



Sentinel Lymph Node Detection in Colorectal Cancer – First Experience

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Abstract

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BACKGROUND: Colorectal cancer (CRC) is the second commonest cancer in women, the third in men, being the fourth commonest cause of cancer death. The most important factor for prognosis and staging in CRC patients is the status of the regional lymph nodes (LN).

AIM: To implement the method for sentinel lymph node (SLN) detection in CRC patients using radiocolloid, and test its detection rate, sensitivity, accuracy, negative predictive value and the possibility for upstaging.

MATERIAL AND METHODS: The study included 40 CRC patients, age 63 ± 14 years, without LNs detected on CT or MRI. SLN detection was performed after endoscopically peri- and intratumoral injection of ^{99m}Tc-SENTISCINT. All patients underwent resection with systemic lymphadenectomy, and the SLNs were detected ex vivo. Pathohistology was performed to all resected LNs.

RESULTS: The identification rate was 95%, the accuracy of the procedure was 92.1%, the negative predictive value was 86.95%, the sensitivity was 83.3%, and the upstage was 22.5%.

CONCLUSION: Identification of SLNs in CRC patients with this method is possible and the detection rate, negative predictive value, accuracy and sensitivity are reliable. We expect to contribute in the upstaging of stage II CRC patients and the selection of appropriate oncology treatment protocols.

Introduction

Colorectal cancer (CRC), as of 2012, is classified as the second most common cause of cancer among women (9.2% of diagnoses) and the third most common among men (10.0% of diagnoses). Also, according to the WHO reports, it is the fourth most common cause of cancer death after lung, stomach and liver cancer. Globally more than 1 million people are diagnosed with CRC each year [1]. The incidence in our country, -according to the data published by the ministry of health, is 25.7/100.000 population, which results in 500-600 newly diagnosed cases per year. Unfortunately, 65-70% of them are in the high stage III with locoregional disease spread and lymph node metastases. The most important

factor for prognosis and staging in CRC patients is the status of the regional lymph nodes (LN) [2]. The 5-year survival rate in patients with loco regional LNs positive for metastases is 25-30% lower compared to patients with disease free LNs [3]. The presence of affected LNs determinates the disease stage and the possible adjuvant chemotherapy inclusion which, on the other hand, influences the rate of disease recurrence, 5-year disease free period and the overall survival rate. Thus, the appropriate staging and treatment of CRC patients decrease the recurrence rate by 40% and the mortality rate by 33% [4]. The staging of CRC patients is performed according to the TNM classification.

Stage I and II patients (No; Mo), according to the recommendations of the American Joint Committee on Cancer (AJCC), undergo only surgical

resection and lymphadenectomy and no adjuvant therapy is included [5, 6]. Stage III patients (N+), according to the recommendations of the AJCC, undergo surgical treatment and standard adjuvant chemo therapy, usually with 5-Fluorouracil [6].

Table 1: TNM classification of CRC

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2	N1/N1	M0
	T1	N2a	M0
IIIB	T3-T4a	N1/N1	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b

The most significant criteria according to which patients are classified into stage II or stage III is the affection of the LNs with metastatic deposits.

Table 2 – Stage II and Stage III characteristics for CRC patients

IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2	N1/N1	M0
	T1	N2a	M0

Chemotherapy is not considered to be standard of care in stage II patients since it proves no benefits for LN negative disease and also inflicts multiple adverse effects. It has to be taken into consideration, however, that this recommendation is only valid when the CRC staging is precise and accurate. Unfortunately, 25-30% of the stage II patients experience loco-regional disease recurrence or metastatic disease [3]. The SEER study (Surveillance, Epidemiology and End Results) presents a dilemma about the survival rate between stage IIB/C and stage IIIA patients. The 5-year survival rate in patient's stage IIB/C is 72.2%, and in the stage, IIIA is 83.4% due to the adjuvant therapy included in stage III [7].

This could be either due to inappropriate or inaccurate staging procedures, a low number of harvested LNs or aberrant lymphatic drainage which leads to final downstaging of this subgroup of patients. The result is the exclusion of adjuvant chemotherapy in otherwise LN positive patients and thus worse

overall survival rate and 5-year disease free period. The standard nodal staging technique is based on the histopathological evaluation on one or two LN sections with hematoxylin and eosin (H&E) staining, and the risk probability of missing metastases with this procedure is relatively high [8]. Introduction of multisection LN analysis, immunohistochemistry (ICH) and molecular reverse transcription polymerase chain reaction (RT-PCR) increases the accuracy of staging, but at the same time is expensive, time-consuming and impractical to be performed on all LNs.

The sentinel lymph node (SLN) is considered to be the first barrier of metastatic disease. SLN biopsy has proven to be reliable in predicting the nodal status for specific subsets of melanoma and breast cancer patients [9-11]. The concept of SLN mapping in CRC is a prediction of the nodal status and increase the accuracy of nodal staging by selecting one or several LNs for detailed histopathological analysis, especially in the high-risk stage II patients, and at the same time, no reduction or alteration in the surgical procedure [12].

This study aimed to implement the method for SLN detection in CRC patients using radiocolloid and test its detection rate, sensitivity, accuracy, negative predictive value and the possibility for upstaging.

Material and Methods

The study was performed as a controlled prospective trial at the University Clinic for Digestive surgery-Skopje, the Institute for Nuclear Medicine-Skopje, the University Clinic for Gastroenterohepatology-Skopje and the Institute for Pathology-Skopje, in the period January 2013 - January 2015. Eighty CRC patients (40 + 40) confirmed on endoscopy (colonoscopy) and biopsy, age 63 ± 14 years, preoperatively classified as stage I or II, without LNs detected on CT or MRI were included. All patients (pts) were familiarized with the procedure and written informed consent was obtained. Exclusion criteria were: stage III or IV pts with LN metastases (N+) or distant metastases (M+), preoperative adjuvant chemotherapy and previous surgical resection. All surgical interventions were performed by one surgeon, all endoscopies by one endoscopist, all scintigraphy findings interpreted by one nuclear medicine specialist and all pathophysiology analysis conducted by one pathologist, all of the above mentioned with at least ten years experience in the appropriate field of expertise.

SLN detection was performed in 40 CRC patients, and it included peri endoscopically- and intratumoral injection (24 h prior to the surgical

procedure) of 4 mCi/4 ml (150 MBq) 99m-Techne-tium-SENTISCINT, subdivided into 4 separate doses (each dose of 1 mCi/1 ml (37 MBq) respectively per injection site) and injected into 4 separate locations through an endoscopic needle. Three of the injections were peritumoral, submucosa, and were injected clockwise at 120 circle degrees around a tumour, and one injection was intratumoral. All endoscopic procedures were video monitored and filmed. In case of intravascular application, the SLN detection procedure was considered unsuccessful. Because radiotracers were used, all endoscopic applications were performed according to the ALARA principles (best diagnostic presentation with the minimum radiation burden to the patient).

SENTISCINT is a MEDI-RADIOPHARMA LTD Hungary commercial kit, composed of human serum albumin nano-sized colloid particles with a diameter of 100–600 nm in the form of sterile lyophilized powder. Quality control was performed with ascendant paper chromatography.

Postinjection, we performed dynamic acquisition in duration of 30 minutes (30 frames, 60 seconds per frame, at 256 x 256 x 16 matrix), followed by 10 minutes static acquisitions in AP position at 1h, 2 h, 4 h and 24 h post injection (600 seconds per acquisition at 256 x 256 x 16 matrix) using the dual headed gamma camera Mediso DHV Nucline Spirit. We used cobalt source Featherlite Co57 flood source MED 3709 for body contour drawing, and the SLN detection was performed with gamma detection probe EUROPROBE SYSTEM CE 0459.

The other 40 pts were treated conventionally (surgically) without SLN detection and were considered as a control group for 5-year survival rate and disease recurrence comparison between the two groups. All 80 CRC patients (40 pts with SLN detection and 40 pts without SLN detection) underwent the same standard surgical technique (total mesocolic or mesorectal excision) which included resection with systemic lymphadenectomy. Promptly after resection, ex vivo, the gamma probe was used to detect the SLN or SLNs, and anatomic diagram was included to detect possible aberrant lymph node drainage.

Pathohistology (HE and immunohistochemistry) was performed to all of the resected lymph nodes, including the SLN. First HE staining was performed (multi-slice), and if the LN was negative, immunohistochemistry was performed with 3 Ab (CK20, CEA and EMA) using the technique Avidin Biotin Immunoperoxidase complex and EnVision (Dako, Denmark) visualization system. To avoid false positive results (reticulum cells or plasma cells), positive cytokeratin cells were considered as tumour cells only when they presented cytomorphological characteristics of a malignant cell. All tumour cell deposits of 2 mm and larger were considered as metastasis, deposits of 0.2 - 2 mm were considered

as micrometastases (MM), and clusters below 0.2 mm were considered as isolated tumour cells (ITC).

Results

Before the trial initiation, a pilot study (learning curve) was performed on ten patients following the exact design as the main study [13]. It included six men and four women, mean age 63 ± nine years, classified preoperatively as stage I or II CRC. The learning curve presented the following results: identification rate of 100%, the accuracy of 90% and sensitivity of 87.5%.

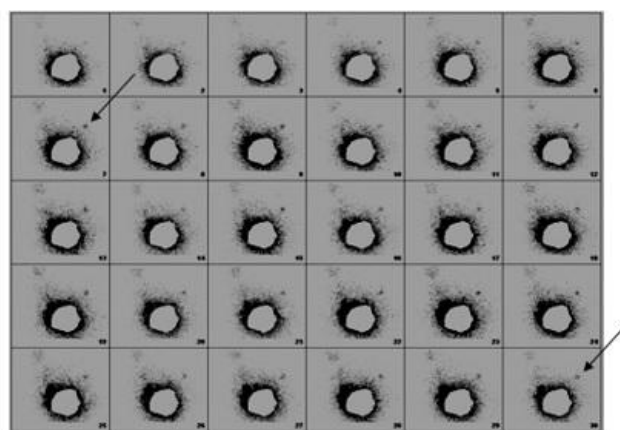


Figure 1: Scintigraphic images obtained during the learning curve-dynamic scintigraphy phase. Bold arrows pointing at the site of early SLN presentation

The first preliminary results from our pilot study were in favour of the main trial initiation and correlated with the scientific data worldwide (14-16).

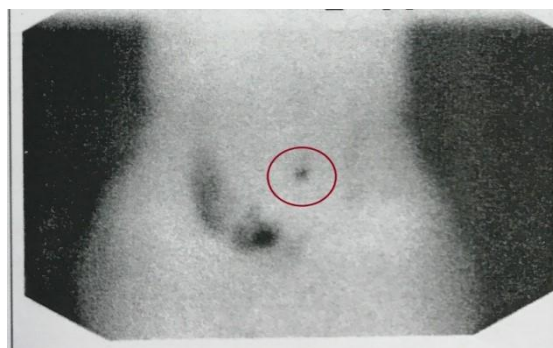


Figure 2: Scintigraphic images obtained during the learning curve-static acquisition 24h post injection. The circle presents the late SLN presentation

We have performed the SLN mapping using radiocolloid in 45 pts so far, but 5 of them were excluded intra- or postoperatively due to exclusion

criteria (1 due to microscopic carcinosis and four due to substantial infiltration or Tu perforation), so the final number of pts that met the inclusion criteria was 40.

The preoperative staging of the patients and the size of a primary tumour were in correlation with the inclusion criteria.

Table 3: Gender distribution and tumour localization

Number of patients: 40		
Gender	Male	(27 pts) 67.5 %
	Female	(13 pts) 32.5 %
Tu localization	Left colon	(20 pts) 50%
	Transversal colon	(10 pts) 25%
	Right colon	(7 pts) 17.5%
	Rectum	(3 pts) 7.5%

The average number of lymph nodes analyzed pathohistologically after resection was 14±2 (all pts had at least 12 or more LN analyzed, according to the gold standard set by AJCC/UICC recommendations).

Table 4: Preoperative (relative) staging of pts and the size of a primary tumour

Number of patients: 40		
Stage	Stage I	(13 pts) 32.5%
	Stage IIA	(11 pts) 27.5%
IIB	Stage IIB	(12 pts) 30%
	Stage IIC	(4 pts) 10%
T (size) – Primary tumor	T1	9pt
	T2	6pt
	T3a/b	22pt
	T4a	3pt

The identification of SLNs using the radiocolloid method in our study was 38/2, which means that out of 40 performed procedures the SLN has not been detected only in two of them thus the detection rate in our study was 95%. In 2 pts two SLNs have been detected. The distance of the detected SLNs vs the tumour location was respectively: 1-3 cm in 15 pts, 3-5 cm in 13 pts and 5-10 cm in 10 pts.

Table 5: Distribution of pts with detected SLNs

Positive regional LN		Negative regional LN	
True positive - a	15	True negative - d	20
False negative - c	3	False positive - b	/
Sum	18		20

Out of the 38 pts with detected SLNs, after the histopathological analysis, the distribution of true positive (SLN is positive, and other regional LNs are positive), true negative (SLN is negative, and other regional LNs are negative), false negative (SLN is negative, but some of the regional LNs are positive) and false positive (/) pts was as shown in Table 3.

Considering the data presented in Table 3, we

have calculated the following parameters.

In 5 patients (12.5%), the SLN was the only positive lymph node for metastases of all examined LNs (relative upstaging). The detection of metastases/micrometastases (N+) with immunohistochemistry, after negative HE staining (No), using the 3 Abs, was positive in 2 pts, so the upstaging in our study was 10% (true upstaging).

Table 6: Sensitivity, Accuracy, Negative predictive value and Detection rate parameters

Parameter	Formula	Value
Sensitivity	$[a / (a+c)] \times 100$	83.3%
Accuracy	$[(a+d) / (a+b+c+d)] \times 100$	92.1%
Negative predictive value	$[d / (d+c)] \times 100$	86.95 %
Detection rate	38/40 pt x 100	95.0%

Parameter	Formula	Value
Sensitivity	$[a / (a+c)] \times 100$	83.3%
Accuracy	$[(a+d) / (a+b+c+d)] \times 100$	92.1%
Negative predictive value	$[d / (d+c)] \times 100$	86.95 %
Detection rate	38/40 pt x 100	95.0%

SLNs with higher colloid uptake (1821 ± 972 counts per 10 seconds) were free of metastases ($p < 0.05$) compared to SLNs with lower colloid uptake (884 ± 431 counts per 10 seconds) that were positive for metastatic deposits ($p < 0.01$). Our data analysis presented a strong correlation between the size of a tumour and the metastatic involvement of SLNs. The number of pts with positive SLNs increased with the increase of the primary tumour size ($p < 0.001$).

Table 7: Correlation between size of a tumour and metastatic involvement of SLN

Correlation between size of tumor and metastatic involvement of SLN		
Size of tumor and type of SLN	Number of patients	Percentage
Positive SLN; Tu ≤ 1cm.	2	5.2%
Positive SLN; Tu 1-2 cm.	6	15.8%
Positive SLN; Tu > 2 cm.	10	26.3%
Negative SLN; Tu ≤ 1 cm.	16	42.1%
Negative SLN; Tu 1-2 cm.	3	7.9%
Negative SLN; Tu > 2 cm.	1	2.7%
All	38	100.0%

Discussion

One of the most important factors for prognosis in colorectal cancer patients is the status of the regional lymph nodes included in the TNM classification. The SLN is the first node that drains a tumour and hence it is most likely to become positive for metastases. A precise identification and PH analysis of the SLN will improve the tumour staging, and consequently, a more appropriate postoperative treatment can be sought. High-risk stage II patients have worse survival rates and five-year disease free period compared to stage IIIA patients. Restaging and upstaging of high-risk stage II patients into stage III

(based on the positive LN status) could improve their survival rate by 33% and five-year disease free period by 40% due to the inclusion of adjuvant chemotherapy. SLNB (sentinel lymph node biopsy) is currently accepted as the standard method of the evaluation of the axillary status of breast cancer pts and the management of malignant melanoma pts. Almost 75% of early staged (stage I and II) breast cancer pts benefit from the technique regarding modification of the extent of the axillary dissection [11]. The SLN detection concept in CRC pts inflicts no reduction or alteration in the surgical procedure, but staging accuracy improvement especially in the subgroup of high-risk stage II pts [17]. The possibility for ultra-staging could either confirm the LN free disease in stage II pts or classify them as real stage II, thus helping them to avoid the unnecessary adjuvant therapy or upstage the LN positive stage II pts into stage III, thus improving their overall survival rate due to adjuvant chemotherapy inclusion.

The first publications on SLN detection in CRC pts used blue dye and presented poor results with low sensitivity and detection rate of only 70%. However, with improved study design, increased number of pts and especially with SLN detection method standardization, the detection rate increased up to 97%, accuracy up to 90,7% and upstaging rate up to 27% [18]. The meta analysis performed in 2012 by E. S. van der Zaag et al. on 57 relevant publications using blue dye for SLN detection in 3934 CRC pts presented the following results: detection rate of 90.7%, the sensitivity of 69.6% and upstaging of 18.9% [19]. Up to date, all scientific data concerning this issue suggests that even though the detection rate and the upstaging rate improved, the sensitivity of the SLN detection method with blue dye remains low. Due to the small particle size, blue dye travels through the lymphatic channels relatively quickly and rapidly passes on to the second echelon LNs [20, 21]. In that manner, at least 4 LNs are considered to be SLNs when using the blue dye detection method and at least four coloured LNs must be analyzed.

Radiocolloid particles are bigger and travel through the lymphatic channels at a much slower rate. Larger colloids yield a significantly higher count rate probably due to slower clearance from the LNs. Furthermore, radiocolloids are incorporated in the first echelon LNs by phagocytosis and remain trapped for a longer period when compared to blue dye, making the LNs detected with this method more likely to be true SLNs [21, 22]. Among the first SLN detection studies in CRC pts using radiocolloid particles (antimony sulphide labelled with 99 mTc), applying the ex vivo injection technique, was the study conducted by Merrie AE et al. in 2001 and it presented detection rate of 88% and sensitivity of 55% [23]. Kitagava et al. reported the first study of SLN mapping in 56 CRC pts using the preoperative endoscopic injection of technetium labelled colloids with a detection rate of

91% and accuracy of 92% [24]. The 2012 study by De Haas R.J. et al. also used the preoperative endoscopic application of radiocolloid as a single tracer for SLN detection in CRC pts and presented detection rate of 86% and upstaging rate of 17% [25].

In our study, we used the preoperative endoscopic method of application of radiocolloid, 24 h before the operation, with three peritumoral and one intratumoral injection thus covering the whole lymphatic tumour drainage based on our previous experience [11]. The statistical analysis presented the following data: sensitivity 83.3%, accuracy 92.1%, and negative predictive value 86.95% and detection rate of 95%. We failed to detect the SLN in 2 pts, and both of them were pts with rectal carcinoma. Most of the publications exclude the rectal carcinoma due to its different pattern of spread. We decided to include the pts with rectal carcinoma in our study and 2 out of 3 pts included the detection of SLN with our method failed. This finding is in correlation with the scientific data in other published studies. The number of pts with rectal carcinoma included in our study is not sufficient for a firm conclusion concerning the issue of whether the SLN detection method using radiocolloids should be incorporated into the management guidelines of this subgroup of pts. Other possible reasons for unsuccessful SLN mapping that are mentioned in the literature could be intraluminal injection, incomplete circumferential injection or large primary tumour size [21]. Both of our pts had T3 primary tumour size which also could have contributed to the omission of SLN detection. Since all the endoscopic procedures were performed by the same endoscopist with large experience in the field of endoscopy and were also video monitored, we exclude the possibility of not detecting the SLN to be due to inappropriate injection of the radiocolloid.

All three false negative pts had advanced tumour size: two of them were T3b primary tumour size, and one was T4a, which might have contributed to the false negative results of the SLN analysis due to possible skip metastases. Large primary tumour size disrupts the lymphatic drainage and alters the lymphatic flow patterns [21]. No aberrant drainage was noted in our study.

The average number of lymph nodes analyzed pathohistologically after resection was $14 \pm$ two which is a reflection of a sufficient oncological resection. All pts had at least 12 or more LNs analyzed, according to the gold standard for the obligatory minimal number of analyzed LNs, set by AJCC/UICC recommendations. In 5 patients (12.5%), the SLN was the only positive lymph node for metastases of all examined LNs (relative upstaging). The detection of metastases/micrometastases (N+) with immunohistochemistry, after negative HE staining (No), using the 3 Abs, was positive in 2 pts, so the upstaging in our study was 10% (true upstaging). The 2012 meta analysis by Nuh N.Rahbari on 4087 pts

from 39 relevant studies concluded that the detection of MM and ITC is associated with worse overall survival rate and increased loco regional disease recurrence of 23% vs 7% of the disease free LNs [26]. This scientific data suggests that not only metastases of 2 mm in size or bigger, but also MM and ITC should be considered for CRC pts upstaging [26].

SLNs with higher colloid uptake were free of metastases vs SLNs with lower colloid uptake, most probably due to lymph node destruction from the metastatic tissue. Our data analysis presented a strong correlation between the size of a tumour and the metastatic involvement of SLNs. The number of pts with positive SLNs increased with the increase of the primary tumour size.

In conclusion, our results confirm that the SLN detection technique implemented in this study is not invasive, safe, with reliable detection rate, accuracy, sensitivity, negative predictive value, upstaging rate and should be incorporated into the surgical guidelines in our country concerning the subset of high-risk stage II CRC pts. SLNs with higher colloid uptake more often were free of metastases, while the occurrence of metastatic SLNs correlated positively with primary tumour size. We plan to continue this study up to a minimum of 100 pts, using the SPECT/CT modality, and we expect that this would further improve the reliability of our method and contribute to the diagnosis and upstage of the CRC patients, which is important for the postoperative oncology treatment protocols.

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