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Intraoperative Sentinel Lymph Node Mapping in Patients with Colorectal Cancer

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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)

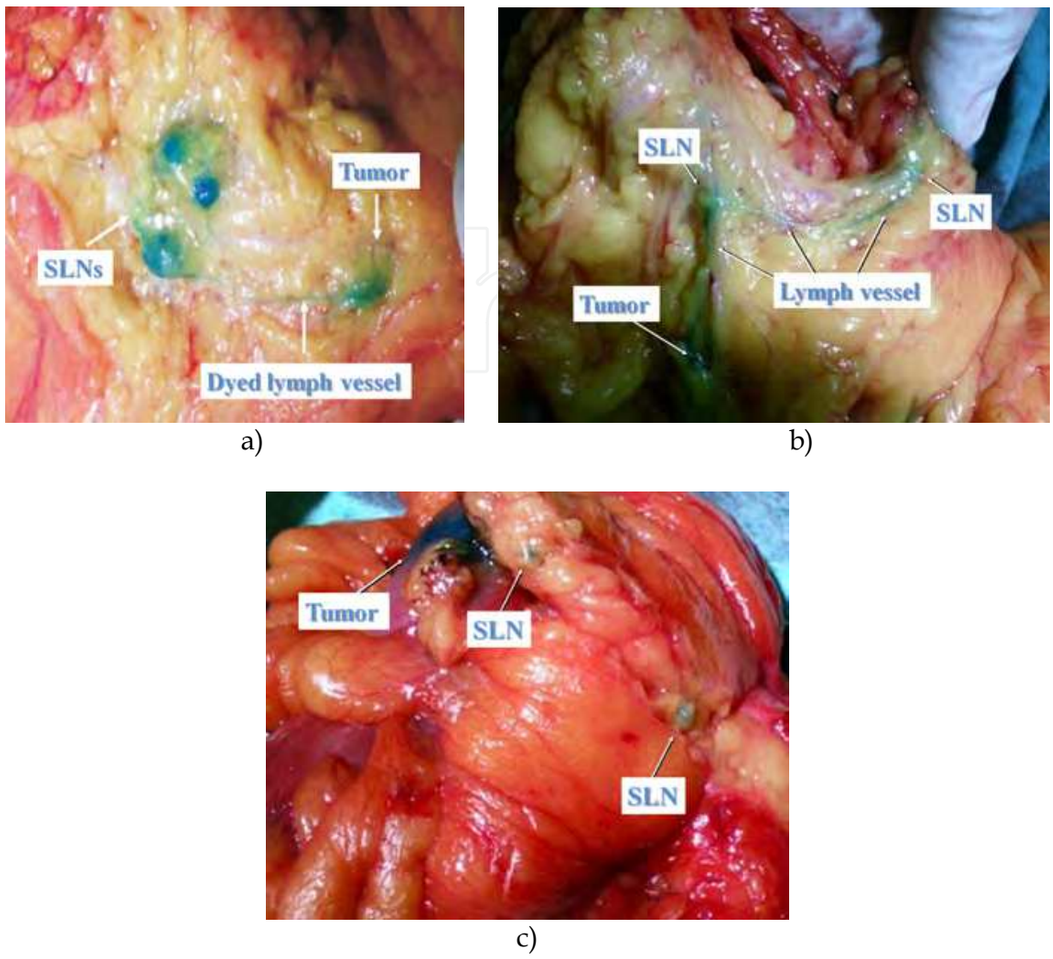
In CRC the resection volume and the lymph dissection are determined by the tumor localization and they have been standardized to a great extent. (Schlag PM et al., 2004) The metastatic lymph nodes in the presence of aberrant lymph drainage can be found beyond the lines of the standard lymph dissection. In these cases the radicality of the surgery requires extension of the lines of lymph dissection. (Paramo JC et al., 2001; Tsioulias 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. (Tsioulias G. et al., 2002; Martinez SR& Bilchik AJ, 2005; Bilchik AJ et al., 2003; Doekhie FS et al., 2005)



a) b)

c)

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.

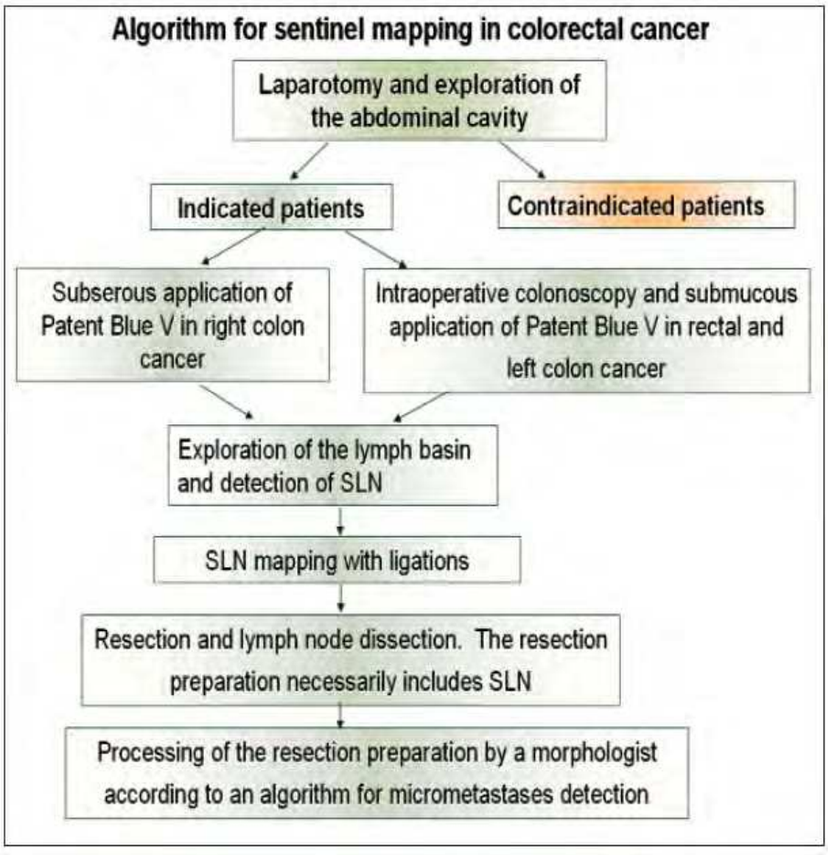


Fig. 2. Algorithm for sentinel mapping in colorectal cancer.

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 mesenterial root of mesentery vessels and

paraaortically, the obturatory 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 20-25μm. 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 Hematoxilin-Eosin. Micrometastases are defined as a focus of tumor cells sized under 2 mm or a focus detected only by means of immunohistochemistry. (Feezor 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).

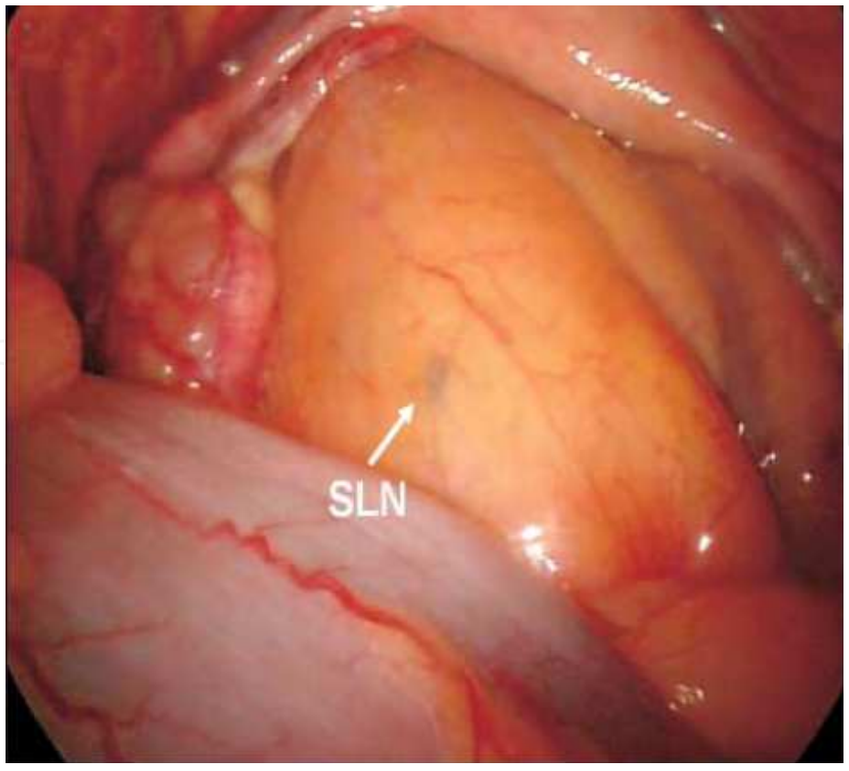


Fig. 3. Laparoscopic view of a SLN.

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.).

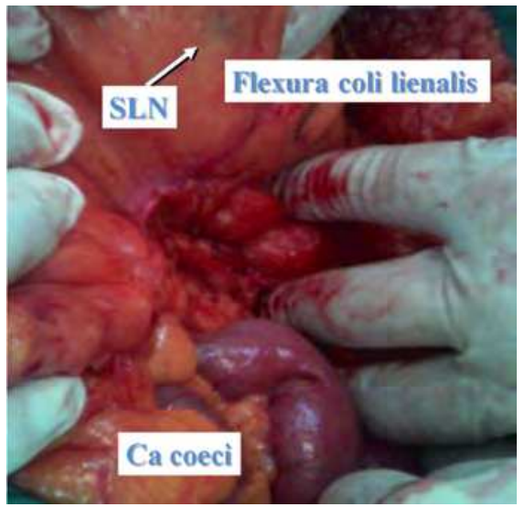


Fig. 4. SLN in the region of flexura coli lienalis.

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 atrery 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, obturatorialy 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 transilumination, probably due to the fatty tissue and insufficient staining of the SLN.

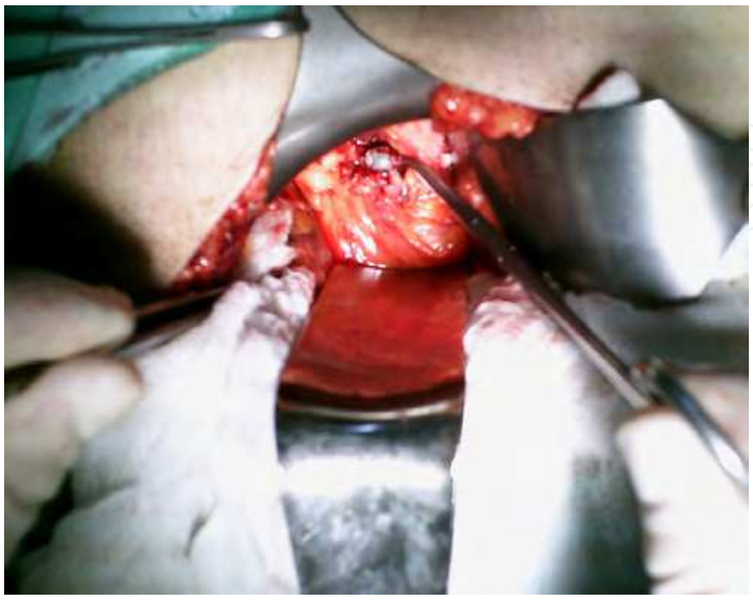


Fig. 5. SLN in the left ilac region – lateral lymph node dissection.

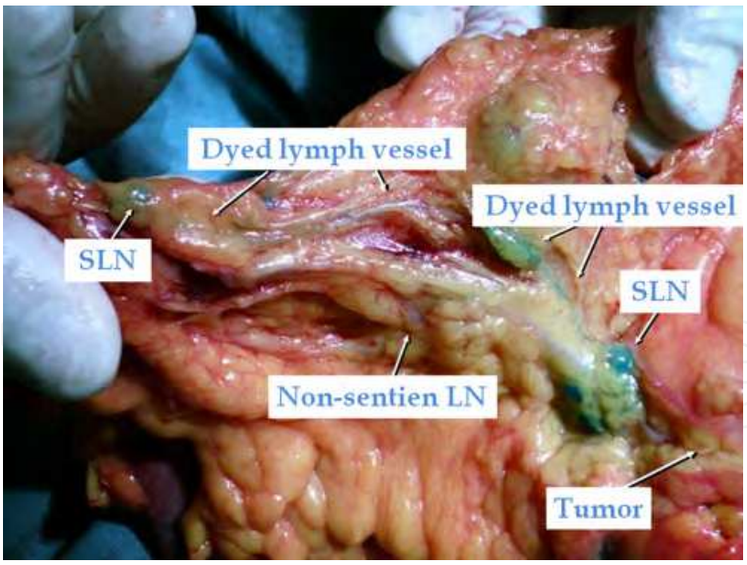


Fig. 6. Direct lymph drainage from the tumor to the root of inferior mesenteric artery. Case of SLN with micrometastasis – example of skip metastasing.

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 transilumination of the mesorectum with halogen light from the fibrocolonoscope. The first stained SLN in the mesorectum are easily found.

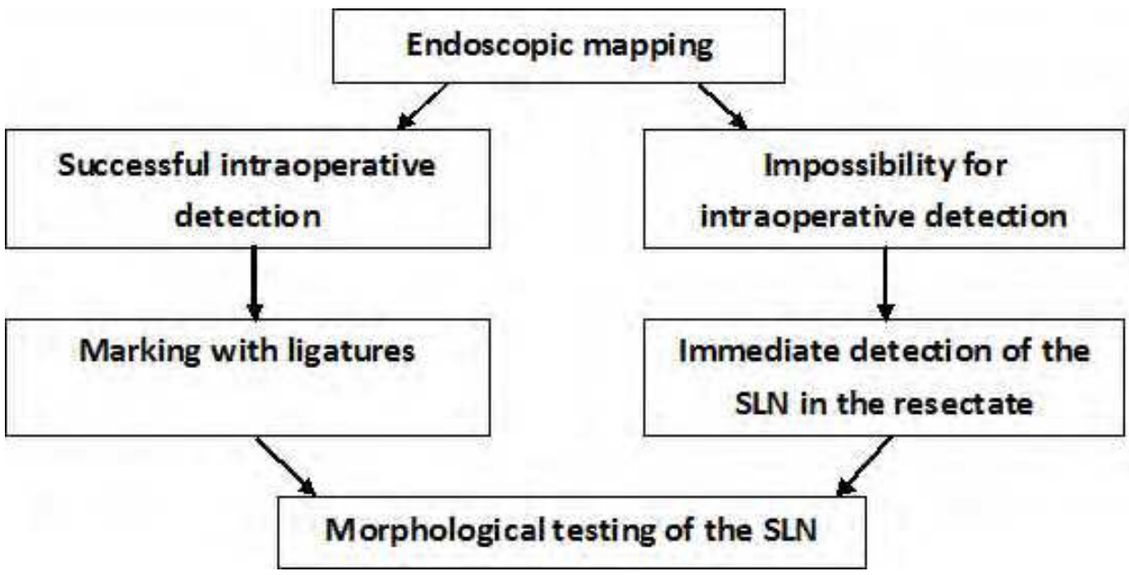
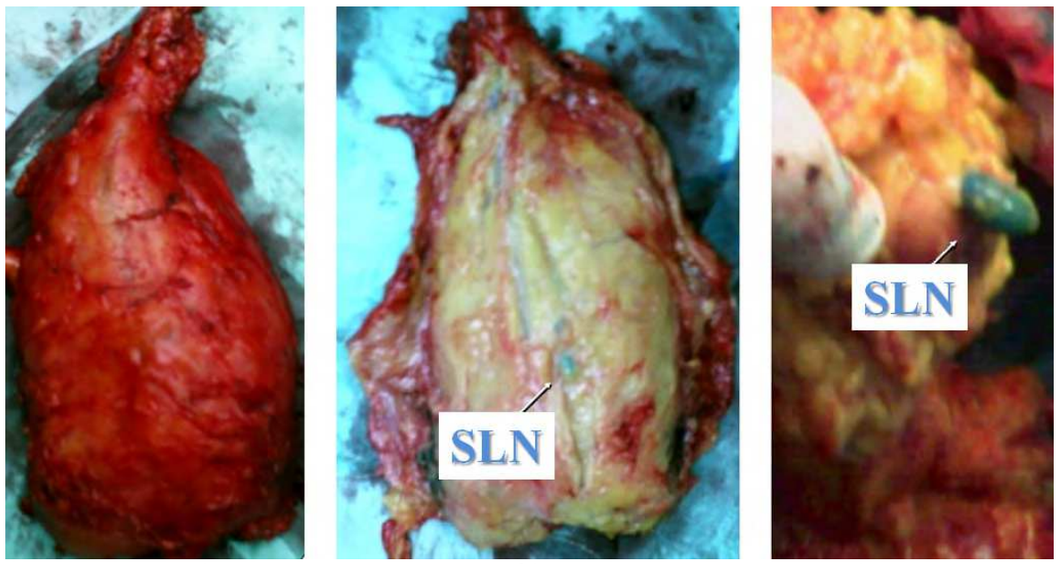


Fig. 7. Algorithm for immediate detection of SLN in the specimen.



a) b) c)

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.

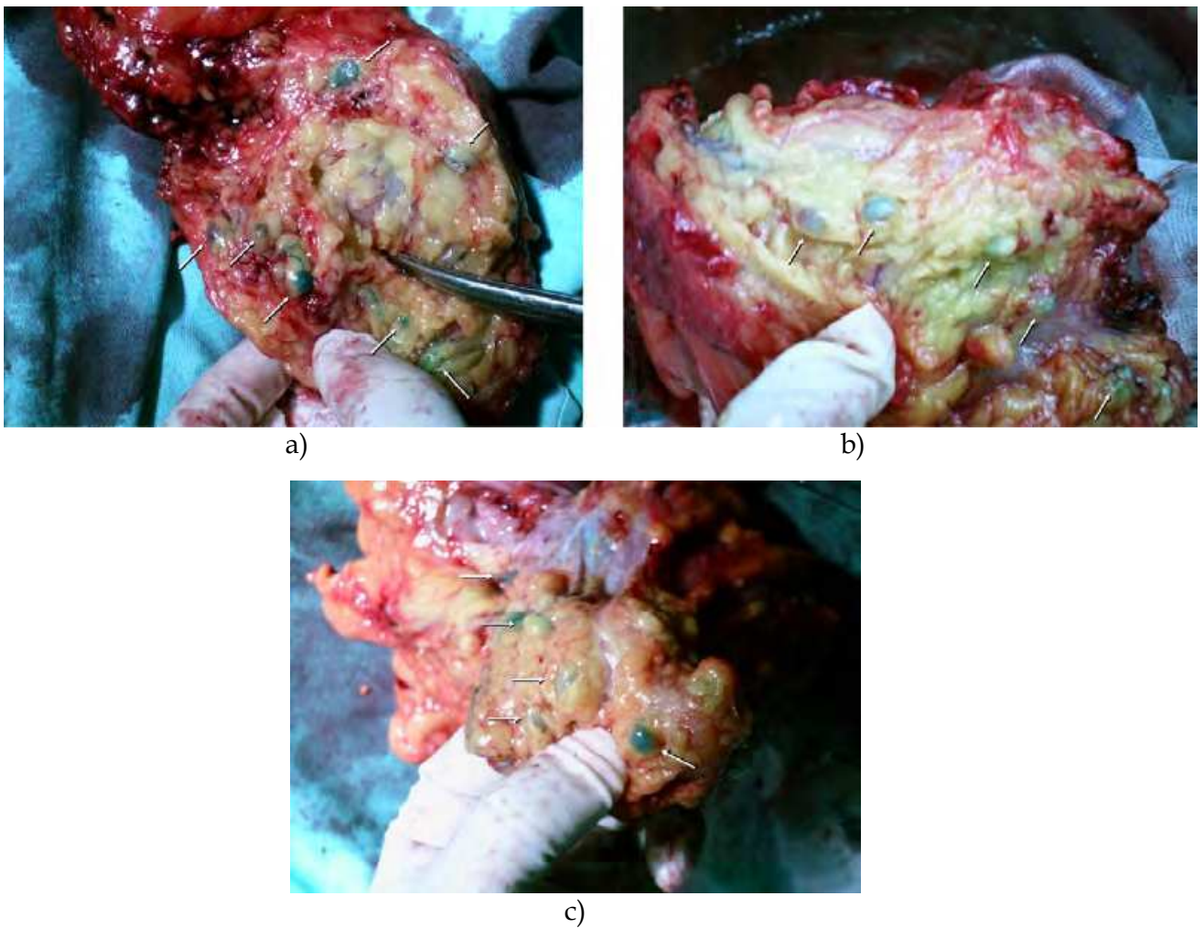
4.2 Application of the method of additional lymph node mapping

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.



a) b)

c)

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.

pN / pT	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.

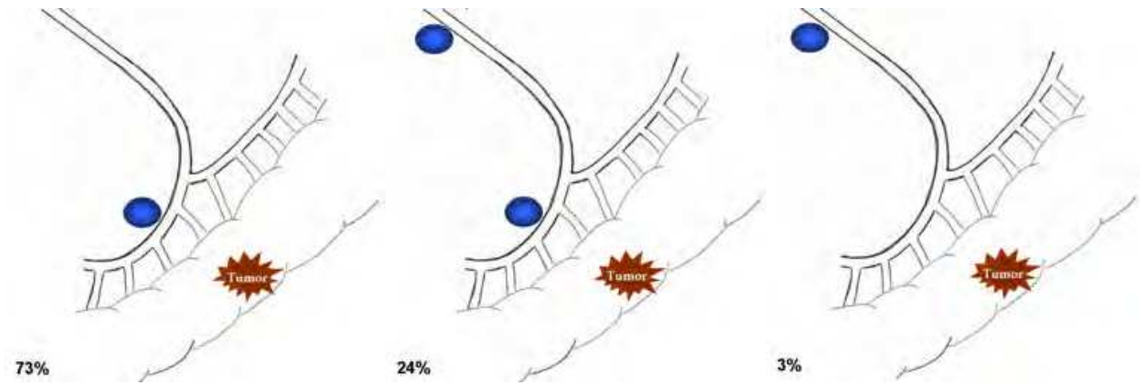


Fig. 10. a) in 73% of the cases the SLN are localized solely in the pericolic or the perirectal fatty tissue. b) in 24% of the cases the SLN are localized simultaneously on the first and upper levels. c) in 3% of the cases the SLN are localized on the second level.

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

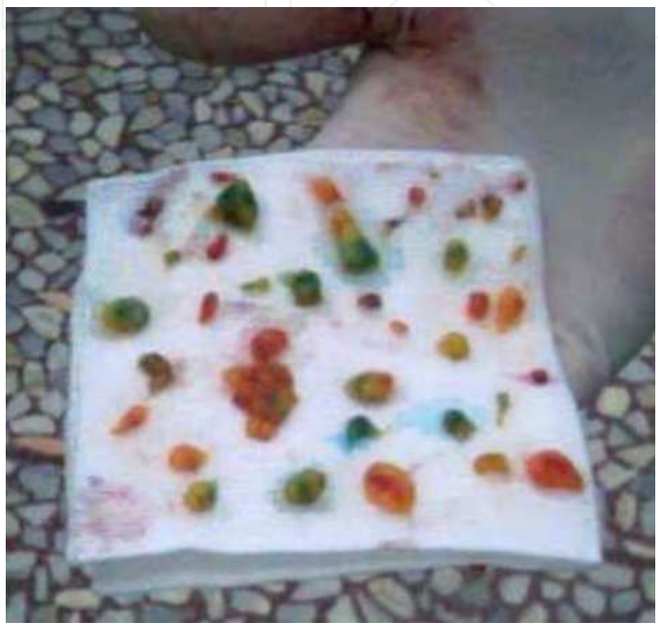


Fig. 11. Thirty-eight stained lymph nodes subject to morphological evaluation from a rectal cancer specimen.

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; Tsioulias 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 occuring in 14% of the cases leading to a change in the initial operational plan (Wood TF et al., 2001). The reccurence 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, Greenson (Greenson 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.

7. References

Adell, G, Boeryd, B, Franlund, B, Sjodahl, R, Hakansson, L: Occurrence and prognostic importance of micrometastases in regional lymph nodes in Dukes B colorectal carcinoma: an immunohistochemical study. Eur J Surg 1996; 162:637-642.

Baton O, Lasser P, Sabourin Jc, Boige V, Duvillard P, Elias D, Malka D, Ducreux M, Pocard M, Ex vivo sentinel lymph node study for rectal adenocarcinoma: preliminary study, World J Surg, 2005, 29(9):1166–1170; discussion 1171.

Bembenek A, Rosenberg R, Wagler E, Gretschel S, Sendler A, Siewert Jr, Nährig J, Witzigmann H, Hauss J, Knorr C, Dimmler A, Gröne J, Buhr Hj, Haier J, Herbst H, Tepel J, Siphos B, Kleespies A, Koenigsrainer A, Stoecklein Nh, Horstmann O, Grützmann R, Imdahl A, Svoboda D, Wittekind C, Schneider W, Wernecke Kd, Schlag Pm, Sentinel lymph node biopsy in colon cancer: a prospective multicenter trial, Ann Surg, 2007, 245(6):858–863.

Bembenek A., Haensch W, Schneider U, Markwardt J, Schlag PM: Immunohistochemical detection of lymphnode metastases The Lancet 2000; 355:144-145.

Bertagnolli M, Miedema B, Redston M, Dowell J, Niedzwiecki D, Fleshman J, Bem J, Mayer R, Zinner M, Compton Carolyn: Sentinel Node Staging of Resectable Colon Cancer: Results of a Multicenter Study. Ann Surg Oncol 2004; 240:624-630.

Bertoglio S, Sandrucci S, Percivale P, Goss M, Gipponi M, Moresco L, Mussa B, Mussa A: Prognostic Value of Sentinel Lymph Node Biopsy in the Pathologic Staging of Colorectal Cancer Patients Journal of Surgical Oncology 2004; 85:166–170.

Bilchik A, Saha S, Wiese D, Stonecypher JA, Wood TF, Sostrin S, Turner RR, Wang HJ, Morton DL, Hoon D. SB. Molecular staging of early colon cancer on the basis of sentinel node analysis: a multicenter phase II trial. J. Clin. Oncol. 2001; 19:1128-1136.

Bilchik A: More(Nodes)+More(Analysis) = Less (Mortality): Challenging the Therapeutic Equation for Early-Stage Colon Cancer Annals of Surgical Oncology 2003; 10:203-205.

Bilchik AJ, Compton C, Close collaboration betweensurgeon and pathologist is essential for accurate staging of early colon cancer, Ann Surg, 2007, 245(6):864–866.

Bilchik AJ, Dinome M, Saha S, Turner RR, Wiese D, McCarter M, Hoon DS, Morton Dl, Prospective multicenter trial of staging adequacy in colon cancer: preliminary results, ARCH SURG, 2006, 141(6):527–533; DISCUSSION 533– 534.

Bilchik AJ, Giuliano A, Essner R, Bostick P, Kelemen P, Foshag LJ, Sostrin S, Turner RR, Morton DL: Universal application of intraoperative lymphatic mapping and sentinel lymphadenectomy in solid neoplasms. Cancer J Sci Am. 1998; 4:351-358.

Bilchik AJ, Nora D, Tollenaar R.A.E.M., van de Velde C.J.H., Wood T, Turner R, Morton DL, Hoon D.S.B: Ultrastaging of early colon cancer using lymphatic mapping and molecular analysisEuropean Journal of Cancer 2002; 38: 977–985.

Bilchik AJ, Nora DT, Sobin LH, Turner RR, Trocha S, Krasne D: Effect of lymphatic mapping on the new tumor-node-metastasis classification for colorectal cancer. J Clin Oncol 2003; 21:668–672.

Bilchik AJ, Nora DT: Lymphatic Mapping of Nodal Micrometastasis in Colon Cancer: Putting the Cart Before the Horse? Annals of Surgical Oncology 2002; 9:529-531.

Bilchik AJ, Saha S, Tsioulias GJ: Aberrant drainage and missed micrometastases: the value of lymphatic mapping and focused analysis of sentinel lymph nodes in gastrointestinal neoplasms. Ann Surg Oncol 2001; 8:82–5S.

Bilchik, A. J., S. D. Trocha. Lymphatic mapping and sentinel node analysis to optimize laparoscopic resection and staging of colorectal cancer: an update. – Cancer Control, 10, 2003, 219–223.

Broll R, Schauer V, Schimmelpenning H: Prognostic relevance of occult tumor cells in lymph nodes of colorectal carcinomas: an immunohistochemical study. Dis ColonRectum 1997; 40:1465-1471.

Choi, HJ, Choi, YY, Hong, SH: Incidence and prognostic implications of isolated tumor cells in lymph nodes from patients with Dukes B colorectal carcinoma. Dis Colon Rectum. 2002 Jun;45(6):750-5; discussion755-6.

Cohen AM, Kelsen D, Saltz L, Minsky BD, Nelson H, Farouk R, et al: Adjuvant therapy for colorectal cancer. Curr Probl Cancer 1998; 22:5–65.

Cohen AM, Kelsen D, Saltz L: Adjuvant therapy for colorectal cancer. Curr Prob Cancer 1998; 22:5–65.

Cohen, A. M., B. D. Minsky, R. L. Schilsky. Rectal cancer. – In: Cancer Principles&Practice. Eds: Helman De Vita Jr., S. Rosenberg, Philadelphia, Lippinkott Co., 1993. p. 929–966.

Cutait, R, Alves, VA, Lopes, LC: Restaging of colorectal cancer based on the identification of lymph node micrometastases through immunoperoxidase staining of CEA and cytokeratins. Dis Colon Rectum 1991 34:917-20.

Dimitrov V, Delijski T: Lymph Node Dissection in anorectal and intestinal tumors. In: Lymph node dissection in breast, gastrointestinal and urogenital carcinomas. Pleven, 2003.

Doekhie FS, Peeters K.C.M.J., Kuppen P.J.K., Mesker W.E., Tanke H.J., Morreau H., van de Velde C.J.H., Tollenaar

Esser, S. et al. The role of sentinel lymph node mapping in staging of colon and rectal cancer. – Dis Colon Rectum, 44, 2001, 850–854.

Feezor RJ, Copeland Edward M. III, Hochwald Steven N: Significance of Micrometastases in Colorectal Cancer Ann Surg Oncol 2002; 9:944-953.

Feig BW, Curley S, Lucci A, Hunt K, Vauthey JN, Mansfield PF, Cleary K, Hamilton St, Ellisa V, Brame M, Berger DH: A caution regarding lymphatic mapping in patients with colon cancer The American Journal of Surgery 2001;182: 707–712.

Feinstein, A. R., D. M. Sosin, C. K. Wells. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. – N Engl J Med, 312, 1985, 1604–1608.

Fielding P: Staging systems. In Cohen A, Winawer S, eds. Cancer of the Colon, Rectum and Anus. New York, McGraw-Hill, 1995, 207.

Giuliano AE, Kirgan DM, Guenter JM: Lymphatic mappingand sentinel lymphadenectomy for breast cancer. Ann Surg 1994; 3:391-401.

Greenlee RT, Murray T, Bolden S, Wingo PA: Cancer statistics. CA Cancer J Clin 2000; 50:7–33.

Greenson JK, Isenhart CE, Rice R, Mojzisik C, Houchens D, Martin EW, Jr: Identification of occult micrometastases in pericolic lymph nodes of Duke s B colorectal cancer patients using monoclonal antibodies against cytokeratin and CC49. Correlation with long-term survival. Cancer 1994; 73:563-569.

Haboubi NY, Clark P, Kaftan SM: The importance of combining xylene clearance and immunohistochemistry in the accurate staging of colorectal carcinoma. J Royal Soc Med 1992; 85:386–388.

Hayashi N, Ito I, Yanagisawa A, et al: Genetic diagnosis of lymph-node metastasis in colorectal cancer. Lancet 1995;345:1257-1259.

Herrera-Ornelas L: Metastasis in small lymph nodes from colon cancer. Arch Surg 1987; 122:1253–1256.

Hiroya T, Bilchik A, Saha S, Turner R, Wiese D, Tanaka M, Kuo Ch, Wang He-Jing and Hoon D: c-MET Expression Level in Primary Colon Cancer Clinical Cancer Research 2003; 9:1480-1488.

Isaka N, Nozue M, Doy M, Fukao K: Prognostic significance of perirectal lymph node micrometastases in Dukes B rectal carcinoma: an immunohistochemical study by CAM5.2. Clin Cancer Res 1999; 5:2065-2068.

Jeffers MD, O'Dowd GM, Mulcahy H, Stagg M, O'Donoghue DP, Toner M. The prognostic significance of immunohistochemically detected lymph node micrometastases in colorectal carcinoma. J Pathol. 1994 Feb;172(2):183-7.

K. Dahl, J. Westlin, W. Kraaz, O. Winqvist, L. Bergkvist and M: Thцrn Identification of sentinel nodes in patients with colon cancer European Journal of Surgical Oncology 2005; 31:381-385.

Kelder W, Braat Ae, Karrenbeld A, Grond Ja, De Vries Je, Oosterhuis Jw, Baas Pc, Plukker Jt, The sentinel node procedure in colon carcinoma: a multicenter study in The Netherlands, Int J Colorectal Dis, 2007, 22(12):1509–1514.

Kitagawa Y, Fujii H, Mukai M, Kubota T, Ando N, Watanabe M, Ohgami M, Otani Y, Ozawa S, Hasegawa H, Furukawa T, Kumai K, Ikeda T, Nakahara T, Kubo A, Kitajima M: The role of the sentinel lymph node in gastrointestinal cancer. Surg Clin North Am. 2000; 80:1799-809.

Kitagawa Y, Fujii H, Mukai M: Current Status and Future Perspectives of Sentinel Node Navigation for Gastrointestinal Cancer. Proceedings of the 3rd International Sentinel Lymph Node Congress 2002; 2:136.

Kitagawa Y, Kitajima M: Gastrointestinal cancer and sentinel node navigation surgery, J. Surg. Oncol. 2002; 79:188-193.

Kitagawa Y, Watanabe M, Hasegawa H, Yamamoto S, Fujii H, Yamamoto K, Matsuda J, Mukai M, Kubo A, Kitajima M: Sentinel Node Mapping for Colorectal Cancer With Radioactive Tracer Dis Colon Rectum, 2002 Nov;45(11):1476-0.

Kitagawa, Y. et al. Current Status and Future Prospects of Sentinel Node Navigational Surgery for Gastrointestinal Cancers. – Ann Surg Oncol, 11, 2004, 3, 242S–244S.

Kitajima M, Kitagawa Y: Universal Applications of Sentinel Node Technology Annals of Surgical Oncology 2004; 11(Supplement):144S-146S.

Liefers GJ, Cleton-Jansen AM, van de Velde CJ, Hermans J, van Krieken JH, Cornelisse CJ: Micrometastases and survival in stage II colorectal cancer. N Engl J Med 1998; 339:223–228.

Lindmark G, Gerdin B, Pahlman L, Bergstrom R, Glimelius B: Prognostic predictors in colorectal cancer. Dis Colon Rectum 1994; 37:1219-1227.

Macintosh, E.: Colorectal carcinoma. In: Cancer patients follow-up by F. Johnson and R. Virgo. St. Louis, Mosby-

Makela, J., H. Kiviniemi: Survival after operation for colorectal cancer. Eur. J Surg. 2000.

Martinez SR, AJ Bilchik: Quality control issues in the management of colon cancer patients Eur J Surg Oncol. 2005; 31:616-629.

Merrie A.E. H, Phillips LV, Yun K, McCall J: Skip metastases in colon cancer: Assessment by lymph node mapping using molecular detection Surgery 2001; 129:684-691.

Merrie, A. E. et al. Diagnostic use of the sentinel node in colon cancer. – Dis Colon Rectum, 44, 2001, 410–417.

Morson BC, Vaughon, EG, Bussey HIR: Pelvic recurrence after excision of rectum for carcinoma. BMJ 1963; 2:13-17.

Morton DL, Chan AD: The concept of sentinel node localization: how it started. Semin Nucl Med 2000; 30:4–10.

Morton DL, Wen DR, Wong JH, et al: Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg 1992; 127:392–399.

Morton, D: Sentinel Node Mapping and an International Sentinel Node Society: Current Issues and Future Directions Annals of Surgical Oncology 2004; 11(Supplement): 137S-142S.

Nieweg OE, Estourgie SH: What is a Sentinel Node and What is a False-Negative Sentinel Node? Ann Surg Oncol 2004; 11(Supplement):169S-173S.

Nieweg OE, Tanis PJ, Kroon BBR: The Definition of a Sentinel Node Ann Surg Oncol 2001; 8:538-541.

O'Connell MJ, Mailliard JA, Kahn MJ: Controlled trial of fluorouracil and low-dose lecucovorin given for 6 months as postoperative adjuvant therapy for colon cancer. J Clin Oncol 1997; 15:246–250.

Oberg A, Stenling R, Tavelin B, Lindmark G: Are lymph node micrometastases of any clinical significance in Dukes stages A and B colorectal cancer? Dis Colon Rectum 1998; 41:1244–1249.

Ota D. M.: Is Intraoperative Lymph Node Mapping and Sentinel LymphNode Biopsy for Colorectal Carcinoma Necessary? Annals of Surgical Oncology Ann Surg Oncol. 2000 Mar;7(2):82-4

Ota D. M: Is Intraoperative Lymph Node Mapping and Sentinel Lymph Node Biopsy for Colorectal Carcinoma Necessary? Annals of Surgical Oncology, 7:82–84.

Palma RT, Waisberg J, Bromberg SH, Simao AB, Godoy AC: Micrometastasis in regional lymph nodes of extirpated colorectal carcinoma: immunohistochemical study using anti-cytokeratin antibodies AE1/AE3. Colorectal Dis 2003; 5:164-168.

Paramo JC, Summerall J, Poppiti R, Mesko ThW: Validation of Sentinel Node Mapping in Patients With Colon Cancer Annals of Surgical Oncology 2002; 9:550-554.

Paramo JC, Summerall J, Wilson Ch, Cabral A, Willis I, Wodnicki H, Poppiti R, Mesko Th W: Intraoperative sentinel lymph node mapping in patients with colon cancer The American Journal of Surgery 2001; 182:40–43.

Patten LC, Berger DH, Rodriguez-Bigas M, Mansfield P, Delpassand Eb, Cleary KR, Fagan ShP, Curley StA, Hunt KK, Feig BW: A Prospective Evaluation of Radiocolloid and Immunohistochemical Staining in Colon Carcinoma Lymphatic Mapping Cancer 2004; 100:2104-2109.

Philips RKS, Hittinger R, Blesovsky L: Large bowel cancer: Surgical pathology and its relationship to survival. Br J Surg 1984; 71:604–610.

Pietra N, Sarli L et al: Role of follow-up in management of local recurrence of colorectal cancer. Dis. Colon Rectum,

Prandi, M. et al. Prognostic evaluation of stage B colon cancer patients is improved by an adequate lymphadenectomy: results of a secondary analysis of a large scale adjuvant trial. – Ann Surg, 235, 2002, 4, 458–463.

R.A.E.M.: The feasibility and reliability of sentinel node mapping in colorectal cancer EJSO 2005; 31:854–862.

Rodriguez-Bigas MA, Maamoun S, Weber TK, Penetrante RB, Blumenson LE, Petrelli NJ: Clinical significance of colorectal cancer: metastases in lymph nodes 5 mm in size. Ann Surg Oncol 1996; 3:124–130.

Saha S, Bilchik A, Wiese D, Espinosa M, Badin J, Ganatra BK, Desai D, Kaushal S, Singh T, Arora M: Ultrastaging of Colorectal Cancer by Sentinel Lymph Node Mapping Technique—A Multicenter Trial. Ann Surg Oncol 2001; 8(Supplement):94S-98S.

Saha S, Dan AG, Bilchik A, Kitagawa Schochet, E, Choudhri Sh, Saha L, Wiese D, Morton D, Kitajima M: Historical Review of Lymphatic Mapping in Gastrointestinal Malignancies Ann Surg Oncol 2004; 11(Supplement):245S-249S.

Saha S, Ganatra BK, Gauthier J: Localization of sentinel lymph node in colon cancer. A feasibility study. SSO 50th Annual Cancer Symposium 1997; 80:54.

Saha S, Monson KM, Bilchik A, Beutler Th, Dan AG, Schochet E, Wiese D, Kaushal S, Ganatra B, Desai D: Comparative Analysis of Nodal Upstaging Between Colon and Rectal Cancers by Sentinel Lymph Node Mapping: A Prospective Trial The American Society of Colon and Rectal Surgeons 200410.1007/s10350-004-0661-5.

Saha S, Nora D, Wong JH, Weise D: Sentinel lymph node mapping in colorectal cancer—a review. Surg Clin North Am 2000; 80:1811–1819.

Saha S, Weise D, Badin J, et al: Technical details of sentinel lymph node mapping in colorectal cancer and its impact on staging. Ann Surg Oncol 2000; 7:120–124.

Schlag PM, Bembenek A, Schulze T: Sentinel node biopsy in gastrointestinal-tract cancer European Journal of Cancer 2004; 40:2022–2032.

Schrag, D. et al. Adjuvant chemotherapy use for Medicare beneficiaries with stage II colon cancer. – J Clin Oncol, 20, 2002, 3999–4005.

Sobin LH, Wittekind C (eds): TNM Classification of Malignant Tumors (ed 6). New York: Wiley, 2002.

Taback B, Bilchik AJ, Saha S, Nakayama T, Wiese DA, Turner RR, Kuo CT, Hoon DS. Peptide nucleic acid clamp PCR: a novel K-ras mutation detection assay for colorectal cancer micrometastases in lymph nodes. Int J Cancer. 2004; 111:409-414.

Tang R, Wang JY, Chen JS: Survival impact of lymph node metastasis in TNM stage III carcinoma of the colon and rectum. J Am Coll Surg 1995; 180:705-712.

Tanis PJ, Nieweg OE, Hart A.A. M and Kroon B.B. R: The Illusion of the Learning Phase for Lymphatic Mapping Annals of Surgical Oncology 2002; 9:142-147.

Thompson JF, Uren RF: What is a 'sentinel' lymph node? Eur J Surg Oncol 2000; 26:103–104.

Trocha SD, Nora DT, Saha SS, Morton DL, Wiese D, Bilchik AJ: Combination probe and dye-directed lymphatic mapping detects micrometastases in early colorectal cancer. J Gastrointest Surg. 2003; 7:340-5; discussion 345-6.

Tsioulias G, Wood T, Morton D: Lymphatic mapping and focused analysis of sentinel lymph nodes upstage gastrointestinal neoplasms. Arch Surg 2000; 135:926–932.

Tsioulias GJ, Wood TF, Spirt M, Morton DL, Bilchik AJ: A novel lymphatic mapping technique to improve localization and staging of early colon cancer during laparoscopic colectomy. Am Surg. 2002; 68(7):561-565.

Tsopelas, C., R. Sutton. Why certain dyes are useful for localizing the sentinel lymph node. – J Nucl Med, 43, 2002, 1377–1382.

Williams NS: Surgical Treatment in Rectal Cancer. In: Surgery of the Anus, rectum and colon, WB Saunders 1993, 939.

Wolmark N, Fisher B, Wieand HS: The prognostic value of the modifications of the Dukes' C class of colorectal cancer. An analysis of the NSABP clinical trials. Ann Surg 1986; 203:115–122.

Wong JH, Bowles BJ, Bueno R, Shimizu D: Impact of the number of negative nodes on disease free survival in colorectal cancer patients. Dis Colon Rectum 2002; 45: 1341–1348.

Wood TF, Nora DT, Morton DL, Turner RR, Rangel D, Hutchinson W, Bilchik AJ: One hundred consecutive cases of sentinel lymph node mapping in early colorectal carcinoma: detection of missed micrometastases. J Gastrointest Surg. 2002; 6:322-329; discussion 229-30.

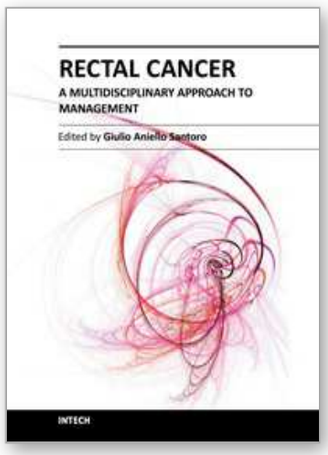
Wood TF, Tsioulias GJ, Morton DL: Focused examination of sentinel lymph nodes upstages early colorectal carcinoma. Am Surg 2001; 66:998-1003.

Wood Thomas F, Saha S, Morton Donald L, Tsioulias George J., Rangel Decio, Hutchinson William Jr., Foshag Leland J., Bilchik Anton J: Validation of Lymphatic Mapping in Colorectal Cancer: In Vivo, Ex Vivo, and Laparoscopic Techniques. Ann Surg Oncol 2001; 8:150-157.

Wood, T. F. et al. Lymphatic mapping improves staging during laparoscopic colectomy for cancer. – Surg Endosc, 15, 2001, 715–719.

Yamamoto, Y. et al. Clinicopathological characteristics of skipping lymph node metastases in patients with colorectal cancer. – Jpn J Clin Oncol, 28, 1998, 6, 378–382.

Yasuda K, Adachi Y, Shiraishi N, Yamaguchi K, Hirabayashi Y, Kitano S: Pattern of lymph node micrometastasis and prognosis of patients with colorectal cancer. Ann Surg Oncol 2001; 8:300–304. Year Book, 1997, 118-47.



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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.

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