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Sentinel lymph node in colorectal cancer - 5 years follow up

Research Article

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Abstract: To assess the impact of micrometastases in sentinel and non-sentinel lymph nodes on long-term survival rates of patients treated for colorectal cancer (CRC). Data of 57 patients diagnosed with CRC and treated in the Department of Surgical Oncology in Gdansk in the years 2002-2006 were retrospectively analyzed. Clinico-histopathological data were analyzed using chi-square tests. The effect on long-time survival rates was analyzed using Kaplan-Meier survival probability estimates. Identification of the SLN was performed using the blue dye staining method. All regional lymph nodes were subject to standard histopathological examination. Additionally in 32(56.14%) patients whose nodes were found negative for metastases on standard staining further immunohistochemical analyses were performed. In the analyzed group SLNB was performed in 42(73.7%) patients with colon cancer and in 15(26.3%) with rectal cancer. Identification of the SLN was possible in 45(78.9%) patients. The sensitivity of SLNB was 33%. False negatives were found in 66%. SLNB is a feasible method in CRC patients. We presume that lack of micrometastases in the SLN and non-SLN cannot be regarded as a prognostic factor.

Keywords: *Colorectal cancer • Sentinel lymph node • Micrometastases • Isolated tumor cells*

1. Introduction

The incidence of colorectal cancer (CRC) is augmenting. In 2002 one million new cases of CRC were registered worldwide, what accounts for 9.4% of all cancer cases diagnosed that year [1]. Similar tendency is observed in Polish population, for instance in 2006 13000 new cases of CRC were reported [2]. The clinical outcome of surgical treatment of CRC varies. Five-year survival rates are 65% for USA, 54% for Western Europe and merely 34% for countries of the East Europe [1]. In Poland 5-years survival for colon cancer is 31.6% and only 28.6% in the case of rectal cancer [3].

Assessment of the regional lymph nodes status is one of the most important factors taken into consideration when deciding on starting eventual adjuvant therapies following surgery [4,5]. Adjuvant chemotherapy is standard postoperative management for patients who were found to have metastases in the regional lymph nodes on routine histopathological examination [6,7]. It has been shown that introduction of chemotherapy in this particular group of patients decreases the risk of disease recurrence by 40% and increases survival by 33% [8]. Then again, in order to facilitate procedures of the assessment of regional lymph nodes (LN), similarly to breast cancer and melanoma, the concept of sentinel lymph node (SLN) was introduced in CRC. The method of SLN identification allows detection of the first lymph node reached by the lymph on the way from primary tumor to regional lymph nodes. Besides, supplementary immunohistochemical analysis of the SLN helps to identify micrometastases in a larger group

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of patients. At present, four alternative methods of SLNB are available. First of them, initially proposed by Morton in melanoma patients, requires injection of a blue dye in the tumor surrounding to visualize the road taken by the lymph to SLN [9]. Second method, described for the first time by Krag and Guliano, involves usage of a radiotracer and hand gamma camera for a localization of the SLN [10]. Third one regards examination of SLND in CRC combining radioactive traces and blue dye [7]. Moreover in the last few years, the fourth method using fluorescence tracers (indocyane green) was attempted. It was intended to mark SLND in breast and gastrointestinal [GI] cancers [11]. Yet, consensus on the gold standard is still to be reached.

In the case of CRC, the blue-dye technique is the method of choice. Sentinel lymph nodes (SLN) are examined by hematoxylin and eosin (H&E) stain. Cases found negative for metastases on routine histopathological examination are subject to further immunohistochemical studies, therefore assessment of SLND in CRC is still not a standard. The later allows for the detection of micrometastases (MM) or isolated tumor cells (ITC) [12-14].

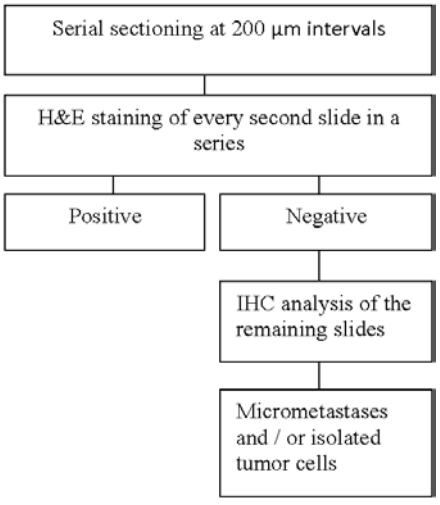
The aim of the study was to assess the significance of detecting micrometastases in SLN and non-SLN on long-term survival rates in CRC patients. Moreover, the impact of SLNB method on pTNM staging was assessed.

2. Material and Methods

2.1. Patients

Patients, referred to the Department of Surgical Oncology during the period from June 2002 through September 2006, were enrolled in the study. SLNB was performed in 57 consecutive cases, including 42 patients (73.7%) diagnosed with colon cancer and 15 patients (26.3%) diagnosed with rectal cancer. The patients classified as clinical stage I or II in accordance to the criteria of American Joint Committee on Cancer entered the study [15]. Clinical stage was determined in view of the results of pre-operative radiological images (abdomen US, CT) and intra-operative examination. Patients with prior history of an abdominal surgery or radiotherapy of abdominal and/or pelvic region were excluded from the study. This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved ethically by Medical University of Gdansk (No. 263/2002). All patients provided informed written consent.

Figure 1. The protocol of histopathological examination of the SLN and non-SLN.



2.2. Procedures

SLN identification was performed according to Saha methodology [6]. For colon cancer and upper rectum SLNB procedure included: opening the abdomen; assessment of surgical respectability of the primary tumor; intestinal mobilization and injection of 1% methylene blue dye subserously at four points in the tumor surrounding. After 10 minutes lymph flow was assessed and the lymph node(s) stained blue were marked with a suture. In the case of a rectal cancer (located in the middle and lower section of the rectum) the dye was administered subserously at four points below the tumor during simultaneous rectoscopy examination performed in the operating room. The nodes present in the mesorectum were assessed for the presence of dye after tumor resection. Afterwards, curative resection was performed. The type of surgery depended on localization of the primary tumor, likelihood of achieving tumor-free resection margins and localization of regional lymph nodes. Colon cancer patients had resection of the primary tumor and regional lymph nodes performed (i.e. right hemicolectomy, transversecolectomy, left hemicolectomy or sigmoidectomy). In the cases of tumors located in the rectum depending on tumor localization anterior resection (in modification according to Dixon) or rectal resection (in modification according to Miles) was performed.

2.3. Histopathology

SLNs and non-SLNs were subject to a detailed histopathological examination. To start with, serial 200 µm micro sections of the nodes were performed. Cases, where nodes were found negative for metastases on classical H&E staining assessed on every second section

Table 1. Demographic, clinical and histopathological characteristics of the colorectal cancer (CRC) patients undergoing SLNB in Gdansk (n=57).

		Overall(n=57)	Colon(n=42)	Rectum(n=15)	p value
Gender	Male	31	22	9	0.61
	Female	26	20	6	
Mean age (years)		67.8	68.1 (SD 8.5)	67.1 (SD 11.5)	0.76
Tumor localization		57	42(73.7%)	15 (26.3%)	
cT - category	cT1	7 (12.3%)	7 (15,9%)	0	0.081
	cT2	16 (28.1)	14 (33.3%)	2 (18.5%)	
	cT3	32 (56.1%)	20 (47.6%)	12 (80%)	
	cT4	2 (3.5%)	1 (4.2%)	1 (1.5%)	
cN - category	cN0	57	42	15	-
Stage according to	I	23 (40.4%)	21 (36.8%)	2 (3.6%)	0.01
cTNM - UICC[15] †	II	34 (59.6%)	22 (38.6%)	13 (21%)	
Stage according to	I	13 (22.8%)	12 (21.1%)	1 (1.7%)	0.22
pTNM - UICC[15]	II	25 (43.9%)	17 (29.8%)	8 (14.1%)	
	III*	19 (33.3%)	13 (22.8%)	6 (10.5%)	
Average number of resected lymph nodes(SLN and non-SLN)		11.95	12	11.7	0.73
Average number of resected SLN		1.3	1.5	0.8	0.025
SLN identification		45 (78.9%)	36 (63.1%)	9 (15.8%)	0.036
Metastases detected on H&E staining		13 (22.8%)	13 (22.8%)	0 (0%)	-
Metastases detected on H&E staining followed by serial sectioning and IHC staining		4 (7%)	2 (3.5%)	2 (3.5%)	-
SLNB sensitivity		33%	28%	50%	-
SLNB specifity		66%	70%	50%	-
Skipped metastases		7/45 (15.6%)	6/36 (13.3%)	1/9 (2.3%)	0.68

Legend: up - staging without reference to the results of SLNB; cTNM – clinical classification of malignant tumors according to UICC [15]; pTNM – pathological classification of malignant tumors according to UICC [15]; † - patients in III and IV stage according to cTNM were excluded;*

in a series, were subject to further immunohistochemical (IHC) analyses. The remaining slides were stained for the presence of micrometastases using monoclonal mouse anti-human cytokeratin clone: AE1/AE3 (DakoCytomation, Denmark) (Figure 1).

2.4. Statistical analysis

Correlations between analyzed parameters were evaluated using chi-square tests (Pearson test and Yates correction for 2x2 tables) and Spearman rank correlation coefficient. Long-time survival rates were analysed using Kaplan-Meier survival probability estimates and verified using log-rank tests. Statistical analysis was performed by using SPSS v. 13.0 (SPSS Inc, USA) and Statistica v. 8.0 (Stat Soft Inc, USA).

3. Results

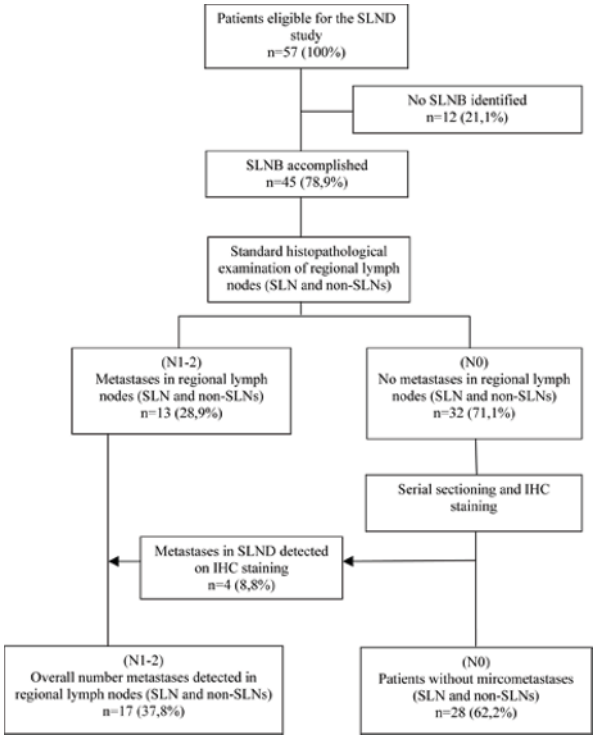
3.1. Demographics

Fifty seven patients (F/M ratio 1:1.2) diagnosed with CRC were enrolled in the study. Average age at diagnosis was 67.8 years, median 68 years (range: 21-84 years, SD 9.3 years). Mean hospitalization time was 7.1 days (median 7; SD 1.5 day). According to cTNM there were 23(40.4%) cases classified as stage I and 34(59.6%) cases as stage II. Clinical and histopathological characteristics of the patients are summarized in the Table 1.

3.2. Histopathology

In accordance with postoperative histopathological examination, pTNM staging was as follows: stage I 13(22.8%) cases; II 25(43.9%) and III 19(33.3%). The up-staging of 19 patients to the stage III resulted from the underestimation of the disease progression in pre-operative studies. The average number of resected regional lymph nodes was 12 (median 11; range 1-27; SD 5.7), whilst mean number of SLNs was 1.3 (median 1; range 0-5; SD 1.1). Identification of the SLN was possible in 45(78.9%) patients, including 36(63.2%) colon cancer cases and 9(15.7%) rectal cancer cases (Table 1). Out of total number of 57 patients, routine histopathological examination of lymph nodes (SLN and non-SLN) was performed in 45 cases only. 13 patients were diagnosed with metastases and 32 patients were found negative

Figure 2. The analyzed group of patients (n=57).



for lymph nodes' metastases. In the group two that had additional IHC analyses performed, assessment of serial sections of SLN identified micrometastases in 4(8.8%) cases. These cases underwent upstaging in view of IHC results. Conversely, in none of the non-SLN micrometastases were found on IHC examination. Long-time survival rates for the two groups of patients: with metastases in SLN and non-SLNs (n=17) versus group with no micrometastases detected in SLN and non-SLNs (n=28) showed no statistically significant differences (p=0.34; Figure 2).

3.3. Treatment

Among 57 patients 18 had right hemicolectomy, 2 transversectomy, 2 left hemicolectomy, 20 sigmoidectomy, 7 anterior resection in modification according to Dixon, 7 rectal resection in modification according to Miles and 1 tumor resection in modification according to Hartman.

3.4. Prognosis

Mean and median time of clinical observation was 7.2 and 5.75 years respectively (range 2.9-7.2 years). 5-years overall survival rate for the whole analyzed group was 72% and median survival time was 5.74 years. During the observation period 19(33.3%) patients died due to cancer progression. For one patient, only death due to post-operative complications has been reported. Long-time survival rates assessed with regard to gender and localization of the primary tumor (colon, rectum) revealed no statistically significant differences. Even though for stage I and II patients 5-years overall survival was 78% opposed to 46% for stage III patients, the difference was not statistically significant. Since only 4 out of 32 cases were found positive for micometastases on IHC, this sub-group was undersized for statistical analysis. The number of regional lymph nodes resected during surgery did not influence long-term survival rates (p=0.48; Table 2).

4. Discussion

The idea of SLN originated in 1977 when Cabanas for the first time reported procedure of SLNB in the case of penile cancer [17]. The author proposed to resect the first lymph nodes through which lymph drains from the tumor (named "sentinel nodes"; SLN). The decision

Table 2. Median survival and 5-years survival rates for colorectal cancer (CRC) patients undergoing surgery in Gdansk (n=49).

		Median survival (years)	5-years survival rate	P value
Gender	Male	5.1	61%	0.40
	Female	4.7	74%	
Tumor localization	Colon	4.5	72%	0.59
	Rectum	4.6	57%	
pTNM	I	4.3	78%	0.18
	II	5.1	78%	
	III	3.9	46%	
Number of regional lymph nodes resected	<12	5.5	64%	0.48
	>12	5.6	71%	
Patients with metastases in SLN and non – SLN (N1-2)	17	-	65%	0.34
Patients with no micrometastases in SLN and in non – SLN (N0)	28	-	79%	

Legend: pTNM - pathological classification of malignant tumours according to UICC [15];

Table 3. Chronology of the studies on clinical application of SNLB in several cancers.

Cancer	Author	Year	Method
Penile cancer	M. Cabanas [17]	1977	dye staining
Melanoma	D.M. Morton [9]	1992	
Breast cancer	D. Krag, A, Guliano [10]	1993	radioactive isotope staining
Vulval cancer	C. Levenback [18]	1994	dye staining
Oral cancer	F. Ionna [20]	1998	
Thyroid cancer	PR. Kelemen [19]	1998	
Colorectal cancer	S. Saha [6]	1999	
Cervical cancer	JD O'Boyle [20]	2000	

Table 4. Summary of SLNB studies in colorectal cancer (CRC).

Author	Number of patients	Method	Detection rate (%)	False-negative rate (%)	Sensitivity (%)	Upstaging by IHC (%)
Saha [2001]	203	dye staining	98	15	85	19
Bilchik[2001]	126	dye staining	96	-	-	8
Wong[2004]	124	dye staining	97	47	53	27
Bertagnolli[2004]	72	dye staining	92	58	42	0
Patten[2004]	57	dye staining	98	50	50	15
Saha[2004]	57	dye staining	100	16	84	-
Kitagawa[2002]	56	radioactive isotope staining	91	18	82	-
Paramo[2002]	55	dye staining	82	7	93	20
Broderick-Villa[2002]	50	dye staining	92	50	50	-
Joosten[1999]	50	dye staining	70	60	40	13
Bembenek[2004]	48	dye staining	96	56	44	-
Kusano[2008]	26	Indocyanine green fluorescence imaging	100	0	82	-
Own results[2009]	57	dye staining	78,9	66	33	8,8

on further resection of more distant lymph nodes could be made in view of the results of SLN histopathological assessment. Latter, the idea of SLN was applied in the management of breast cancer and melanoma. The hitherto studies on SLNB in a number of cancers are summarized in the Table 3 [8,10,11,17-19].

By definition, sentinel lymph node (SLN) is a lymph node with the highest probability of metastases [9]. The studies on application of SLNB in clinical settings arise from the need to recognize lymph node status prior to main surgery. Lymph node status is the crucial factor influencing decision-making on the necessary extent of the surgery. Besides, SLNB might improve histopathological assessment of the specimens through establishing the lymph node burdened with the highest risk for metastases [6,7,20,21]. For gastrointestinal cancer patients, in addition to the presence of distant hematogenic metastases, the presence of metastases to the lymph nodes is a decisive prognostic factor [4,22].

In the consequence of a lack of a reliable method of assessment of the lymph nodes' status before and during surgery, it is recommended to resect appropriate local lymphatic system during surgery (for example in gastrointestinal cancer, melanoma, breast cancer). The evaluation of the eventual presence of metastases in lymph nodes depends on the number of resected lymph nodes and applied histopathological methods [23].

In the case of melanoma and breast cancer patients SLNB methodology becomes more and more readily acceptable part of clinical management. An increasing number of evidence reports published worldwide provide further confirmation that SLNB in early breast cancer is a reliable tool to assess the status of lymph nodes. In this manner SLNB provides indications for removal of axillary lymph system [24,25]. One of the main research issues in the study on SLNB application in CRC is the question of determining whether its introduction could improve the diagnostic accuracy of procedures

used to estimate the stage of disease progression. Comprehensive evaluation of the SLN by application of a range of methods including serial sectioning and IHC staining might help to detect metastases that would not be recognized during routine histopathological examination. It is particularly important since there is a possibility that patients initially diagnosed as clinical stage II (having no metastases to the lymph nodes) might be up-staged to stage III (those who have metastases present in the lymph nodes) and thus be qualified for adjuvant chemotherapy. Summary of the SLNB studies in CRC is presented in the Table 4 [7,20,21,26-33].

The first study reporting SLNB in colon cancer was published by Saha et al. in 1999. He presented the results of a blue-dye SLNB performed in 203 patients with colon and rectal cancer. The initial results were exceptionally promising given that the detectability of SLN was 98%, sensitivity 85% and false negative ratio merely 15%. Such high-quality results were attributable to added method of micro sections and IHC staining. In the reported group, 19% of patients in view of SLNB were up-graded from stage II to stage III [7,30].

Subsequent publications, even though recount SLN detectability at the rate of 70-100%, nevertheless point out to a low sensitivity of the method and high rate of false negative results. Consequently, at present SLNB method is perceived to be of limited practical significance, especially for rectal cancer patients [19]. Worse results achieved in the sub-group of rectal cancer patients are justified by the difficulties in identification of a stained lymph node in the mesorectum and distinctive anatomical structure of the rectum [6,30].

For our group of patients SLN detectability was 78.9%. However, as a result of low sensitivity (33%) and high rate of false negative results (66%) the study was discontinued in 2006. Despite the discouraging results the patients already enrolled in the study were still followed so as to assess the impact of SLNB on long-term survival rates.

Two groups of patients were identified: the first with micro- and macro- metastases in SLN and non-SLNs and the second with no micrometastases detected in SLN and no macro metastases in non-SLNs. No statistically significant differences in long-time survival rates were observed (p=0.34).

Implementation of SLNB in CRC patients improved evaluation of lymph nodes not only qualitatively, but also quantitatively. Larger number of resected lymph nodes affects staging and long-term survival rates. For state-of-art assessment of stage of disease progression it is indispensable to resect 6-15 lymph nodes [5,34]. From the review of the available literature it seems that the implementation of SLNB methodology had positive effect on number of resected lymph nodes and in this way on long-term survival rates of the patients [23]. Yet, in our study the number of resected lymph nodes did not affect overall survival rates of the patients (p=0.48).

Currently, the presence of metastases in the regional lymph nodes diagnosed on routine histopathological examination using H&E staining is the indication to start adjuvant therapies following surgery. So far no consensus has been reached regarding the starting of adjuvant chemotherapy in patients found positive for micrometastases (MM) or isolated tumor cells (ITC) on IHC staining. Definitions of MM (dimensions of the metastases 0.2-2mm) and ITC (metastases less then 0.2mm) were published in 1999 what has encouraged studies of the application of SLN method in research of new prognostic factors in CRC [12]. More frequent detection of MM was possible through introduction of analytical methods such as: micro sectioning, IHC analyses and PCR technique. The preferred diagnostic approach would be the analysis of all regional lymph nodes using all of the above mentioned methods. However these procedures are too laborious and too expensive. Therefore, in clinical practice, they are limited to SLN assessment. In the recent years several reports were published on the role of MM and/or ITC in CRC in relation to risk of local recurrence, the risk of distant metastases and the impact on patient's prognosis. Broll et al. suppose that the presence of MM in SLN detected by IHC might result in higher rates of local recurrences and distal metastases, however there is no effect on overall survival of the patients [36]. Conversely, Liefers et al. reported that presence of MM in SLN has a significant impact on overall survival in colorectal patients. For patients having no metastases detected 5 years survival rates were 91% while for those found positive for MM 5 years survival rates were merely 50% (p=0.02)(36). In 2002 Rosenberg confirmed that presence of MM is a statistically significant factor influencing long-time survival rates [38]. However, there are also reports from other groups showing that MM has no effect on overall survival or that the prognostic role of MM is not unequivocally established [3,14]. Against this background there is no consensus as to whether patients who are positive for MM and/or ITC should receive adjuvant chemotherapy. There is a need for multicentre prospective study to validate the prognostic significance of MM and or ITC detection in CRC patients. In the presented group of patients, out of 32 cases classified as negative on standard H&E histopathological examination 4(8.8%) were found positive for micrometastases in the supplementary IHC analysis what resulted in clinical up-staging of these cases.

Surgical resection of the primary tumor with an adequate margin and removal of the local lymphatic system is the current state-of-art strategy of treatment for CRC patients. The extent of resection of lymph nodes depends on the localization of the primary tumor and involves one or more main vessels along which successive stations of lymph nodes are located. The possibility to detect aberrant lymphatic drainage [ALD] is an additional advantage of SLNB. ALD is described in as much as 14% of cases and its presence may be an indication for extension of the surgical field and resection of additional lymph nodes [16,30]. ALD was reported for the tumors located in the right colon [5]. In the presented material no ALD was observed, therefore SLNB did not affect the extent of the performed lymphadenectomy.

In summary SLNB is a feasible method in CRC patients. Notwithstanding, it is not considered to be a standard strategy of management used to determine the stage of disease progression. The indications to start adjuvant chemotherapy in patients positive for MM and/or ITC remain open for discussion. SLNB may have an effect on the extent of resection of the local lymphatic system. The significance of MM in SLND in CRC has been controversial.

In patients with CRS integration of immunohistochemical analysis to classical histopathological assessment of the regional lymph nodes allows more accurate assessment of lymph nodes status. In a few percent of patients the obtained results might raise the pathological stage of the disease (pTNM) and hence result in proper qualification of the patient for neoadjuvant treatment.

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