SENTINEL LYMPH NODE MAPPING IN PATIENTS WITH COLORECTAL CANCER

Ignatov V., N. Kolev, K. Ivanov, A. Tonev, D. Hristov, I. Minev,
T. Temelkov, R. Madjov*

*Department of General and Operative Surgery, *Department of Surgery, University Hospital
"St. Marina", Varna, Bulgaria*

Reviewed by: Assoc. Prof. R. Radev, MD, PhD

ABSTRACT

BACKGROUND/AIMS: In about 1/3 of the patients with colorectal cancer without metastases which have been radically operated recurrences are observed and these patients die from cancer. This requires improvement of the surgical methods radicality as well as a more accurate determination of the indications for adjuvant chemotherapy administration. The introduction of a method for evaluating the degree of the metastases in colorectal cancer would highlight these issues. To this purpose we apply the method of sentinel mapping. **METHODOLOGY:** For a period of one year we performed intraoperative sentinel mapping on 103 patients who had been operated for colon or rectal cancer. We used the dying method with Patent Blue V. An algorithm was worked out for sentinel mapping in colorectal cancer. **RESULTS:** We achieved 100% performance success and 97% sensitivity. We increased the volume of the surgical intervention in 100% of the patients and elevated the clinical stage of 20% of the patients in Ist and IInd stage by means of ultrastaging with immunohistochemistry. **CONCLUSIONS:** We conclude that sentinel lymph nodes mapping in colorectal cancer is a diagnostic method which is convenient for the surgeons allowing them for an individualized approach toward each patient.

Keywords: colorectal cancer, sentinel lymph node, staging, intraoperative dye mapping, upstaging

INTRODUCTION

A sentinel lymph node (SLN) is defined as the first lymph node/nodes receiving direct drainage from the tumor (1-7; 9-19;21-27,40,42,43,45) and consequently possessing the greatest metastatic potential. (8-17;20;26,27,40,42,43,45) Sentinel 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?

The most important factor affecting the outcomes of the surgical treatment and the survival rate is the presence of metastases. (10-13,21,28-38,40,43,45-48,56,57,58) The presence of lymph metastases places the patients from Ist and IInd stage into IIIrd stage which significantly deteriorates the prognosis and the survival rate (TNM). (10,12,21,36,39,59) The atypical lymph drainage occurs in about 8-14% of the patients. (1,9,10,21,41,44,45) The failure to detect it is one of the reasons for the recurrences due to the incorrect staging and adjuvant therapy administration. (22,45,85) It results from specific anatomical features or lymph flow.

The atypical lymph metastases is observed:

- in terms of the localization level of the metastatic lymph nodes (jumping or "skip" metastases)

- in affecting the atypical lymph basin (aberrant lymph drainage) for the given localization of the primary tumor.

In CRC the size of the resection and the lymph dissection are determined by the tumor localization and they have been standardized to a great extent. (96)

The metastatic lymph nodes in the presence of aberrant lymph drainage can be found beyond the limits of the standard lymph dissection size. In these cases the radicality of the surgery requires the extension of the lymph dissection size. (22,67,73) 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%, the lymph nodes are detected with the size over 5 mm, the metastatic potential being determined based on the increased size. (74) According to literary data 50 – 78% of the metastatic lymph nodes are sized under 5 mm (1,93,97,98)

This is a reason for the unsatisfactory possibilities of the preoperative and intraoperative diagnostics of the lymph metastases. Lymph mapping with dye visualizes the lymph vessels and the sentinel LN very well in the surgical field even if they are very small in size less than 5 mm and are otherwise undetectable. (1,93,97,98)

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. The visualization of a blue vessel is a guarantee that the “true” SLN will be removed and investigated. (Figure 1-4.)

Figure 1. SLN in the mesocolon

2. SLN in the mesorectum

Figure 3. A tiny SLN

Figure 4. We applied the method of the sentinel mapping in five patients with CRC who had been operated laparoscopically. These patients were not included in this study.

Recurrences are observed in 20 – 40% of the operated patients in the Ist and IInd stage. (85,93,95) In half of the patients with recurrences it was established that they were due to metastatic lymph nodes which have not been detected and removed during the surgery. (78-84) For these patients the following was true:

- adequate lymph dissection not performed;
- the disease has not been correctly staged;
- no indications have been given for adjuvant chemotherapy administration (22,91)

According to the TNM system the micrometastases are designated with the index (mi) and their presence places the disease in IIIrd stage, determining the relevant treatment and prognosis. (89, 90)

For the assessment of the lymph status it is obligatory to investigate morphologically at least 12 lymph nodes. (85,93) 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 indicating the administration of adjuvant therapy which would improve the prognosis in these “problem” 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 (49-52, 86,87), others aren't support this suggestion. (53-55,88)

If the all LNs are to be investigated, the methods for micrometastases detection are costly, labor and time consuming. (85,67,89)

METHODOLOGY

We performed intraoperative sentinel mapping for a period of one year (2004-05) in 103 patients operated for colon or

rectal cancer. An algorithm was worked out for sentinel mapping in colorectal cancer. (Figure 7.) The dying method with Patent Blue V was used.

Figure 7. MORPHOLOGICAL INVESTIGATIONS

The SLN tagged by the surgeon are sent to the morphological laboratory together with the resection.

- Routine processing to a paraffin block
- 10 resections in every 20-25 µm
- Immunohistochemistry with cytokeratin 20 per 1 resection (usually the 5th one)
- The remaining resections together with the preparations from the case are dyed with Hematoxylin – Eosin

Micrometastases - a focus of tumor cells sized under 2 mm or a focus detected only by means of immunohistochemistry.

Indications:

- 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.

Contraindications:

- Presence of distant metastases;
- Preceding local excision of the primary tumor;
- Metachronic 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 surgical interventions affecting the anatomy of the lymph basin;
- Complicated colorectal cancer (emergency operation);
- Class after ASA IV–V.

After the laparotomy and the abdominal cavity exploration, in the absence of distant metastases and lack of 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 submucosally we applied 0,5-2 cc Patent Blue V on 2 to 4 locations peritumorally.

Since in right colon cancer the intraoperative colonoscopy up to the caecum is technically difficult to perform and is time-consuming, in these tumor localizations we injected the dye subserously by means of a needle and a syringe 0,5-2 cc on 2 to 4 locations peritumorally.

In 1 to 10 minutes' time the blue-dyed lymph node (s) are 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 ligations. It is important that the procedure is performed technically accurately and precisely timed since the dye gradually colours the whole lymph basin and the SLN can lose their colour with time.

According to the tumor localization we perform thorough exploration of the regional lymph basin, the whole mesacolon, the stem of the mesenterial vessels and paraaortally, the obturated fossae and along the course of the iliac vessels in order to detect SLN and the presence of atypical lymph drainage.

RESULTS

Patients' distribution is shown on Table 1.

Table 1.

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

The mean number of the lymph nodes in the resection preparation is 14.7 in cancer of the colon vs. 13.2 in cancer of the rectum.

Table 2.

	Colon cancer	Rectal cancer
	n (%)	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)

The mean number of SLN in cancer of the colon is 1.9 vs. 1.6 in cancer of the rectum.

One, two, three and four SLN were detected in 40%, 39%, 19% и 2% of the patients, respectively.

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 2.)

False negative results were reported when in the presence of metastases, they were not detected in the SLN. We observed false negative results in 3 patients. All of them had large T4 tumors infiltrating in adjacent organs. Therefore, we suggest that such patients are relatively contraindicated for sentinel mapping. We performed mapping in such patients only in the first 24 cases.

In most cases the SLN were located in proximity to the primary tumor. 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.

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 a. mesenterica inferior, which necessitated its high ligation with additional dissection around the root.
- In the remaining 4 we detected SLN in the left or right iliac region and we performed lateral lymph node dissection.

In the rest of the cases when no SLN or enlarged lymph nodes were detected in the lateral ligaments, obturated fossae or parailiacally, we did not consider appropriate to perform lateral lymph node dissection in patients with rectal cancer.

Figure 5.

On Figure 5, it is shown the visualisation of direct lymph drainage from cancer of the rectum T2 to SLN from the IIIrd level in the root of *arteria mesenterica inferior*. 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, e.g. skip metastasing.

On Figure 6, it is shown a case with rectal cancer T3, in whom SLN is positive in the right iliac fossa

The relation between the T stage of the primary tumor and the presence of lymph metastases after sentinel mapping is shown on Table 3.

Table 3.

	<i>T_{x,1,2}</i>	<i>T₃</i>	<i>T₄</i>
	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>
Patients	48 (47)	44 (43)	11 (10)
Presence of lymph node metastases	9 (19)	40 (90)	11 (100)
Micrometastases	7 (15)	3 (7)	0 (0)

DISCUSSION

- The sentinel mapping in CRC facilitates the detection of atypical lymph drainage of the primary tumor
- Since the SLN have the highest metastatic potential, they should be included in the resection preparation through adequate extension of the size of the lymph dissection, when necessary.
- The detection of MM in SLN reveals the exact status of the whole lymph basin, the correct staging of the disease and serves as a prognostic factor facilitating the appropriate treatment.
- By means of this method the lymph nodes with greatest metastatic potential can be detected, removed and investigated even if they are of very tiny sizes of up to 2-3 mm.
- MM are more frequently detected in the lower T-stage of the primary tumor.

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

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