The Importance of the Mesorectal Lymph Nodes in Rectal Cancer Surgery

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Introduction: Regarding the rate of local recurrences, improvement of survival rates and quality of life, the treatment of rectal cancer has registered a remarkable progress during the last two decades. This was possible through multidisciplinary and gradual development of rectal cancer management, where surgical resection remains the "key factor" and all surgical interventions considered radical involve mesorectal excision. The status of lymph nodes is probably the only and most important marker of global survival in patients with rectal cancer, which is associated with the risk of systemic dissemination rather than local recurrence.

Material and method: The aim of this study was to analyze the importance of mesorectal lymph nodes, in case of rectal cancer disseminated locally and in remote organs, based on treated rectal cancer cases at the 1st Surgery Clinic, Tîrgu Mureş between January 2000 and December 2009. During this period, out of the 618 recorded rectal cancer cases, in 505 cases the patients underwent surgical intervention where besides the rectal tumor, the perirectal lymphatic tissue was also excised.

Results: The performed histopathological examinations revealed in 223 cases lymph node invasion (stage III and stage IV). We also studied different surgical interventions regarding lymph node excision performed during rectal cancer surgery, analyzed the average number of excised perirectal (mesorectal) lymph nodes and the average number of lymph nodes with histopathologically confirmed tumor metastasis resulted from rectal resection.

Conclusion: In our study, we found that in surgical interventions involving resection with anastomosis the average number of lymph nodes per specimen is biger than the number recorded subsequent to abdominoperineal rectal resection.Therefore the resection with mesorectal excision is the best option for rectal cancer surgery any time is possible.

Keywords: rectal cancer, lymph node metastasis, mesorectal excision, rectal resection

Introduction

Colorectal cancer is the third most common cancer worldwide and the leading cause of cancer morbidity and mortality in Europe and the USA. The 5-year survival rate in patients with colorectal cancer is about 64% for all stages (SEER cancer statistics) even if there is an increased risk of local recurrence and the risk of distant metastasis (this may occur even if a resection is considered curative) [1]. 45% of all colorectal cancers are located in the recto-sigmoid junction and the rectum [2].

Material and method

In this study, we analyzed rectal cancer cases hospitalized and treated in Tîrgu Mureş, at the 1st Surgery Clinic between January 2000 and December 2009. Our primary aim was the investigation of the mesorectal excision through the analysis of the number of mesorectal lymph nodes present in the rectal cancer resection specimen. As a secondary objective, we researched the relationship between the type of performed surgical intervention and the average number of lymph nodes collected for histopathologic processing during different operative techniques, the presence of lymph node metastasis in the mesorectum and how these facts influence the course of a surgical intervention according to the stage of tumor. For a good and easy documentation, the patients' records were introduced in an MS Access database and processed in MS Excel.

Results

During the studied period of time our medical records totaled 618 patients with rectal cancer, out of which 353 were male and 265 female patients, the ratio between the two genders being of 1.33 /1. Their ages ranked between 30 and 86, with a mean age of 67.

A gender based distribution of cases according to the studied years is represented in Figure 1. It is clear that the presence of rectal cancer in male patients is prevalent, but during 2004–2005 the number of reported cases was higher among female patients (2004 – women: 31 cases, men: 29 cases, 2005 – women: 43 cases, men: 24 cases).

Regarding the total number of patients undergoing primary surgery (excluding cases with local or remote recurrences) the location of tumor was recorded at the level of the recto-sigmoid junction in 16.3% (n = 96) of the cases, in the upper third of the rectum 33.7% (199 cases), in the middle third 18.1% (n = 107) and in the lower third of the rectum and anal canal occurred in 31.9% (188 cases).

Macroscopic analysis revealed the prevalence of infiltrating ulcerative type tumor (IU), which totaled 227 cases, followed by the ulcerative vegetating type (UV) with 196 cases. Furthermore the vegetating type was recorded in 50 cases, the infiltrating type in 31 cases, ulcerative in 19 cases, circular in 7 cases, polypoid and mucinous types in 2 cases each, nodular type 3 cases and the macroscopic histologic type of tumor was not recorded in 81 cases. The presence of circumferential tumor in the rectal wall was re-

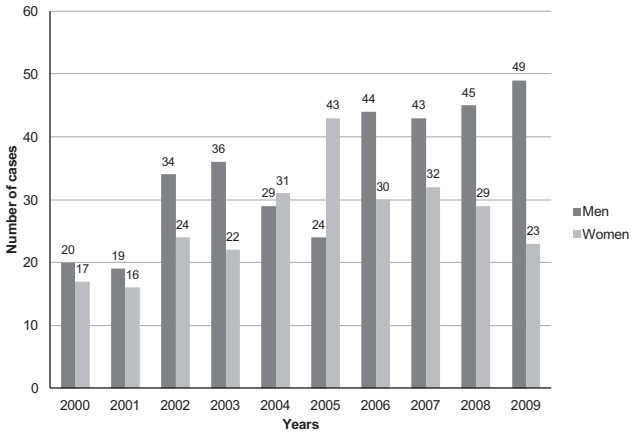

Fig. 1. Gender based distribution of cases according to the studied years

corded in 139 cases, out of which 33 were in stage T4. Tumoral perforation with peritumoral abscess was diagnosed intraoperatively in 31 cases (5.02%). At the microscopic level the vast majority of tumors were adenocarcinomas (AC) recorded in 464 cases, followed by mucinous adenocarcinoma (MAC) in 108 cases, undifferentiated carcinoma (UC) 3 cases, epidermoid carcinoma (EC) 3 cases, signet ring cell carcinoma (SRC) 4 cases, respectively anaplastic carcinoma (AC) in 3 cases and mucinous carcinoma (MC) in 2 cases. Mixed type carcinoma was present in 3 cases as combinations of AC+ MAC, AC+UC, respectively MAC + UC. Malignant melanoma and sarcoma were registered in one case each, and other type of tumor (OT) usually not located in the rectum was present in 3 cases, one of them proved to be a metastasis of papillary AC and the microscopic type of tumor was not recorded in 23 cases.

The degree of tumor differentiation (grading) showed the following results: Well differentiated – 45 cases, Moderately differentiated – 272 cases, Poorly differentiated – 31 cases, Undifferentiated – 168 cases. Tumor grading was not recorded in a number of 102 cases, because a part of the unlabeled rectal tumors were subjected to irradiation preoperatively and the remaining unlabeled tumors presented local or remote recurrences or in case of inoperable tumors when tissue could not be sampled intraoperatively undergoing exploratory laparotomy with/ without colostomy.

For staging we used the TNM and modified Astller-Coller classifications, the latter being used for a more accurate tumor expression in advanced cancer cases, stages C1, C2 and C3. Dukes classification was mentioned and sometimes used for the simplicity of expression in the text. Out of the total 618 cases of rectal cancer, there were less than half, 280 cases, in stages I and II, and 243 cases in stages III and IV, which proves that patients visit the doctor later, after the onset of first symptoms, when treatment options are limited in many cases and their costs are increased. In 95 cases staging was not performed due to accidental omission, tumor cell disorder caused by different types and degree of tumor differentiation or preoperative radiotherapy.

Table I. Rectal cancer staging

STAGE	TNM	DUKES	MAC	NUMBER	%
0	TisN0M0			4	0.64%
I	T1N0M0	A	A	21	3.39%
	T2N0M0	A	B1	103	16.66%
IIA	T3N0M0	B	B2	142	22.97%
IIB	T4N0M0	B	B3	10	1.61%
IIIA	T1-2N1M0	C	C1	19	3.07%
IIIB	T3-4N1M0	C	C2/C3	103/7	16.66%/1.13%
IIIC	anyTN2MO	C	C1/C2/C3	2/63/8	0.32%/10.19%/ 1.29%
IV	anyTNM1		D	43	6.95%
Not specified				95	15.44%

Table I comprises specific details of tumor staging of the studied casuistry.

The Status of Mesorectal Lymph Nodes

The status of lymph nodes is probably the only and most important marker of global survival in patients with rectal cancer, which is associated with the risk of systemic dissemination rather than local recurrence [4]. The 5-year survival rate in patients with positive lymph node rectal cancer is significantly lower than in patients with negative lymph node rectal cancer (40% vs 60%)[5]. The Manual of Total Mesorectal Excision (TME) states that at least 12 lymph nodes should be examined before a patient is classified as N0 [2]. Wang et al., who examined microscopically the entire mesorectum sectioned at 5 mm intervals suggest that the ideal or maximum number of lymph nodes in the TME specimen is 32 [6].

Scientific evidences regarding extended lateral lymphadenectomy in rectal cancer are still insufficient, especially when patients are not suspected of having lymph node metastases. When metastases is suspected in the lateral lymph nodes, these should be removed if this is technically possible. A biopsy of the suspected lymph nodes outside the field of surgical resection should be performed with the purpose of staging (eg. iliac and paraaortic lymph node biopsy). The apical ganglion should be marked for the histological examination. Lateral lymph node dissemination seems to depend on the location of low tumor invasion, tumor penetration depth, number of involved nodes in regions other than the lateral area and low degree of differentiation [21].

Based on the above mentioned observations as well as the fact that the rectal resection specimen should contain

Table II. The analysis of TME specimen from the prospective of mesorectal lymph node invasion

No. of lymph nodes / Stage	>12	<12	Positive lymph nodes	No. of lymph nodes (avg)	
				Total	Positive (+)
I–II	89	186	–	9	–
III	74	119	193	12	5
IV	23	20	30	15	6

Table III. The average number of lymph nodes present in the rectal cancer resection specimen in relation to the performed different surgical procedures

Type of operation	LN / Stage	Perirectal (PR)		Perisigmoid (PS)		Periaortic (PA)	
		Total	+	Total	+	Total	+
Dixon	I–II	9	–	2	–	0	–
	III	10	4	2	0	0	0
	IV	11	3	3	1	0	0
Hartmann I	I–II	9	–	2	–	0	–
	III	10	4	3	1	0	0
	IV	14	6	3	2	0	0
Miles	I–II	5	–	1	–	0	–
	III	7	3	2	1	0	0
	IV	12	7	0	0	0	0
SSP	I–II	8	–	1	–	0	–
	III	10	4	1	0	1	1
	IV	14	5	1	0	1	0

minimum 12 perirectal lymph nodes for an accurate staging, we analyzed the total excision of the mesorectum with regard to the number of lymph nodes present in the surgical resection specimen. Out of the total 618 patients 505 underwent surgical intervention while besides the rectal tumor the perirectal lymphatic tissue was also excised. The performed histopathological examinations did not reveal any information about the situation of lymph nodes in 47 cases, but in 223 cases, they recorded lymph node invasion with tumor cells (stage III and IV). 186 cases were recorded as having more than 12 mesorectal lymph nodes in the resection specimen and in the absence of the circumferential resection margin infiltration they were labeled as presenting a corresponding excision of the mesurectum (grade 2 and 3 Quirke). In 325 cases the number of lymph nodes present in the resection specimen was less than 12 (Table II). While in stages II and III this fact is important only as a technical detail in stages III and IV the presence of a larger number of lymph nodes in the resection specimen is important because of staging (implicitly in the postoperative adjuvant treatment) and prognosis. Stage III recorded 74 cases with more than 12 lymph nodes in each resection specimen and 119 cases with less than 12 lymph nodes in each resection specimen. Overall, the average number of excised lymph nodes per specimen, for operated patients in stage III, was 12 lymph nodes, out of which 5 presented tumor invasion. Regarding stage IV, there were 23 cases out of the total 43 comprising more than 12 lymph nodes per resection specimen and 20 cases with less than 12 lymph nodes per specimen, but tumor invasion was found only in 30 stage IV patients (the rest of the cases being TxN0M1). The average number of excised lymph nodes per specimen was 15, out of which tumor invasion was present in 6 lymph nodes.

Chi square Test, $p = 0.0086$ ($p < 0.05$), there is a statistically significant association between the number of lymph nodes invaded with tumor cells and tumor stage III and IV.

Our study aimed to further research lymph node excision in the framework of various operations practiced in rectal cancer surgery. We analyzed the average number of excised perirectal (mesorectal), perisigmoid and periaortic lymph nodes and the average number of lymph nodes with histopathologically confirmed tumor metastasis resulted from rectal resection (Table III). The obtained results derive from the analysis and data processing of 231 Dixon, 67 Hartmann I, 175 Miles type operations and 66 operations that successfully realized sphincter saving (low Dixon, Parks, Mansell-Weir, Babcock-Bacon). While in stages 1 and 2 the average number of analyzed lymph nodes was 11 after the Dixon and Hartmann I operations and 9 subsequently to the sphincter saving type operations, after the Miles operation we found that the average number of lymph nodes was 5 in case of perirectal excision and 1 in case of perisigmoid excision. For those who underwent SSP (Sessile serrated adenoma) type operations the avarage number of lymph nodes per specimen in stage I and II was 9 out of which 8 were perirectal and 1 sigmoid.

Table IV. The average number of lymph nodes present in the rectal cancer resection specimen in relation to the tumor stage

LN / Stage	Dixon		Hartmann I		Miles		SSP	
	Total	+	Total	+	Total	+		
I–II	11	–	11	–	6	–	9	–
III	12	4	13	5	9	4	12	5
IV	14	4	17	8	12	7	16	5

Subsequently to stage III, Dixon type operations the average number of sampled lymph nodes was 12 out of which 4 presented tumor invasion. The Hartman operation sampled for analysis an average of 13 lymph nodes out of which 5 presented lymph node metastasis and SSP type operations presented an average of 12 lymph nodes in each resection specimen out of which 5 proved to be positive. Out of the total number of 12 lymph nodes 10 were situated in the perirectal, 1 in the perisigmoid and 1 in the periaortic area. The Miles operation sampled an average of 9 lymph nodes out of which 4 proved to be positive, 3 of them were present in the mesorectum and 1 in the sigmoid mesocolon. In case of Dixon type operations performed in stage IV patients the collected samples revealed an average of 14 lymph nodes, 11 situated in the perirectal and 3 in the perisigmoid region out of which 1 perirectal and 3 perisigmoid lymph nodes presented tumor cell invasion. The Hartmann operation revealed an average of 17 lymph nodes per excised specimen out of which 14 were located in the perirectal and 3 in the perisigmoid area. There were 6 perirectal and 2 perisigmoid lymph nodes invaded with tumor cells. Subsequently to the Miles type procedure we obtained in average 12 perirectal lymph nodes out of which 7 presented tumor invasion. Conservative operations of the anal sphincter presented 16 lymph nodes in the resection specimen, out of which 14 were situated in the perirectal, 1 in the perisigmoid and 1 in the periaortic area; furthermore lymph node metastasis was found in 5 perirectal lymph nodes. Data resulted from the graphical

analysis indicates that in operations involving resection with anastomosis there is an average number of lymph nodes per specimen which is bigger compared to what was recorded subsequently to abdomino-perineal resection.

Chi square Test, p = 0.81 (p >0.05), there is no statistically significant association between the total number of lymph nodes and type of surgery regarding stage III and stage IV tumor.

Chi square Test, p = 0.99 (p >0.05), there is no statistically significant association between the number of positive lymph nodes and type of performed surgery.

Fisher Test p = 1.00 (p >0.05), there is no statistically significant association between the number of stage III and stage IV positive and negative lymph nodes, in case of DIXON surgery.

Fisher Test p = 0.72 (p >0.05), there is no statistically significant association between the number of stage III and stage IV positive and negative lymph nodes, in case of HARTMANN surgery.

Fisher Test p = 0.67 (p>0.05), there is no statistically significant association between the number of stage III and stage IV positive and negative lymph nodes, in case of MILES surgery.

Fisher Test p = 0.70 (p>0.05), there is no statistically significant association between the number of stage III and stage IV positive and negative lymph nodes, in case of SSP surgery.

Discussions

The importance of the mesorectum results from the fact that lymph node or occult (hidden) metastases can occur at its level (most often micrometastases), which may not be eliminated in case of an incomplete or partial resection [7,8]. The increased interest for the TME technique in recent years promoted it as a "gold standard" for radical rectal cancer surgery [9,10]. After 1982 many publications and articles supported the idea of total mesorectal excision in case of local recurrence as well as for the prevention of genitourinary complications [11]. However several authors have reported very low local recurrence rates (6.5 to 7.3%) even in conditions in which TME was not always practiced [12]. When performing the technique of total mesorectal excision the lymph nodes situated in the mesorectum are removed, but the lymph nodes situated in the lateral area are not involved. Metastases in the lymph nodes are associated with the risk of systemic dissemination rather than local recurrence. The 5-year survival rate in patients with positive lymph node rectal cancer is significantly lower than in patients with negative lymph node rectal cancer (40% vs 60%) [4,5]. While some authors assert that positive lymph nodes present a similar risk to local recurrence as positive CRM (circumferential resection margin) other studies reject this idea. Thus, Heald and his research team, recently published prospective data collected from 170 rectal cancer patients who underwent TME surgery [13]. While positive lymph node patients experienced a higher local recurrence rate than negative lymph node patients, the recurrence rate in patients with positive lymph nodes was only 7.5%, which is a low recurrence rate in the present conditions of lymph node metastases. Wang et al., who studied 18 rectal specimens examining microscopically the entire mesorectum sectioned at 5 mm intervals suggest the ideal or possible maximum number of lymph nodes present in a TME specimen [6]. During their research they examined 992 lymph nodes, in average 32 lymph nodes/specimen out of which in 148 lymph nodes they found metastases (15%). It is noteworthy that 922 lymph nodes (93%) out of the total studied ones and 104 (70%) of those which proved to be positive were less than 5 mm in diameter. Topor and Galandiuk studied on resection specimens and on cadavers the location of mesorectal lymph nodes. They concluded that most lymph nodes are the size of millimeters (in average 0.5–3 mm) and most of them (92%) are situated in the posterior quadrant of the mesorectum in the 2/3, middle and superior area [14,15]. Andreola et al. asserted that 45% of mesorectal lymph nodes that present metastasis are less than 5 mm in diameter and 14% of patients with lymph node metastasis presented dissemination only in these millimetric lymph nodes [16]. Wang et al. during their research found that 5.8% of lymph nodes were smaller than 0.5 mm. They detected occult lymph node metastases in 29% cases investigated by them [6].

In practice, the recovery of even 12 lymph nodes can be difficult in many cases, as the results of the Dutch TME trial revealed, where 82% of the patients who underwent radiotherapy and had negative lymph nodes were examined with less than 12 lymph nodes [17]. However, each time as many lymph nodes as possible should be identified and examined, according to the principle that the more lymph nodes are examined the more accurate staging is attained. Caplin et al. showed that patients with less than 7 examined negative lymph nodes presented similar prognosis to patients with positive lymph nodes, and Tepper et al. pointed out that patients with 14 examined lymph nodes have a better relapse-free interval than those with 8 examined lymph nodes [2,18]. In our study, in stage III patients the average number of lymph nodes excised per specimen was 12, out of which on average we detected tumor invasion in 5 lymph nodes. The average number of lymph nodes in stage IV patients was 15 (reporting to 30 resection specimens), out of which 6 presented tumor metastases. Data resulted from the graphical analysis indicates that in operations involving resection with anastomosis there is an average number of lymph nodes per specimen which is higher compared to what was recorded subsequently to abdomino-perineal resections (stage III – 12:9; stage IV – 14:12). A possible explanation is the fact that in operations which involves resection and anastomosis (this includes Dixon and SSP operations) the proximal level of resection is often higher than in abdomino-perineal resection, so it can include a part of perisigmoidian and periaortic lymph nodes(as seen in Table III). In fact, according

with the study the of Topor and Galandiuk, most part of mesorectal lymph nodes (92%) are located in the 2/3 superior area of the posterior quadrant and theoretical the number of mesorectal lymph nodes are constant in both types of operations. It was noted by Quirke and others, based on histopathological study of the rectal specimens, that the incidence of circumferential invasion in abdomino-perineal resection is higher than in case of anterior resection of rectum [19]. This has led to a wide spread idea of a "cylindrical specimen" and the incomplete excision of mesorectum in abdomino-perineal resection in the surgical world[20]. McCall et al. found in one of his study, that the local recurence was higher after abdomino-perineal resection (19.3%) than in anterior resection of rectum (16.2%) [21]. In fact, establishing a minimum number of 12 lymph nodes to be examined may lead to substaging, by omitting to search for lymph nodes close to the rectal wall that are more difficult to be distinguished. In order to increase efficiency in the discovery of mesorectal lymph nods and not only, a series of techniques have been developed such as fat stretching, alcohol treatment, cedarwood oil clearance, ether-based methods, etc. [22]. In reality visual routine investigations, palpation and dissection remain the standard practices to discover lymph nodes.

Extensive pelvic lymphadenectomy at the level of lymph nodes in the lateral compartment, recommended by Japanese authors, present a high risk of hypogastric nerve damage, which comprise both sympathetic and parasympathetic fibers [7,23]. Ueno et al. indicated in patients who underwent different types of rectal resections with total mesorectal excision and lymph node dissection from the lateral area, lymph node dissemination in 16.8% cases (41 patients out of the total 455). 10 out of these 41 patients presented metastases excluding lymph nodes from the lateral area. Given the frequency of metastatic disseminations, Ueno considers that the territories of shameful internal arteries, internal iliac and obturator arteries are the "weak point" of lateral dissemination, 88% of lateral area metastases were found in one of these regions. The author concludes that lateral lymphatic dissemination dependens on low tumor localization, the depth of parietal invasion, dissemination in other lymphatic areas and low degree tumor differentiation [24]. During their research, Maeda and Kahawara injected preoperatively dye with carbon particles (CH40) and indocyanine green into the rectal submucosa and performed postoperatory analysis of the resection specimen. Subsequently to these investigations they observed that the main site of metastases in the lateral lymphatic area is at the level of lymph nodes found in the internal iliac artery (9–27%), but global dissemination in supraperitoneal as well as subperitoneal tumors is represented by dissemination in the axial lymph nodes (75–87% for supraperitoneal respectively 18–73% for subperitoneal tumors) [25,26].

Lymphoscintigraphy studies conducted by European and American scientists regard lymphatic drainage into the lateral lymph node area of minor importance [27,28]. Although Japanese scientists regard this area of great importance in subperitoneal rectal cancers, lymph node excision in the lateral compartment remains controversial [29]. Pelvic lymphadenectomy, practiced in Japan, does not have prominent advantages in comparison with TME regarding survival rate. The greatest disadvantage of pelvic lymphadenectomy is the high percentage of sexual and urinary dysfunctions. That is why this procedure is not performed as a routine surgical intervention in the treatment of rectal cancer in European and American hospitals [30].

All lymph nodes prone to metastasize located farther from the vessels of origin must be excised and sent to biopsy or the resection area should be extended in order to include the suspected lymph nodes. However, the phenomenon of "jumping" metastasis over a sentinel lymph node without tumor invasion may be present in only 5% of the cases [31,32]. Recent studies have suggested the possible location of positive lymph nodes and discontinuous tumor deposits in the mesorectum [33].

Wang et al. studied 18 TME specimens examining microscopically the entire mesorectum sectioned at 5 mm intervals and they found discontinuous tumor deposits in the mesorectum in over 60 % of the studied cases. Half of them were localized in the posterior mesorectum. Laterally localized tumor deposits were found more often in the ipsilateral than controlateral area [6].

The TME laparoscopic technique is feasible and is supported by many authors because it is minimally traumatic, illumination is great, provides easy access of instruments into the pelvic cavity and early postoprative mobilization and recovery, allowing the rapid initiation of adjuvant therapy [34,35]. The results of local recurrence and remote survival rate, as well as the surgical resection specimen are comparable to those attained in open surgery, but these studies were performed in specialized centers and in small carefully selected group of patients [36].

Conclusions

1. According to Heald, TME in rectal cancer surgery meets the functional and oncological objectives.
2. In our study, resection with anastomosis reveals a greater number of mesorectal lymph nodes than abdominopelvic resection.
3. When lymph nodes located outside the resection area are likely to metastasize, excision and biopsy should be performed or the resection area should be extended.
4. The number of lymph nodes excised by performing the saving-sphincter type operation technique are enough (over 12) to determine a favorable prognosis and adequate life style for longer time.

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