

## COMPARATIVE ANALYSIS OF ENDOSCOPICALLY SUBMUCOSAL VS. OPEN SURGERY SUBSerosal APPLICATION PATENT BLUE V – INTRAOPERATIVE METHOD FOR DETECTION OF LYMPH NODE METASTASIS IN PATIENTS WITH COLORECTAL CANCER

Valentin Ignatov, Krasimir Ivanov, Rosen Madjov\*, Temelko Temelkov, Nikola Kolev, D. Hristov, Anton Tonev

*Department of General and Operative Surgery*

*\*Department of Hepato-Biliary Surgery*

*University Hospital "St. Marina"*

### ABSTRACT:

**Introduction:** The lymphatic status is acknowledged as the most important prognostic factor in patients with colorectal cancer. In our clinic, the intraoperative sentinel lymph node mapping with Patent Blue V is routine method of choice for better staging of lymph node status and achieves an adequate extent of surgical procedure in patients with colorectal cancer. **Aim:** To compare the results from application of methods of intraoperative endoscopic submucosal and open surgery subserosal sentinel lymph node mapping in patients with colorectal cancer. **Results:** The study was undergone in 136 patients with diagnosis of colorectal cancer and sentinel lymph node mapping. An analysis and comparison is done and the results of the two methods were compared. Our data show that the sensitivity is comparable and is respectively 97% and 100% and the methods are reliable enough. **Conclusion:** Endoscopic submucosal application of the dye marker is the only eligible method for the subperitoneal localization of rectal cancer. The surgical approach and the extent of the lymph dissection have to be conformable to the status of lymph node basin, staged with the help of objective diagnostic tool, such as intraoperative sentinel lymph node mapping. This leads to increasing level of curative surgical treatment in cases of colorectal cancer.

**Key words:** Sentinel lymph node mapping, endoscopy

In the diagnostics, staging and treatment of the patients with colorectal cancer are included specialists from many different areas of medicine: surgeons,

oncologists, specialists in imaging diagnostics, radiotherapists, pathomorphologists, genetists and etc. The surgeon is the main force in those processes. The method of choice is based upon complex of criteria and data about the stage of differentiation, a presence of extra cellular or intracellular mucous secreting, the stage of tumor cell invasion in the lymphatics, arterioles, venules and in perineural space, the angiogenesis of the tumor, the mitotic index, the grade of lymphocytic infiltration in the tumor and the count of T-lymphocytes in the peripheral blood. The molecular and genetic prognostic factors from the primary tumor and metastatic origin, as well as morphological exploration and the ultrastaging of oncological disease are main fields of investigation.

The surgical treatment is the base of complex medical treatment, which aims to cure definitely the patients with colorectal cancer. Good results from the curative process are obtained by modeling an individual protocol to every single patient which conformable to the present medical consensuses.

The quality of a surgical treatment is defined as well as the choice of appropriate operative approach, but also from the tumor characteristics, the vessels that uptake the lymph flow, and the modalities for preoperative and intraoperative staging.

Undergoing an operation in adequate extent is a premise for precise morphological exploration of the oncological disease and defines the approach in the postoperative treatment. The curative procedures gain the best effect when the patient is diagnosed in I-st or II-nd clinical stage of the oncological disease, before the presence of tumor metastasis.

The lymph node status is the most important

prognostic factor for patients with colorectal cancer. The exact preoperative staging of the lymph node status is unsettled problem because of the sensitive methods for preoperative diagnosis – PET, CT, MRI and radioimmuno-guided detection cannot be used as routine methods in every patient. The clinical examination and intraoperative exploration are not so sensitive and specific methods and could only to led the surgeon in certain direction. There aren't established special intraoperative diagnostic methods for the lymphatic status, in accordance with the surgeon can change his operative behavior for obtaining a radical treatment. The standard histomorphological intraoperative examination is low-sensitive and can not to define the presence or absence of micrometastasis in lymph nodes. One of the present problems is the inability to exact determination of the lymph node status during the standard morphological examination of resected specimen. The morphologists can not obtain enough lymph nodes and the ultra staging techniques are not introduced in the routine practice for the lymph nodes with highest metastatic potential – the sentinel lymph nodes.

The consequences of unprecised examination of lymph node basin lead to developing of recurrence in 1/3 of the patients underwent curative resections for non – metastatic colorectal cancer.

The first report of SLNM in colorectal cancer was a feasibility study presented in 1997 at the Society of Surgical Oncology's 50th Annual Cancer Symposium in Chicago. 1 This series of 10 patients was followed by a series of 56 patients presented at the 17th International Cancer Congress in Brazil in 1998. 2 This report confirmed the high (98%) feasibility of the technique and demonstrated its high (95%) degree of accuracy for predicting the status of the nodal basin. In 1999, Joosten et al. 3 in the Netherlands published a report of SLNM in 50 patients with colorectal cancer. On the basis of a feasibility rate of 70% and a false-negative rate of 60%, they concluded that SLNM was not a reliable method of staging colorectal cancer. However, their injection method and especially the timing of pathological examination differed from those described by us. Their results underscore the importance of adhering to strict technical details of the procedure and following a specific protocol for handling and processing of the specimen by the pathologist. A subsequent publication in the Annals of Surgical Oncology 4 outlined the technical details associated with excellent feasibility (99%) and accuracy (96%) rates as reported in our original studies.

In December 2000, a review by Saha et al. 5 included coauthor Wong's technique of ex vivo lymphatic mapping in colorectal cancer. Kitagawa's group 6 focused on the use of SLNM in esophageal, gastric, and colorectal

cancers and for the first time described the use of radiolabeled tracers and a hand-held gamma probe for successful lymphatic mapping in colorectal cancer. Thorn 7 in 2000 and Merrie et al. 8 in 2001 combined blue dye and radioactive tracer for mapping, as previously described in breast and melanoma. The success rates of dual-agent mapping were 100% 7 and 88%. 8 In 2001, Wood et al. 9 reported a series of 75 patients who underwent lymphatic mapping by in vivo, ex vivo and laparoscopic techniques. 9 The overall success rate of mapping was 96%, and the rate of occult micrometastasis was 17%.

The first large series of ex vivo SLNM in colon and rectal cancers was published by Wong et al. 10 in 2001. Laparoscopic SLNM has been attempted at a few centers for colorectal and gastric cancers, with high success rates 9, 11 comparable to those associated with mapping performed during open laparotomy. Also in 2001, Bilchik et al. 12 first reported molecular profiling of colon cancer with use of the RT-PCR technique for multiple markers in 40 patients. This study showed a high correlation between the expression of p53, beta-HCG, c-Met, and uMAGE in a primary tumor and the presence of micrometastases in regional lymph nodes.

**Aim:** To compare the results from application of methods of intraoperative endoscopic submucosal and open surgery subserosal sentinel lymph node mapping in patients with colorectal cancer.

#### **MATERIAL:**

We made a prospective study for a period of 2004 – 2006, in 242 patients, operated for colorectal cancer. The investigation was conduct in the clinic of general and operative surgery in the University Hospital "St. Marina", Varna.

In 136 of the cases we applied the method of intra-operative sentinel lymph node mapping.

#### **METHODS:**

We applied the next modes of lymphatic mapping:

1. Intraoperative submucosal sentinel lymph node mapping in 114 patients with colon and rectum cancer.
2. Intraoperative subserosal sentinel lymph node mapping in 22 patients with colon cancer.

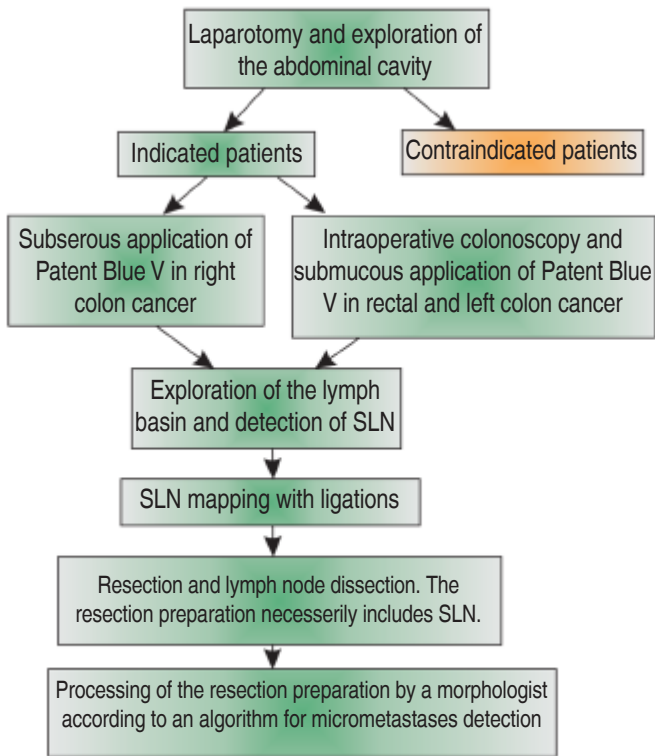
#### **STATISTICS:**

In the statistical processing of our data we used the following methods:

1. Estimating the indexes for the relative share.
2. Estimating of the average values.
3. Tables
4. Charts

We developed and suggest the following algorithm for intraoperative sentinel lymph node mapping in patients of colorectal cancer.

**Algorithm for sentinel mapping in colorectal cancer**



**Fig. 1.**



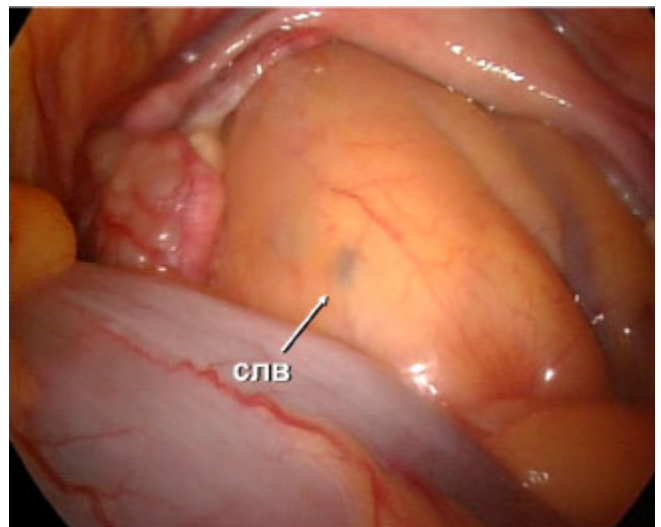
**Fig. 2.**



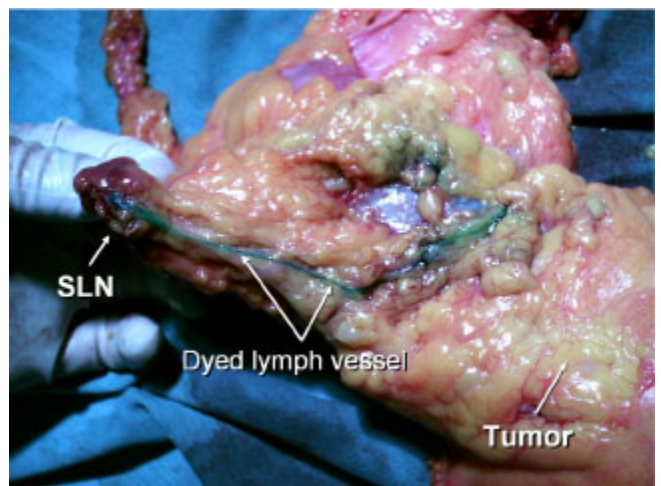
**Fig. 3.**



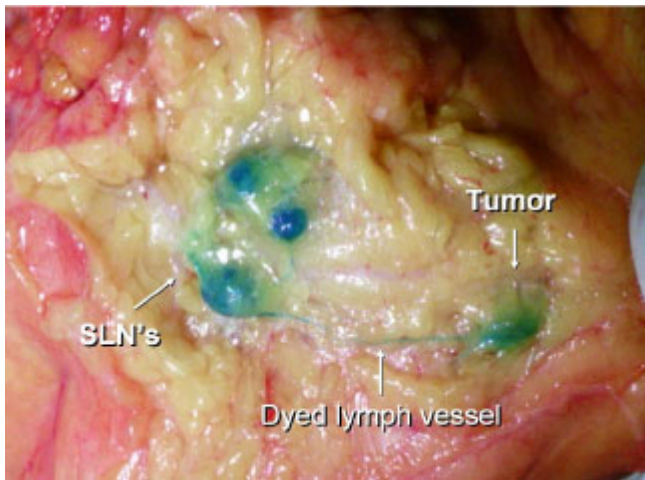
**Fig. 4.**



**Fig. 5.**



**Fig. 6.**



**Fig. 7.**

**RESULTS:**

We present the distribution of the patients in localization, sex and age in the following

**Fig 8. Distribution of the patients**

Localisation	Colon cancer	Rectal cancer	Total
Groups of patients			
Patients (n)	65	71	<b>136</b>
Male (n)	30	33	<b>63</b>
Female (n)	35	38	<b>73</b>
Average age (years)	63	66	<b>65</b>

**Fig. 11** Summarized results from the application of intraoperative sentinel lymph node mapping in cases of colorectal cancer.

Cases	Colon cancer		Rectal cancer		Total	
	n	%	n	%	n	%
Patients	65	48	71	52	<b>136</b>	<b>100</b>
Successful SLNM	65	100	71	100	<b>136</b>	<b>100</b>
Presence of LN metastases	34	52	38	54	<b>72</b>	<b>53</b>
False-negative	-	-	3	4	<b>3</b>	<b>2</b>
Metastases only in SLNs	8	12	9	13	<b>17</b>	<b>13</b>
Founded micrometastases	6	9	8	11	<b>14</b>	<b>10</b>

**Fig. 9.** Average numbers of lymph nodes and sentinel lymph nodes in the resected specimen.

Localisation	Colon cancer	Rectal cancer
Lymph nodes		
Lymph nodes (n)	15,2	13,6
Sentinel LN (n)	1,9	1,6

**Fig. 10.** Distribution of the patients in dependence of founded sentinel lymph nodes

Patients (n)	n	%
Lymph Nodes		
1	54	40
2	53	39
3	26	19
4	3	2

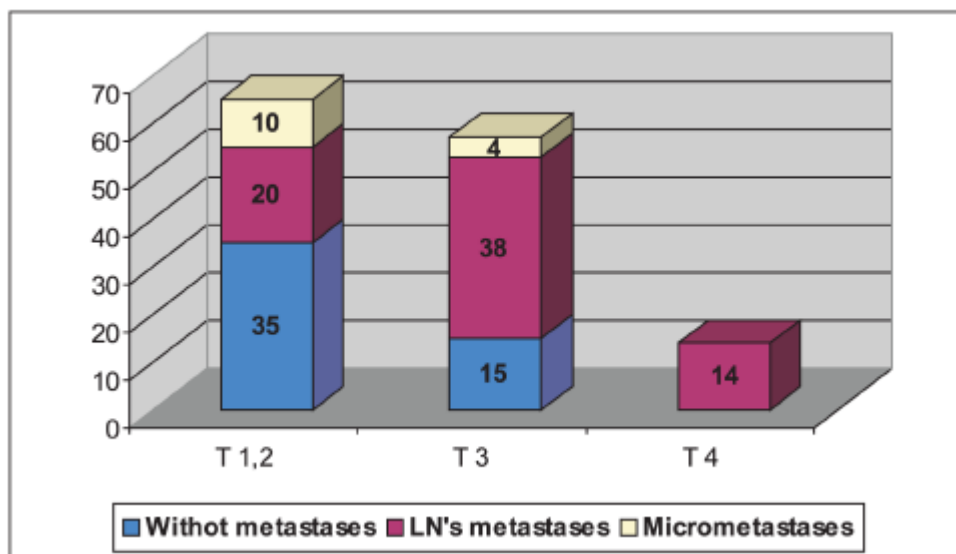
We found metastases and micrometastases in 57% (112 of 196) of the SLNs, compared with 9% (198 of 2208) in non-SLNs

In case of absence of metastases in SLNs, the possibility for presence of non-SLNs is only 0.6% (4 of 658)

**Fig. 12** Ratio between T-stage of the primary tumor and the presence of lymph node metastases after application of SLNM

Metastases in LN	T1,2		T3		T4	
	n	%	n	%	n	%
Petients	65	48	57	42	14	10
Presence of LN's metastases	20	31	38	66	14	100
Micrometastases	10	15	4	7	-	-

**Fig. 13.** Ratio between T-stage of the primary tumor and the presence of lymph node metastases after application of SLNM



From the group of 136 patients, 65 (48%) of them were with T<sub>1,2</sub> – stage of the primary tumor; 57 (42%) of them were with T<sub>3</sub> – stage of the primary tumor; 14 (10%) of them were with T<sub>4</sub> – stage of the primary tumor. It is underlined that from the T<sub>1,2</sub> group of 65 patients, 20 (31%) of them were with presence of LN's metastases and 10 (15%) of them were with micrometases. From the T<sub>3</sub> group of 57 patients, 38 (66%) of them were with presence of LN's metastases and 4 (7%) of them were with micrometases. From the T<sub>4</sub> group of 14 patients, 14 (100%) of them were with presence of LN's metastases and 0 (0%) of them were with micrometases. It is demonstrated that the micrometastases were founded more frequently in cases of lower T-stage of the primary tumor.

#### CONCLUSION:

1. Endoscopical submucosal application of lymph node dye is the only appropriate method for intraoperative sentinel lymph node mapping in the cases with subperitoneal localisations of the rectal cancer.
2. The analysis of the results from the application of intraoperative endoscopic submucosal sentinel lymph node mapping and intraoperative subserosal sentinel lymph node mapping shows that the two methods are comparable highly sensitive and reliable, respectively 97% and 100%.

---

## REFERENCES:

1. Saha S, Ganatra BK, Gauthier J, et al. Localization of sentinel lymph node in colon cancer. A feasibility study. SSO 50th Annual Cancer Symposium 1997; 80: 54.
2. Saha S, Espinosa M, Wiese D, et al. Accurate staging of colorectal cancer by sentinel lymph node mapping. A prospective study. Proceedings of the 17th International Cancer Congress 1998;2:1005–11.
3. Joosten JJ, Strobbe LJ, Wauters CA, et al. Intraoperative lymphatic mapping and the sentinel node concept in colorectal carcinoma. *Br J Surg* 1999; 86: 482–6.
4. Saha S, Wiese 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: 120–4.
5. Saha S, Nora D, Wong JH, et al. Sentinel lymph node mapping in colorectal cancer—a review. *Surg Clin Of N Am* 2000; 80: 1811–9.
6. Kitagawa Y, Fugii H, Mukai M, et al. The role of the sentinel lymph node in gastrointestinal cancer. *Surg Clin North Am* 2000; 80: 1799–809.
7. Thorn M. Lymphatic mapping and sentinel node biopsy: is the method applicable to patients with colorectal and gastric cancer? *Eur J Surg* 2000; 166: 755–8.
8. Merrie AE, van Rij AM, Phillips LV, et al. Diagnostic use of the sentinel node in colon cancer. *Dis Colon Rectum* 2001; 44: 410–7.
9. Wood TF, Saha S, Morton DL, et al. Validation of lymphatic mapping in colorectal cancer: in vivo, ex vivo, and laparoscopic techniques. *Ann Surg Oncol* 2001; 8: 150–7.
10. Wong JH, Steineman S, Calderia C, et al. Ex vivo sentinel node mapping in carcinoma of the colon and rectum. *Ann Surg* 2001; 233: 515–21.
11. Kitagawa Y, Ohgami M, Fujii H, et al. Laparoscopic detection of sentinel lymph nodes in gastrointestinal cancer: a novel and minimally invasive approach. *Ann Surg Oncol* 2001; 8: 86–9S.
12. Bilchik AJ, Saha S, Wiese D, et al. Molecular staging of early colon cancer on the basis of sentinel node analysis: a multicenter phase II trial. *J Clin Oncol* 2001; 19: 1128–36.

### Address for correspondence:

D-r Anton Tonev,  
MBAL “St. Marina”, Department of General and Operative Surgery  
1, Hr. Smirnenski str., 9000 Varna, Bulgaria  
phone: +359/885 100 621,  
E-mail: teraton@abv.bg;