiently reliable. Their sensitivity varies between 20% and 50%, only lymph nodes with size over 5mm are detected and the metastatic potential is determined based on the increased size. (Kitagawa Y. et al., 2000) According to literary data 50% to 78% of the metastatic lymph nodes are sized under 5 mm. (Saha S. et al., 2004; Rodriguez-Bigas MA et al., 1996; Haboubi NY et al., 1992; Paramo JC et al., 2002). This is a reason for the unsatisfactory capability of the preoperative and intraoperative diagnostics of the lymph metastases. Lymph node mapping with dye visualizes the lymph vessels and the SLN very well in the surgical field even if they are very small in size less than 5mm, otherwise undetectable. (Saha S. et al., 2004; Rodriguez-Bigas MA et al., 1996; Haboubi NY et al., 1992; Paramo JC et al., 2002).

The direct tumor drainage in the SLN is demonstrated by means of blue stained lymph vessel linking the tumor to the SLN, when marked with dye (Fig.1.a), b), c))

Recurrences are observed in 20 - 40% of the operated patients in the first and second stage. (Martinez SR & AJ Bilchik , 2005; Rodriguez-Bigas MA et al., 1996; Wolmark N. et al., 1986) In half of the patients with recurrences it was established that they were due to metastatic lymph nodes, which have not been detected and remove during the surgery. (Dimitrov V. et al., 2003; Macintosh E., 1997; Makela J.& Kiviniemi H., 2000; Morson BC et al., 1963; Pietra N. et al., 1998) For these patients the following was true: adequate lymph dissection was not performed; the disease has not been correctly staged; no indications have been given for adjuvant therapy (Saha S. et al., 2000; Cohen AM et al., 1998).

According to the TNM system the micrometastases are designated with the index "mi" and their presence stages the disease as third stage, determining a relevant treatment and prognosis. (Bilchik AJ et al., 2003; Sobin LH, 2002)

For the assessment of the lymph status it is obligatory to investigate morphologically at least 12 lymph nodes. (Martinez SR& Bilchik AJ, 2005; Rodriguez-Bigas MA et al., 1996). If lymph metastases are not detected, it is advisable to search for micrometastases (MM) A great number of authors in the literature suggest that the presence of MM is a poor prognostic factor and therefore are indicative for adjuvant therapy which would improve the prognosis in these "troublesome" 30% of the patients "without metastases". The prognostic value of the metastases in CRC requires further investigations in the future. In their studies a number of authors confirm the prognostic value of MM (Broll R. et al., 1997; Greenson JK et al., 1994; Isaka N. et al., 1999; Palma RT et al., 2003; Yasuda K. et al., 2001; Liefers GJ et al., 1998), others aren't support this suggestion. (Adell G. et al., 1996; Choi HJ et al., 2002; Lindmark G. et al., 1994). If the all LNs are to be investigated, the methods for micrometastases detection are costly, expensive and time consuming. (Tsioulis G. et al., 2002; Martinez SR& Bilchik AJ, 2005; Bilchik AJ et al., 2003; Doekhie FS et al., 2005)

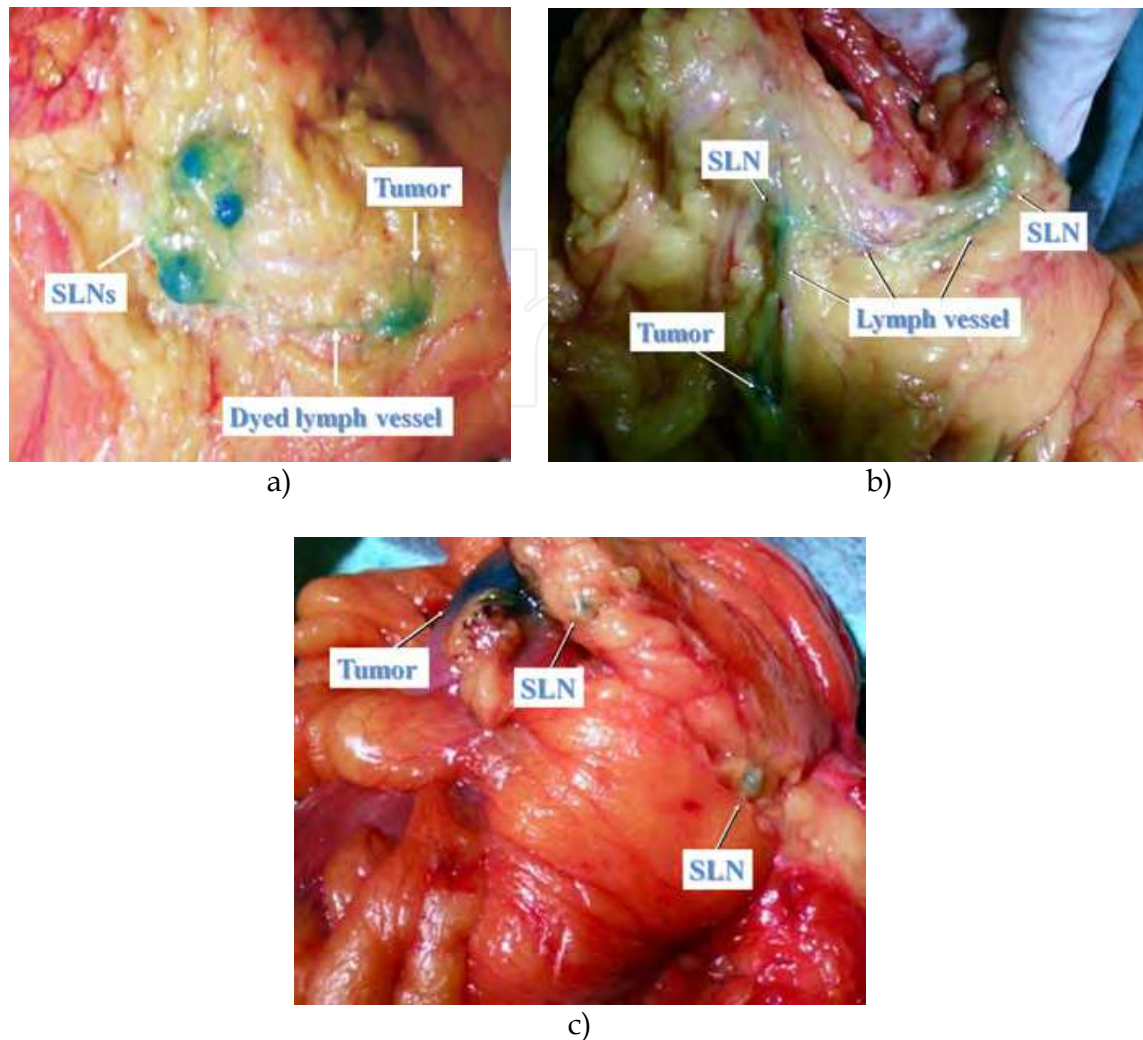


Fig. 1. Intraoperative view of stained lymph nodes and lymph vessels with Patent Blue V.

2. Methodology

2.1 Intraoperative procedure

We performed intraoperative sentinel mapping in 103 consecutive patients operated for colon or rectal cancer. An algorithm was worked out for sentinel mapping in colorectal cancer. The dying method with Patent Blue V was used.

a. Indications or inclusion criteria:

- Patients with invasive colorectal cancer
- Histological diagnosis and preoperative staging performed not later than 3 months before the surgery;
- Life expectancy over 5 years (age up to 80 years);
- Class after ASA I-III.

b. Contraindications and exclusion criteria:

- Presence of distant metastases;
- Preceding Previous local excision of the primary tumor;
- Metachronous colorectal cancer (with some exceptions);
- Recurrent colorectal cancer;

- Presence of cancer in another organ localization during the past 5 years, especially in the cases when the colorectal cancer is difficult to be differentiated histologically;
- Preceding Previous surgical interventions affecting the anatomy of the lymph basin;
- Complicated colorectal cancer (emergency operation);
- Class ASA IV-V.

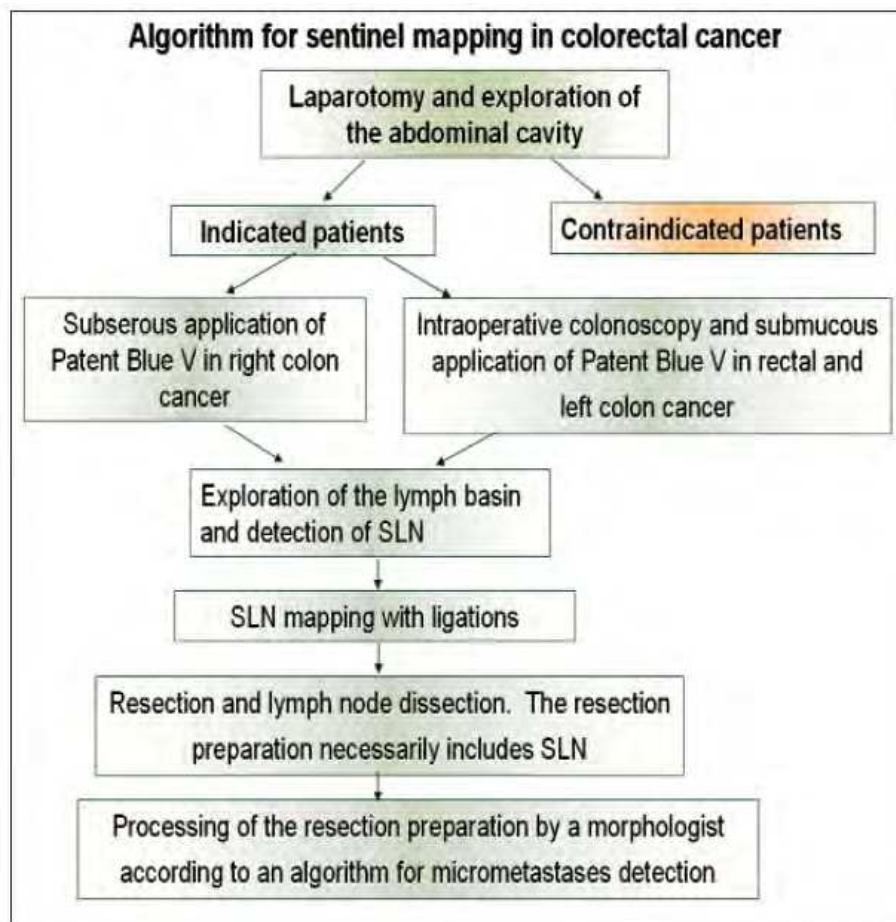


Fig. 2. Algorithm for sentinel mapping in colorectal cancer.

After the laparotomy and the exploration of the abdominal cavity in the absence of distant metastases and no palpatory data for the presence of lymph metastases in patients with cancer of the rectum and the left colon, we performed intraoperative colonoscopy. By means of an endoscopic injector we applied submucosally 0,5-2 cc of Patent Blue V peritumorally on 2 to 4 locations. Since in right colon cancer the intraoperative colonoscopy to the caecum is technically difficult and is time-consuming, we injected the dye subserously in these tumor localizations by means of a needle and a syringe (0,5-2cc) peritumorally on 2 to 4 locations. In 1 to 10 minutes time the blue-stained lymph node(s) is visualized, connecting the primary tumor with blue-dyed sentinel lymph node(s). We assume the first 1-4 blue-dyed lymph nodes to be sentinel and we mark them with ligatures. It is important that the procedure is performed accurately and precisely timed after the gradually coloring of the whole lymph basin, because the SLN can lose their color with time.

According to the tumor localization we perform thorough exploration of the regional lymph basin, the whole mesocolon, the stem of the mesenteric root of mesentery vessels and

paraaortically, the obturator fosses and along the course of the iliac vessels in order to detect SLN and the presence of atypical lymph drainage.

We applied the method of the sentinel mapping in five patients with CRC who had been operated laparoscopically - figure 3.

2.2 Morphological investigations

The SLN tagged by the surgeon are sent to the morphological laboratory together with the specimen where a routine processing to a paraffin block is performed with 10 resections in every 20-25 μ m. Immunohistochemistry with cytokeratin20 is performed per one resection (usually the fifth one). The remaining resections together with the preparations from the case are dyed with Hematoxylin-Eosin. Micrometastases are defined as a focus of tumor cells sized under 2 mm or a focus detected only by means of immunohistochemistry. (Fezoz RJ et al., 2002)

2.3 Statistical analysis

The statistical results were reported as detection rate of the sentinel lymph node, accuracy and sensitivity of the test, and false negative rate; formulas, for the assessment of these parameters were as follows: The staging benefit was calculated by comparison between *pN* staging in the sentinel lymph node group and *pN* staging in the non-sentinel lymph node group. The comparison between groups was performed using the *chi-square* test; the significance was assumed for $p < 0.05$ (95% confidence interval). The statistics were performed using XLSTAT 2010 (Addinsoft 1995-2010).

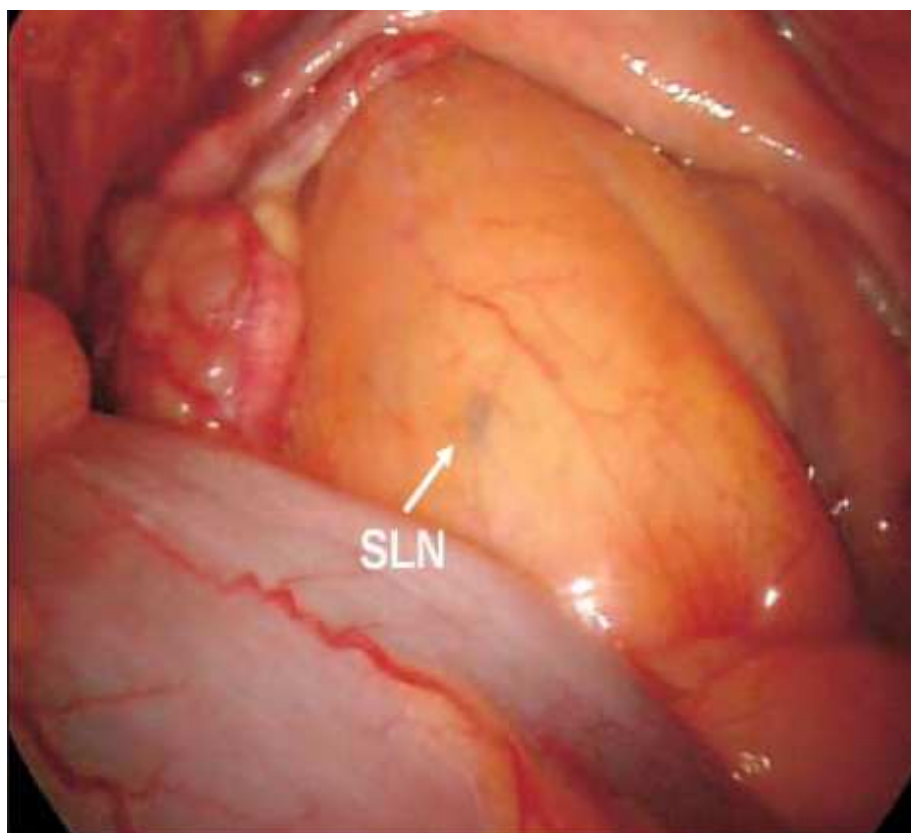


Fig. 3. Laparoscopic view of a SLN.

3. Results

The distribution of the patients is shown on Table 1. The relation between the T stage of the primary tumor and the presence of lymph metastases after sentinel mapping is shown on Table 2. Metastases were detected in 57% of the SLN (105 out of 184) as compared to 9% metastases incidence in the nonsentinel LN (198 out of 2208). In the absence of metastases in SLN the likelihood for metastases occurrence in the nonsentinel LN is only 0,6% (4 out of 657 nonsentinel LN). (Table 3)

TABLE 1		
	Colon Cancer	Rectal Cancer
Patients	48	55
Male	22 (46%)	25 (45%)
Female	26 (54%)	30 (55%)
Average age (years)	63	66

Table 1. Distribution of patients according to cancer localization.

TABLE 2		
	T3 n(%)	T4 n(%)
Patients	44 (43)	11 (10)
Presence of lymph node metastases	40 (90)	11 (100)
Micrometastases	3 (7)	0 (0)

Table 2. Relation between tumor stage and metastases, including micrometastases.

TABLE 3		
	Colon cancer n (%)	Rectal cancer n (%)
Patients	48	55
Successful mapping	48 (100)	55 (100)
Presence of lymph node metastases	24 (50)	27 (49)
False negative rate	0 (0)	3 (5)
Metastases only in SLN	8 (17)	9 (16)
Detected MM	5 (19)	6 (21)

Table 3. SLN in colorectal cancer – rate of success, rate of detection, false negative rate, rate of metastases only in SLN, rate of detected micrometastases (MM).

The mean number of the lymph nodes in the specimen is 14.7 in cancer of the colon vs. 13.2 in cancer of the rectum. The average number of SLN in cancer of the colon is 1.9 vs. 1.6 in cancer of the rectum. False negative results were reported in the presence of metastases, not detected in the SLN. We observed false negative results in 3 patients. All of them had large T4 tumors infiltrating adjacent organs. Therefore, we suggest that such patients are relatively contraindicated for sentinel mapping. In most cases the SLN were located in proximally to the primary tumor. One, two, three and four SLN were detected in 40%, 39%, 19% and 2% of the patients, respectively.

In spite of this we detected a presence of atypical lymph drainage with positive SLN outside the limits of the standard resection in 10 (10%) of the patients. In 3 out of these 10 patients the aberrant SLN were the only site of lymph metastases. In 5 patients we performed extended right hemicolectomy with the inclusion of the lineal flexure and its mesocolon because we detected SLN in the region of the flexure (Fig. 4.).

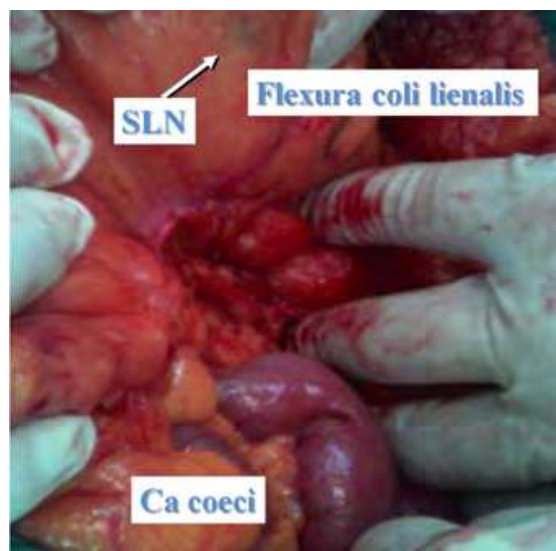


Fig. 4. SLN in the region of flexura coli lienalis.

We extended the size of the lymph dissection in 5 patients with rectal cancer. In one of them we detected SLN in the root of inferior mesenteric artery, which necessitated its high ligation with additional dissection around the root. In the remaining 4 cases we detected SLN in the left or right iliac region and we performed lateral lymph node dissection (Fig. 5). In the rest of the cases when no SLN or enlarged lymph nodes were detected in the lateral ligaments, obturatorial fosses or along the iliac vessels, we did not consider appropriate to perform lateral lymph node dissection in patients with rectal cancer.

On Figure 6, it is shown the visualization of direct lymph drainage from cancer of the rectum T2 to SLN from the IIIrd level in the root of inferior mesenteric artery. In the same patient the morphological investigation did not reveal metastases in any of the LN in the surgical preparation. The immunohistochemical study of the only SLN revealed MM, i.e. skip metastasing. In nine of the ten patients with extended resections were found metastases in the lymph nodes, and in one - no metastases. The analysis of the results shows that in 9 of 10 patients with extended resection, based on the results from the intraoperative sentinel lymph node mapping, were dissected metastatic sentinel lymph nodes located beyond the lines of the standard resection, by which we achieved surgical radicalism. In 7 patients with

rectal cancer intraoperative visual detection of SLN during mobilization of the rectum was impeded even after additional introduction of the colonoscope in the mobilized rectum and transillumination, probably due to the fatty tissue and insufficient staining of the SLN.

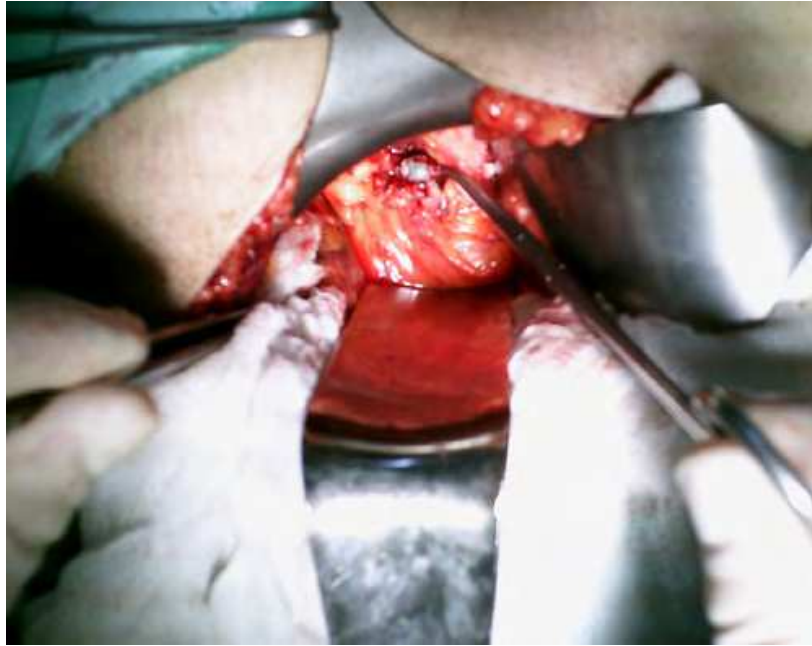


Fig. 5. SLN in the left iliac region – lateral lymph node dissection.

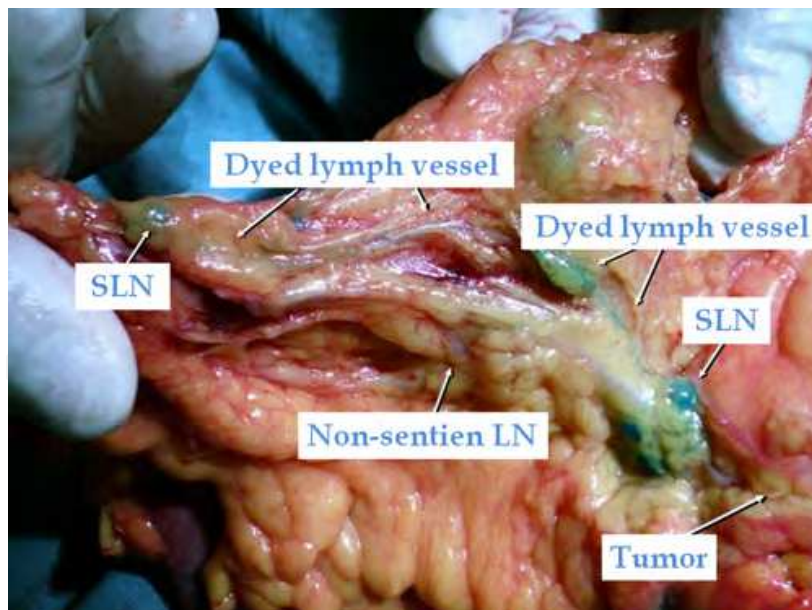


Fig. 6. Direct lymph drainage from the tumor to the root of inferior mesenteric artery. Case of SLN with micrometastasis – example of skip metastasing.

In the same patients we performed detection of the SLN in the mesorectum after destruction of the fascial layers in the presence of pathologist immediately after the resection of the rectum in the operation room. The detection of the SLN was preceded by making biopsy of the circumferential margin, which is an important predictive factor for the disease. In these 7

cases we followed the protocol on Fig. 7. 100% success rate without false-negative results was achieved by adherence to the protocol of procedure in the cases with immediate postoperative detection (Fig. 8). The only disadvantage in these 7 patients is the presence of higher number SLN (3-5) average 3.6 vs. 1.6 in the patients with intraoperative detection, which is explained with delay in the detection with average 20 minutes, during which time the dye has spread to more lymph nodes.

4. Additional methods of sentinel lymph node mapping

The practical application of the method is facilitated with the following additional methods:

4.1 Method for immediate ex vivo detection of mesorectal SLN after failure of the intraoperative detection.

The intraoperative detection of SLN in rectal cancer is easy, because the blue-stained SLN are in contrast with the yellowish fatty tissue and gain distinction during exploration of the pelvis and are visible through the mesorectal fascia. The visualization of SLN in the mesorectum is helped by transillumination of the mesorectum with halogen light from the fibrocolonoscope. The first stained SLN in the mesorectum are easily found.

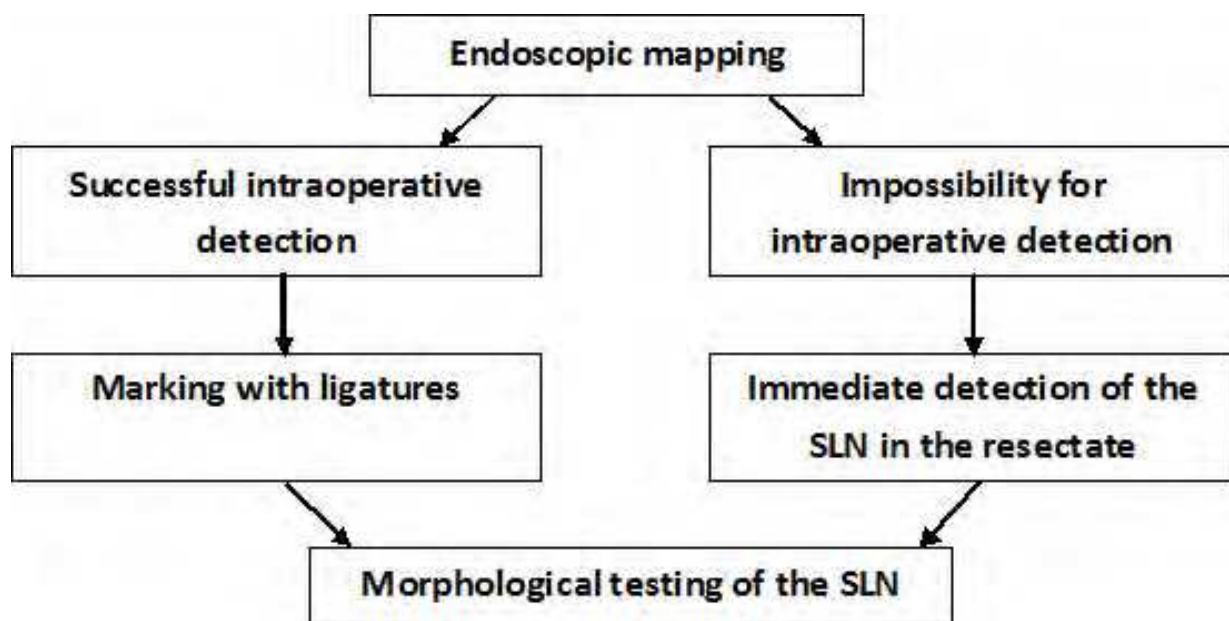


Fig. 7. Algorithm for immediate detection of SLN in the specimen.

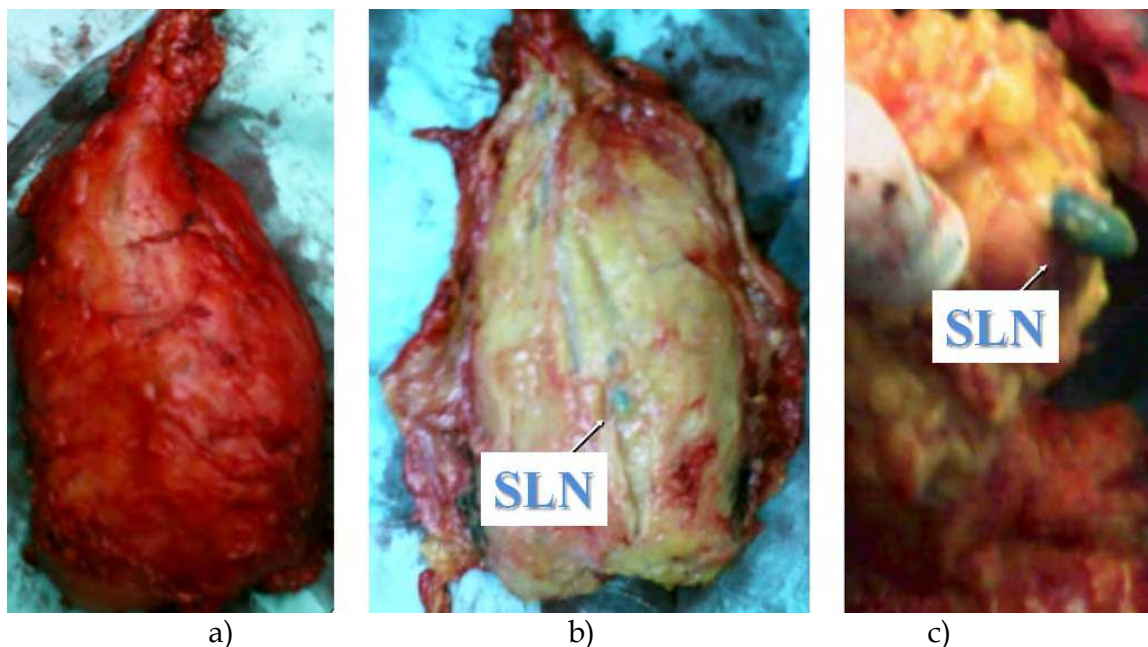


Fig. 8. Method of immediate postoperative detection. a) the SLN are not visible through fascia propria recti; b) after removal of fascia propria recti one SLN was visualized in the mesorectum; c) the visualized SLN – close view.

4.2 Application of the method of additional lymph node mapping

An existing problem remains the examination of insufficient number of lymph nodes in patients with colorectal cancer. This leads to decreased probability for discovery of metastatic lymph nodes and inaccurate staging. The main reason is the small size of the lymph nodes, which are not found by palpation in the fatty tissue of the specimen. Aiming maximal increase in the number of discovered and examined lymph nodes we developed method for additional lymph mapping of the specimen and we evaluated the results together with a pathologist. The method of additional lymph mapping was applied in 103 patients with colorectal cancer and SLN mapping. The method was applied on fresh specimen immediately in the operating room. Intraoperative SLN mapping has been performed and the SLN were identified and marked with ligatures. Additionally 2-3cc Patent Blue V was applied subserosally and submucosally. This method vastly stains the whole lymph node basin. Fig 9. (a,b,c)

4.3 Results from the additional methods

The results we achieved show that the lymphatic system of the specimen facilitates the spread of the dye. In postoperative lymph node mapping the dye stains vastly the lymph nodes and the lymphatic vessels. The evaluation of the lymphatic status in colorectal cancer relies not only on quantitative criteria, e.g. number of examined lymph nodes, but also on qualitative characteristics on the lymph nodes: their size, distance from the primary tumor, sentinel or non-sentinel lymph nodes.

After analyzing the data from the morphological examination after application of the intraoperative SLN mapping and the additional lymph nodes mapping of the specimen we achieved the following results. The number and the average number of examined lymph nodes in relation to pT and pN is shown on Table 4.

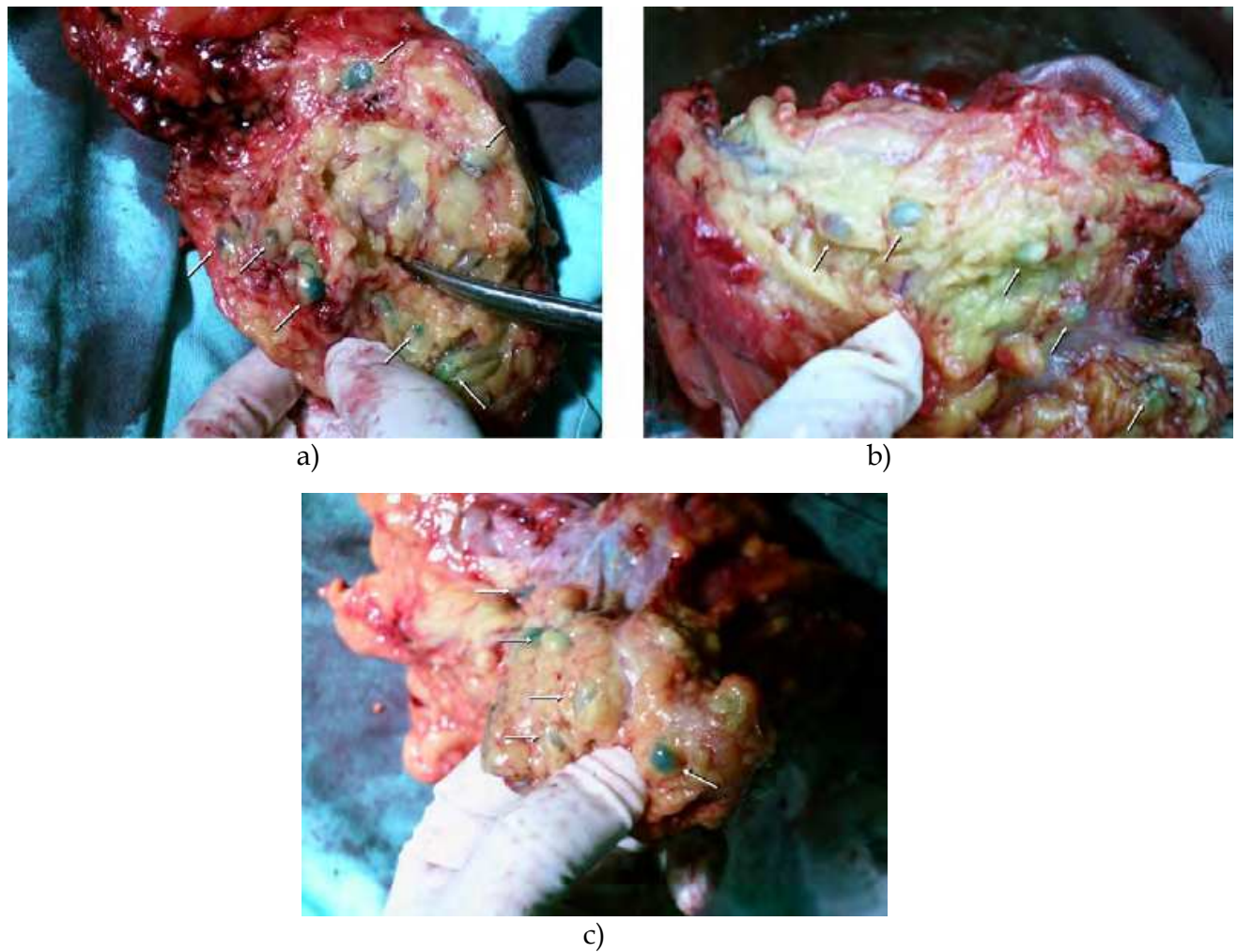


Fig. 9. a),b),c) Intraoperative view of the additional lymph node mapping.

pT \ pN	pN0 (n)	pN1 (n)	pN2 (n)
pT1	18,3 (n = 10)	17,2 (n = 4)	-
pT2	17,2 (n = 35)	14,2 (n = 11)	16,1 (n = 5)
pT3	17,6 (n = 19)	16,5 (n = 16)	16,8 (n = 22)
pT4	-	12,1 (n = 7)	12,4 (n = 7)

Table 4. Relation of number patients to pT and pN

From these data it is understood, that no clear relation between the tumor infiltration (pT) and the number of metastatic lymph nodes (pN). In pN0 the largest and the least number of examined lymph nodes was established in pT1 and pT2 tumors. A larger number of examined lymph nodes are found in patients with pT3 pN2 tumors, comparable to the number of examined lymph nodes in pT3 pN0 and pT3 pN1 tumors. The data for the

number of patients, average number of examined lymph nodes and the length of the specimen in relation to the tumor localization are shown on Table 5.

pT \ pN	pN0	pN1	pN2	Total
pT1	10	4	0	14
pT2	35	11	5	51
pT3	19	16	22	57
pT4	0	7	7	14
Total	64	38	34	136

Table 5. Relation of the average number of examined LN in relation to T/N

We analyzed the data in relation to the size of the examined lymph nodes, the distance from the primary tumor and the localization of the lymph nodes in relation to the rest of the lymph nodes and the primary tumor. The average size of the examined lymph nodes was 4.5mm. The average size of the lymph nodes in colorectal cancer with presence of lymph metastases was larger - 4.7mm in comparison to 4.3mm without presence of lymph metastases, as 53% of the metastatic lymph nodes are less than 5mm.

Along with the size of the examined lymph nodes the distance of the lymph node from the primary tumor and its localization in the mesocolon or the mesorectum also have relationship to the metastatic potential of the lymph node. We analyzed the results in relation to the localization of the sentinel lymph nodes in patients with colorectal cancer. The results for the localization of the SLN are shown on Figure 10.



Fig. 10. a) in 73% of the cases the SLN are localized solely in the pericolic or the perirectal fatty tissue. b) in 24% of the cases the SLN are localized simultaneously on the first and upper levels. c) in 3% of the cases the SLN are localized on the second level.

We established that the average size of the metastatic lymph nodes was larger than that of the non-metastatic lymph nodes. As in 53% of the metastatic lymph nodes their size is less than 5mm, the size is not a certain criteria for evaluating its metastatic potential.

Significantly promising criteria is the result after application of diagnostic method for evaluation of the lymphatic status - intraoperative SLN mapping, which discovers

metastatic lymph nodes in 98% of the cases. The data show that the closer the lymph node to the tumor is, the higher its metastatic potential is.

The examination of higher number of lymph nodes is connected with increased possibility for more accurate evaluation of the lymphatic status. The application of the method made it possible to detect more than 12 lymph nodes in the specimen and to shorten the time for detecting of maximal number lymph nodes in examination of the specimen. Fig. 11



Fig. 11. Thirty-eight stained lymph nodes subject to morphological evaluation from a rectal cancer specimen.

Localization	Number of patients	Average number of lymph nodes	Average length of the specimen
Coecum	12	17,1	27,5
Ascendens	6	16,2	22,1
Hepatic	4	19,7	27,2
Transversum	5	17,3	23,4
Lienalis	1	13,2	15,8
Descendens	9	15,4	25
Sigma	28	12,8	21,2
Rectum	71	14,7	15,7
Total	136	17	22,2

Table 6. Number of patients, average number of lymph nodes and average length of the specimen in relation to the tumor localization.

5. Discussion

Surgical treatment is the basis of the complex therapeutic approach aimed at a lasting cure for patients with colorectal cancers. The quality of surgery is determined apart from the choice of appropriate operating method, but also the characteristics of the tumor in his lymph drainage and possibilities of preoperative and intraoperative staging.

Carrying out an operation with adequate volume fulfils the oncologic criteria and is a prerequisite for precise morphological staging of cancer, which determines the postoperative treatment. Treatment of colorectal cancer is the most successful in stages I and II of the disease before the tumor is metastatic.

The consequences of inaccurate assessment of lymph status lead to development of recurrence in one third of operated patients with "nonmetastatic" colorectal cancers.

The lymph node status is the most important prognostic factor in colorectal cancer. Not always and everywhere can be done accurate preoperative assessment of the lymph status. Clinical examination and intraoperative exploration are only indicative and have relatively low sensitivity and specificity. Prompt intraoperative histological examination has low sensitivity and cannot detect the presence of lymph node micrometastases.

Leaving metastatic lymph nodes located beyond the standard lymph dissection is the cause for recurrence after the radical surgery. The problem is the lack of method for intraoperative assessment of atypical lymphatic drainage. (Bilchik AJ et al., 2001) According to the literature metastatic lymph nodes in the presence of aberrant lymphatic drainage can be found beyond the standard volume of lymph node dissection. In these cases the oncologic principles require to expand the volume of lymph node dissection. (Kitagawa Y. et al., 2004) SLN mapping changes the volume of resection in 8% of cases. Aberrant drainage is not uncommon in patients with tumors of the digestive tract (Cohen, AM et al., 1993). Some authors (Yamamoto, Y. et al., 1998) shows metastasis in 10% of 452 patients with colorectal cancers. Aberrant lymphatic drainage is found in 29% of cases (Bilchik, A J,& Trocha SD, 2003) and may later expand the volume of resection (Bilchik AJ et al., 2001), therefore all the blue stained lymph nodes must be accurately located and marked. Regional lymphatic basin of the colon is removed and sent for morphological examination. Reported values for the successful SLN localization ranged from 58 to 100%. (Bilchik AJ et al., 2001; Bilchik AJ et al., 2003; Tsioulis GJ et al., 2002) Applying this method we achieved success in about 94% of cases. Another important advantage of in vivo SLN mapping in colorectal cancer is detection of patients with aberrant lymphatic drainage occurring in 14% of the cases leading to a change in the initial operational plan (Wood TF et al., 2001). The recurrence in nodal-negative patients is attributed to residual nodal disease after inadequate lymphadenectomy or aberrant lymphatic drainage. (Prandi M. e al., 2002; Schrag, D. et al. 2002) Aberrant lymphatic drainage can be due to anatomical variations or due to altered lymph drainage caused by metastatic involvement of the lymphatic system (Bilchik AJ et al., 2001; Bilchik AJ et al., 2003; Saha S. et al., 2001). In colorectal cancer the standard oncological resection is recommended regardless of the status of SLN. Sometimes, however, it appears that aberrant drainage continues beyond the normal lines of resection. This unusual pattern of lymph drainage was observed in 8% of patients with CRC, where the lines of the lymphatic and organ resection should be extended beyond the conventional (Saha, S. et al. 2004).

The method of intraoperative SLN mapping achieves better intraoperative visualization of the lymph nodes with the highest metastatic potential even if they are very small and detects the presence of aberrant lymphatic drainage and skip metastases. Our study found

aberrant lymphatic drainage in 2% of patients and skip metastases in 3% of patients with lymph mapping. We expanded the volume of surgical procedure in 7% of the patients in which positive lymph nodes were detected beyond standard lymphatic dissection. In three of them skip metastases were observed and in other three patients was observed aberrant lymphatic drainage. All the patients' sentinel lymph nodes revealed the presence of metastases or micrometastases after ultrastaging.

The examination of insufficient number of lymph nodes is the reason leading to a reduced chance of detection of metastatic lymph nodes and inaccurate staging of the disease. The cause is the small size of lymph nodes that are not detected by palpation in adipose tissue of the specimen. Our results from the application of the method of additional lymph node mapping indicate that it allows quickly discovering and exploring the maximum number of lymph nodes and contributes to the precise staging of colorectal cancer. We found that the average size of metastatic lymph nodes was 4.7 mm. Our results show that the lymphatic system of the specimen has potential for diffusion of the dye. The postoperative lymph node mapping stains the lymphatic vessels and the lymph nodes.

We found that in case of right colon cancer it is appropriate to apply the method of intraoperative subserosal SLN mapping. The rectal cancer and the left colon cancer are more suitable to perform intraoperative colonoscopy and to apply the method of intraoperative endoscopic submucous sentinel marking. The analysis of the results from the application of the methods of intraoperative endoscopic submucous SLN mapping and intraoperative subserous SLN mapping indicates that both methods are equally reliable and highly sensitive. Additionally the method of intraoperative SLN mapping is equally applicable to patients with colon and rectal cancer.

The ultrastaging of sentinel lymph nodes aids the accurate staging and treatment of patients with colorectal cancer. By application of the method of intraoperative sentinel marking and the ultrastaging of lymph nodes is achieved upstaging of the disease and determination of exact definitive diagnosis in 20% of patients.

The method is convenient because it is not related to the need for expensive equipment and supplies and does not require a complex organization, the training of the surgeons is easy and the staff readily agrees for application of the method.

Our own results and literature data show that intraoperative SLN mapping is a method with high success rate and sensitivity for intraoperative diagnosis of the lymph status.

The surgical approach and the volume of lymphatic dissection should respond to the state of the lymphatic basin, estimated using an objective diagnostic method such as intraoperative SLN mapping. This leads to an increase of surgical radicalism in the treatment of colorectal cancer, which is proved in our study.

Surgeons and oncologists are aware that ensuring of optimal conditions for patients with colorectal cancer requires precise surgery, if necessary combined with adjuvant therapy. In order to provide quality treatment for colorectal cancer a multidisciplinary team including GPs, surgeons, imaging diagnostic specialists, gastroenterologists, oncologists and pathologist, etc is required.

SLN mapping increases the number of collected lymph nodes, as well as the sensitivity of nodal assessment. In addition, in cases with aberrant lymph drainage extensive resection is performed, containing remote SLN. A multidisciplinary approach is required to standardize the detection and assessment of the SLN, contributing to colorectal cancer staging. Detection of micrometastases in the lymph nodes is generally recognized as pN1(mi), but the risk of

recurrence is unknown. Large prospective studies are essential to determine the clinical significance of nodal micrometastases. The introduction of coordinated screening programs for low-risk patients or tracking of high-risk patients, the application of more sensitive methods for preoperative staging, the advance in treatment and methods of morphological evaluation create opportunities for improving the survival and the quality of life of patients with colorectal cancers. (Bilchik A. et al., 2001; Bilchik, A J,& Trocha SD, 2003; Esser, S. et al., 2001; Feinstein, AR et al., 1985; Merrie, AE et al., 2001; Paramo JC et al., 2001; Tsopelas, C.& Sutton R., 2002; Wood, TF et al., 2001).

The accuracy may increase with the increasing of the number of lymph nodes sectioned, and with involving of immunohistochemistry or molecular markers' panels as demonstrated in many studies, but will also increase the cost and the workload for pathologists (Bilchik AJ et al., 2006; Bembenek A. et al., 2007; Kelder W. et al., 2007). Even though the accuracy was good for colon and rectal cancer, the sensitivity of the method somewhere is reported very low (66.66% for colon and 50% for rectal cancer), and the false-negative rate was high (23.07% for colon cancer and 18.18% for rectal cancer). The sensitivity of the method varies in the literature between 54% in the study of the Bembenek , and 88.2–89% in the study of Bilchik AJ *et al.*, and Kelder W *et al.* (Bilchik AJ et al., 2006; Bembenek A. et al., 2007; Kelder W. et al., 2007). The smallest false-negative rate was achieved by Bilchick AJ *et al.* (7.4%), but other authors reported a significantly higher rate of false-negative results (46% for colon cancer in the study of Bembenek AE *et al.* and 43% in rectal cancer in the study of Baton O *et al.*) (Bilchik AJ et al., 2006; Bembenek A. et al., 2007; Baton O. et al., 2005). Thus, with such high risk of failure (lower detection rate, low sensitivity and high false-negativity rate), the technique of sentinel lymph node in rectal cancer is obviously not feasible; in colon cancer, the method may be improved by increasing the number of the examined lymph nodes, and using specific immunohistochemical staining methods. However, doing so, it will not represent a relief for pathologist, but probably will increase the quality of the *pN* staging. In this matter, our study has shown an increase in the detection of the positive lymph nodes (37.2% *N+* in sentinel lymph node group *vs.* 26.67% in the control group), but statistical significance was not reached. Moreover, the quality of the upstaging was not determined by the examination technique itself (micrometastases were detected in only two cases – 9.37% upstaging rate), but probably by the increased number of the identified and examined lymph nodes in the studied group *vs.* comparison group (the blue staining of the lymph node in the study group made it easy to identify them, and probably an increasing awareness and close collaboration between the surgeon and pathologist) (Bilchik AJ&Compton C., 2007). In literature, there are better results in upstaging the *pN* category, using the sentinel lymph node technique, varying from 15% for rectal cancer (Baton O *et al.*, 2005) to 18–23.6% in colon cancer (Bilchik AJ et al., 2006; Bembenek A. et al., 2007; Kelder W. et al., 2007).

The high incidence of distant metastasis of CRC in patients whose nodes are negative may be due to insufficient numbers or sections of lymph nodes. Bilchik A.&Compton C., 2007 Because multiple sectioning and IHC staining cannot be routinely used to examine all lymph nodes in a CRC specimen, we focused on the first regional node(s) to receive lymphatic drainage from a primary tumor. In melanoma and breast cancer, lymphatic mapping and excision of the SN is used to determine the tumor status of the entire nodal basin and avoid complete lymph node dissection in node-negative patients. The application of the SN technique in CRC is different because all regional lymph nodes are routinely removed en bloc with the primary tumor. However, as in melanoma and breast cancer,

examination of the SN allows the pathologist to focus on the regional node(s) most likely to contain tumor cells and thus improve tumor cell detection and accuracy of staging. The tumor occludes the lymphatic vessels resulting in drainage to another (nonsentinel) node. Because these nodes are large and solid, it is unlikely that SN and lymphatic mapping will be of value in this group of patients. The prognostic significance of nodal micrometastases by either CK-IHC or RT-PCR in CRC remains unclear. In a recent study in patients initially reported as node negative, re-examination using CK-IHC and carcinoembryonic antigen (CEA)-IHC demonstrated evidence of micrometastases in 26% of the node negative patients (Bilchik et al., 2001). However, the presence of nodal micrometastases did not significantly affect 5-year survival. Similarly, Jeffers (Jeffers MD et al., 1994) detected CK-IHC micrometastases in 25% of 77 patients who's CRCs were initially staged as Duke's B. Again, the presence of nodal micrometastases had no significant effect on survival; however, random micro sectioning may have missed tumor cells, thereby causing insignificant survival differences between the two groups. More recently, Greenon (Greenon JK et al., 1994) demonstrated that micrometastatic disease missed by routine HE staining but identified by CK-IHC had an adverse effect on survival. The lack of consensus in the literature in part reflects the absence of standard antibody titers and staining techniques; there are considerable interinstitutional variations in the analysis of CRC lymph nodes by CK-IHC. Although to date no randomized study has demonstrated significance for the detection of micrometastases by CKIHC, the American College of Surgeons Oncology Group currently is conducting a multicenter trial (Z-0010) to assess the utility of CK-IHC in detecting micrometastases, of SNs draining primary breast carcinoma. Clinical outcome studies of marker expression in CRC are also limited. Hayashi (Hayashi N. et al., 1995) demonstrated decreased survival in patients with p53 or K-ras mutations in colonic lymph nodes. In another study of patients whose CRC was staged Duke's B by conventional techniques, Liefers (Liefers GJ et al., 1998) reported a 5-year survival rate of 50% for patients whose nodes expressed CEA, versus 91% for those whose nodes did not express CEA. Several other investigators have reported that histologically negative lymph nodes contained evidence of occult metastases by RT-PCR using CK20 30 or guanylyl cyclase C 31 in qualitative assay systems. However, guanylyl cyclase C, CEA, and cytokeratin are expressed by normal tissues and therefore may introduce false-positive results. Our group and others have questioned their utility for the detection of micrometastatic CRC. Our approach has been to use a combination of mRNA markers in a semi-quantitative assay to detect occult micrometastases. Focused analysis of multiple sections of the SN by CK-IHC and RT-PCR provides a unique tool for accurate staging of CRC. As demonstrated in our study, lymphatic mapping of the SN also can identify unexpected nodal drainage patterns that alter the margins of surgical resection. Focused examination of SN diagnoses micrometastatic disease missed by conventional techniques. Although the significance of micrometastatic disease is yet to be defined in CRC, it is likely to be an important stratifying factor in choosing those who may benefit from adjuvant chemotherapy

6. Conclusions

The method of intraoperative SLN mapping using Patent Blue V is an accurate and objective diagnostic method for assessment of the lymphatic status in patients with colorectal cancer. The method is an objective criterion for intraoperative surgical behavior.

The method of intraoperative SLN mapping is applied with high success in patients with colon and rectal cancer. The method has 100% success rate and 98% sensitivity.

The analysis of the results from the application of methods of intraoperative endoscopic submucous SLN mapping and intraoperative subserous SLN mapping indicates that both methods are equally reliable and highly sensitive.

The method of intraoperative SLN mapping achieves better intraoperative visualization of lymph nodes with the highest metastatic potential, even if they are very small. It was found that the average size of metastatic lymph nodes was 4.7 mm. The method can detect the presence of aberrant lymphatic drainage and lymphatic skip metastases.

The sentinel lymph node reflects with high reliability the status of the entire lymphatic basin. Metastatic lymph nodes beyond the standard volume of lymphatic dissection are detected by intraoperative SLN mapping. By increasing the surgical volume was achieved greater radicalism in 7% of patients with colorectal cancers. It does not increase the postoperative morbidity.

Our study demonstrates that metastases in sentinel lymph nodes are found 6 times more frequently than in other lymph nodes. In 98% of cases the metastases are found in the sentinel lymph nodes.

In the absence of metastases in sentinel lymph nodes, the likelihood of metastases in other lymph nodes is only 0.6%.

Only through the application of the method of intraoperative SLN mapping and the ultrastaging of the lymph nodes it is liable to achieve more precise clinical staging of disease and determining of exact definitive diagnosis in 20% of patients.

The method of additional lymph node mapping allows quick discovery and exploration of maximum number lymph nodes, which contributes to the accurate staging of colorectal cancer.

The endoscopic submucous application of the lymphatic marker is the only appropriate method for intraoperative SLN mapping in case of subperitoneal localization of rectal cancer.

We conclude that SLN mapping in colorectal cancer is a convenient diagnostic method allowing the surgeon to individualize the approach to every single patient. Further studies are needed to validate if routine use of this method will increase the survival rates of patients operated for colorectal cancer.

We can conclude that the operational approach and the volume of the conducted lymphatic dissection must comply with the status of the lymphatic basin, assessed by an objective diagnostic method such as the intraoperative sentinel lymph node mapping. This leads to increased surgical radicalism in the surgical treatment of colorectal cancers. Our recommendation is that the method should be promoted and clinical trials should follow.

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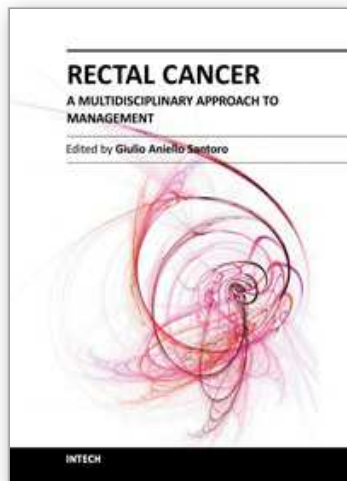
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Dramatic improvements in medicine over the last few years have resulted in more reliable and accessible diagnostics and treatment of rectal cancer. Given the complex physiopathology of this tumor, the approach should not be limited to a single specialty but should involve a number of specialties (surgery, gastroenterology, radiology, biology, oncology, radiotherapy, nuclear medicine, physiotherapy) in an integrated fashion. The subtitle of this book "A Multidisciplinary Approach to Management" encompasses this concept. We have endeavored, with the help of an international group of contributors, to provide an up-to-date and authoritative account of the management of rectal tumor.

How to reference

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InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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