

Lymph node retrieval after resection of rectal cancer following preoperative chemoradiotherapy

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Key words: rectal cancer; preoperative chemoradiotherapy.

Summary. *Background.* According to the current guidelines of proper TNM staging, 12 lymph nodes per specimen are crucial. This study assessed the role of preoperative radiochemotherapy on the number of lymph nodes detected in the tumor-bearing specimen.

Material and methods. Retrospective data of 138 patients who underwent surgery for stage II and III rectal cancer without preoperative radiochemotherapy during the period of 2004–2006 (control group) were compared with prospective data of 38 patients who received preoperative radiochemotherapy during the period of 2007–2008 (study group). The number of patients with metastatic lymph nodes, number of lymph nodes per specimen, number of metastatic lymph nodes per specimen, and the size of the tumor between the groups were compared.

Results. Positive lymph nodes were detected in 88 (64%) patients in the control group as compared with 9 (21%) patients in the study group ($P < 0.05$). The mean number of lymph nodes per specimen in the control group was 13.5, while in the study group, the mean number of lymph nodes per specimen was 6.29 ($P < 0.05$). There was a significant difference in the mean number of metastatic lymph nodes per specimen between the groups (5.12 in the control group versus 2.11 in the study group; $P < 0.05$). The mean size of the tumor was 4.37 cm in the control group and 2.45 cm in the study group ($P < 0.01$).

Conclusions. Preoperative radiochemotherapy for advanced rectal cancer significantly decreased the number of lymph nodes detected in the tumor-bearing specimen. This also resulted in a significant decrease in the number of metastatic lymph nodes detected in the specimen, and fewer patients with stage III (N+) cancer were diagnosed. Preoperative radiochemotherapy could induce a significant downsizing and downstaging of advanced rectal cancer, but great care in operative and pathologic examination techniques must be taken to ensure appropriate staging.

Background

Carcinoma of the rectum is a common malignancy, especially in developed countries. Together with malignant tumors of the colon, colorectal cancer ranks as the third most common cancer in the world. The crude incidence of rectal cancer in the European Union is 35% of the total colorectal cancer incidence, i.e. 15–25/100 000 cases per year. Recent estimates for incidence and mortality of cancer in Europe continue to rank colorectal cancer as the second most common cause for cancer-related death (1). Surgery still remains the therapeutic mainstay of rectal cancer. Recently, data supporting the use of preoperative radiation-based therapies have been accumulating.

According to the results of the CAO/ARO/AIO-94 study (2) and the National Surgical Breast and Bowel Project R-03 study (3), preoperative chemoradiotherapy is considered as the standard treatment for patients with stage II and III rectal cancer in some

European countries and North America. According to the clinical recommendations on the treatment of locally advanced rectal cancer set by ESMO, preoperative radiotherapy is recommended since it reduces local recurrence rates. A dose of 25 Gy (5 Gy/fraction) and immediate surgery or 46–50 Gy (1.8–2 Gy/fraction) with or without chemotherapy (5-Fu) and surgery after 6 weeks are possible. Preoperative treatment is preferred since it is more effective and less toxic than postoperative treatment (4).

Treatment of rectal cancer needs a multidisciplinary approach: careful preoperative radiological staging, adequate operative techniques, and careful pathologic examination. Accurate staging is vital for the treatment of rectal cancer. According to the recommendations of the International Union Against Cancer (UICC) (5) and current guidelines set by the Royal College of Pathologists in the United Kingdom, a minimum number of 12 lymph nodes per specimen must be found by the pathologists for

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proper staging (6). Several authors have reported significantly reduced five-year survival for patients with fewer than 12 nodes found in the tumor-bearing specimen (7–9). Number of metastatic lymph nodes detected in the tumor-bearing specimen is also important, contributing to poor survival and prognosis (9).

On the other hand, preoperative chemoradiotherapy is associated with the reduction in tumor bulk and increased tissue fibrosis that makes nodal identification more difficult (10).

The hypothesis that fewer lymph nodes are detected in the tumor-bearing specimen after preoperative radiochemotherapy was confirmed by several authors (7, 11, 12). We performed our study with the aim to assess the role of preoperative radiochemotherapy on the number of the lymph nodes detected in the tumor-bearing specimen and to discuss the role of tumor downstaging for these patients.

Methods

The data of 176 patients with locally advanced rectal cancer (locally advanced cancer was defined as clinical stage II and III cancer) were analyzed. All patients underwent conventional curative resection between January 1, 2004, and December 31, 2008, in the Department of Surgery, Kaunas University of Medicine, Lithuania. *The control group* consisted of 138 patients who underwent curative surgery for rectal cancer in our department without preoperative radiochemotherapy during the period of 2004–2006; patients were defined as having postoperative stage II or III rectal cancer (data were analyzed retrospectively). Patients with stage I and IV rectal cancer were excluded from this group of patients. *The study group* consisted of 38 patients who received preoperative radiochemotherapy followed by surgical resection (data were analyzed prospectively). Data for this group were taken from the prospective trial “Preoperative Chemoradiation Versus Short-Term Radiation Alone with Delayed Surgery for Stage II and III Resectable Rectal Cancer” (<http://clinicaltrials.gov>; identifier: NCT00597311). This preoperative treatment of rectal cancer in the Department of Coloproctology of Kaunas University of Medicine has been used since January 2007. The trial compares two preoperative strategies for the treatment of stage II and III rectal cancer: short-term radiotherapy (5×5 Gy) and delayed surgery after 6 weeks versus conventional chemoradiotherapy (50 Gy + 5 Fu/Lv) and surgery after 6 weeks as well. Preoperative staging includes endorectal ultrasound, pelvic CT, and MRI. Patients with preoperative stage II (T3/4N0M0) and stage III (any TN+M0) rectal cancer were enrolled into the study and referred for preoperative chemoradiotherapy. Preoperative radiochemotherapy was routinely used

only for very advanced, mainly T4, tumors before this trial until 2007.

Both groups of patients were operated by the same team of surgeons according to the same surgical standards, and specimens were analyzed by the same pathologist. The search for lymph nodes was performed in a standardized manner, cutting the specimen every 3 cm. Degreasing of the tissue samples with alcohol was not performed. Surgery was performed 6–7 weeks after completion of radiochemotherapy. Surgical procedures included anterior resection, Hartmann’s procedure, proctectomy with coloanal anastomosis, and abdominoperineal resection. Patients who underwent laparoscopic rectal resections were excluded from the study. Radical resection of the cancer-bearing specimen includes the lymph nodes adjacent to the inferior mesenteric artery and total mesorectal excision with preservation of the pelvic autonomic nerves. The patients were staged according to the 6th UICC pTNM staging system after the final histopathologic examination. Postirradiated resection specimens were evaluated for tumor size, depth of tumor penetration, number of lymph nodes per specimen and lymph node metastases.

Statistical analysis was performed using the statistical software package SPSS, version 10.0 (SPSS, Chicago, IL). Mann-Whitney test was used for the comparison of differences. A *P* value of <0.05 was considered statistically significant.

Results

A total of 138 patients underwent surgery without receiving preoperative radiochemotherapy (control group), and 38 patients were treated with neoadjuvant radiochemotherapy before the surgery (study group).

Our control group included 45% of males and 55% of females with a mean age of 69 years (SD, 9.63; range, 41–89 years); in the study group, there were 76% of males and 24% of females with a mean age of 63 years (SD, 9.45; range, 40–80 years). The sphincter preservation rate was 55% for patients operated without neoadjuvant treatment versus 71% for those randomized to chemoradiotherapy group, (*P*>0.05), abdominoperineal resection – 24% and 13%, respectively. No differences were detected between the patients who received and those who did not receive preoperative radiochemotherapy regarding the surgical procedures performed for curative resection of rectal cancer (Table 1). Distribution of the patients by T stage is shown in Table 2.

The mean tumor size measured in the cancer-bearing specimen was 4.37 cm (SD, 1.6) in the control group vs. 2.45 cm (SD, 1.1) in the study group, showing that the reduction of tumor size was significant (*P*<0.01) (Table 1).

Table 1. General characteristics of the patients

Characteristic	Control group (N=138)	Study group (N=38)
Mean age, years	69±9.63	63±9.45
Gender, %		
Males	45	76
Females	55	24
Type of surgery, n (%)		
Anterior resection	70 (51)	20 (53)
Hartmann's procedure	29 (21)	6 (16)
Proctectomy with coloanal anastomosis	5 (4)	7 (18)
Abdominoperineal resection	34 (24)	5 (13)
Tumor size, cm	4.37±1.6	2.45±1.1

TNM classification criteria require a minimum number of 12 lymph nodes per specimen to be examined pathologically in order to determine the precise stage of cancer. The results of our study revealed that a sufficient number of lymph nodes detected in the tumor-bearing specimen were found only in 5% of all study group patients, while the percentage of the patients with a sufficient number of lymph nodes in the control group was 55% (Table 3).

We detected a significant difference between the groups regarding the mean number of lymph nodes in resected tumor-bearing specimen. Pathologic examination revealed that in the patients who received preoperative radiochemotherapy, the mean number of lymph nodes in the tumor-bearing specimen was 13.5 (SD, 7.2), while in the patients who did not undergo preoperative radiochemotherapy, it was 6.29 (SD, 2.9) ($P<0.001$) (Table 3).

A total number of patients who had positive lymph nodes were 88 (64%) in the control group in comparison with 8 (21%) patients in the study group ($P<0.05$) (Table 3). Pathologic examination showed that the mean number of metastasis-positive lymph

Table 2. Distribution of patients according to T stage

T stage	Control group n (%) (N=138)	Study group n (%) (N=38)
Tx	5 (4)	0
T0 (complete response)	0	5 (13)
T1	2 (1)	5 (13)
T2	11 (8)	7 (18)
T3	101 (73)	20 (53)
T4	19 (14)	1 (3)

nodes was 5.12 (SD, 4.8) in the control group as compared with 2.11 (SD, 1.36) in the study group ($P=0.007$), while the ratios of cancer-infiltrated lymph nodes were 38% and 34% in the control and study groups, respectively, showing no significant difference between the groups (Table 3).

Discussion

Neoadjuvant chemoradiation therapy for locally advanced rectal cancer continues to gain wide acceptance and is a widely practiced treatment before surgical resection. According to some authors, this therapy could improve resectability, sphincter preservation, and local control. Although preoperative radiotherapy or chemoradiotherapy significantly reduces local recurrence, survival benefit is controversial, because the reduction in local recurrence does not necessarily translate into improved survival rate (2, 13–15).

Local recurrence rates, disease-free and overall survival remain the most important endpoints for rectal cancer patients. Pathologic stage after surgical resection together with circumferential resection margin seems to be the most important factors affecting these endpoints.

Table 3. Characteristics of specimens and distribution of patients by N stage

Characteristic	Control group (N=138)	Study group (N=38)	P value
Average No. of lymph nodes found per specimen	13.5±7.2	6.29±2.9	<0.001
Average No. of tumor-positive lymph nodes per specimen	5.12±4.8	2.11±1.36	0.007
Lymph node ratio of tumor-positive lymph nodes, %	38	34	NS
Lymph nodes in tumor-bearing specimen, n (%)			
<6 lymph nodes	12 (9)	16 (42)	<0.05
6–12 lymph nodes	50 (36)	20 (53)	<0.05
≥12 lymph nodes	76 (55)	2 (5)	<0.05
N stage, n (%)			
N+	88 (64)	8 (21)	<0.05
N0	50 (36)	30 (79)	<0.05

NS, not significant.

Onaitis et al. (16) analyzed 141 patients after neoadjuvant chemoradiation and resection. The conclusions were made that the presence of tumor in resected lymph nodes conferred much lower chances of recurrence-free and overall survival, and the T-stage response to preoperative treatment did not correlate with either local recurrence rates or long-term survival.

Kim et al. (17) analyzed 142 patients who received preoperative chemoradiotherapy. The results showed that the 5-year survival rate of patients with positive lymph nodes was 42.3% and that of patients with negative lymph nodes was 73.8% ($P=0.0004$). Multivariate analysis revealed that the pathologic N stage and operation method in postirradiated specimens were the independent prognostic factors. According to the data of their study, the operation method was not the confounding factors that attenuated statistical power of pathologic N stage. Thus, the authors conclude that nodal status in the postirradiated tumor specimen was the strongest factor affecting prediction of long-term oncologic outcomes. The 5-year survival disease-free rates for patients with stage II and III cancer were 49.7% and 33.6%, respectively.

Similar results reported by Habr-Gama et al. (18) showed that the final pathologic stage after surgical resection following neoadjuvant treatment is an important prognostic factor and affects disease-free and overall survival.

Lindebjerg et al. in their study concluded that not only lymph node status but also tumor response after preoperative chemoradiotherapy was a strong prognostic factor (19).

It seems that most of the authors agree that nodal status is one of the most important prognostic factors for patients with rectal cancer receiving or not preoperative treatment, but what about the number of lymph nodes in the tumor-bearing specimen, accuracy of pathologic findings and staging?

The trial by Wichman et al. showed that preoperative radiochemotherapy in advanced rectal cancer induced a significant decrease in the mean number of lymph nodes being detected in the tumor-bearing specimen (19 vs. 13, $P<0.05$). Furthermore, significantly fewer metastatic lymph nodes (3.1 versus 1.4, $P<0.05$) were detected, and fewer patients with stage III rectal cancer were diagnosed. According to the results of their study, inadequate numbers of lymph nodes for proper staging according to the UICC standards were resected in 13 (7.1%) patients of the control group and 11 (11.9%) patients of the study group.

A significant decrease in the mean number of lymph nodes was found in our study too. The mean number of 13.5 lymph nodes per specimen were detected in the group of patients without neoadjuvant

treatment, while a mean of 6.29 lymph nodes per specimen were detected in the group of patients after preoperative chemoradiation ($P<0.001$). The mean number of metastatic lymph nodes per specimen was significantly smaller in the patients following preoperative radiochemotherapy when compared with the patients receiving surgery alone (2.11 versus 5.12). The percentages of patients diagnosed with stage III (N+) disease in the control and study group were 64% and 21%, respectively, ($P<0.05$), and the inadequate number of lymph nodes was determined in 45% and 95%, respectively.

Although the results of these two studies are quite similar, some differences can be highlighted. We found fewer nodes per specimen both in the control and study groups (mean number, 13.5 versus 19 and 6.29 versus 13). The percentage of patients with an inadequate number of lymph nodes was also different (45% versus 7.1% and 95% versus 11.9%).

Mean numbers of lymph nodes found in the tumor-bearing specimen differ from author to author, and those reported in the study by Wichman et al. are quite high comparing with data reported by other authors: Tekkis et al. reported 11.7 lymph nodes per specimen (20), Evans et al. 13.8 (12), and Norwood et al. 14.8 (7). These authors reported data of all colorectal cancer patients; therefore, the number of lymph nodes for rectal cancer patients is even lower. It is difficult to comment on differences in the number of lymph nodes per specimen among the authors, because it depends on many factors. Norwood et al. reported that neoadjuvant treatment, operation type, specimen length, and age were important. Tekkis et al. pointed out that the following factors, such as age, ASA grade, Dukes stage, operative urgency, type of resection and preoperative radiotherapy, independently predicted lymph node harvest, while Evans et al. noted that operation type, T-stage, the reporting pathologists and neoadjuvant therapy affected lymph node retrieval. As we see, some factors are the same, but some differ from author to author. It could be that younger patients with lower ASA grade and undergoing elective surgery were present in the study by Wichmann et al., or it might be that more advanced surgical and pathologic techniques used.

In our study, we did not analyze all the factors affecting lymph node harvest, as the main goal was to assess the role of chemoradiotherapy on the number of lymph nodes in the tumor-bearing specimen and practical role of downstaging.

All patients were operated on electively in the same centre, by the same group of surgeons (5 coloproctologists), and the specimens investigated by the same pathologist, using standard methods of lymph node search. We assume that groups were homogenous in terms of quality of surgery and resected

specimens. The pathologist found fewer lymph nodes in the study group, and we draw a conclusion that neoadjuvant therapy significantly reduced the mean number of lymph nodes found in the specimen, reduced the mean number of metastatic lymph nodes per specimen and number of patients with stage III disease. What is practical significance of that?

On one hand, smaller number of metastatic nodes and smaller number of patients with stage III cancer are related to better prognosis as mentioned above. On the other hand, fewer lymph nodes found in the specimen is associated with inadequate staging and poorer prognosis and survival (7–9). Patients with higher nodal harvests as compared with fewer nodal harvests are more likely to have the probability of identifying more metastatic nodes (12). It means that some patients with Dukes stage A or B cancer most probably really have Dukes stage C cancer, with correspondingly reduced survival (7). This assumption could be confirmed by the tumor-positive lymph node ratio, which was not different between the patients of control and study groups (38% vs. 34%). Maybe this could explain why preoperative chemoradiotherapy for advanced rectal cancer patients does not necessarily translate into improved survival.

In our opinion, pathologic examination of the resected specimens is the most important factor. Is it inflammation or tissue fibrosis, or shrinking of the lymph node after the chemoradiotherapy that makes the identification of lymph nodes more difficult? Wichmann et al. offer to standardize pathologic techniques of lymph node retrieval and specimen preparation in order to avoid incomplete staging of patients who received preoperative treatment. More advanced pathologic methods for the detection of lymph nodes in the specimen should be used (degreasing with alcohol). Nevertheless, pathologists

always should try to identify all lymph nodes in the resected specimen, which ideally should be 12 in number. Sometimes it is difficult to achieve this goal, especially after preoperative chemoradiotherapy. Several authors conclude that current tumor classification according to the UICC should be revised regarding the number of lymph nodes necessary for proper classification, when a patient receives preoperative treatment (11). Nevertheless, suboptimal lymph node harvest should always be taken into account, when planning postoperative treatment. Patients participating in our clinical trial mentioned above, after receiving preoperative chemoradiotherapy, always receive postoperative chemotherapy irrespective of postoperative pathologic stage. We think that the preoperative (not postoperative) stage by endorectal ultrasound and MRI is most important, planning the treatment for rectal cancer patients, but its another very long and interesting discussion. Finally, ongoing trials comparing various preoperative treatment regimens of rectal cancer will show importance of the nodal status of the disease, tumor response to therapy, survival, and recurrence rates in the future.

Conclusions

Preoperative radiochemotherapy for advanced rectal cancer significantly decreased the number of lymph nodes detected in the tumor-bearing specimen. This also resulted in a significant decrease in the number of metastatic lymph nodes detected in the specimen, and fewer patients with stage III (N+) cancer were diagnosed. Preoperative radiochemotherapy could induce a significant downsizing and downstaging of advanced rectal cancer, but great care in operative and pathologic examination techniques must be taken to ensure appropriate staging.

Ikioperacinio chemospindulinio gydymo įtaka limfmazgių skaičiui pašalintame tiesiosios žarnos vėžio preparate

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Raktažodžiai: tiesiosios žarnos vėžys, ikioperacinis chemospindulinis gydymas.

Santrauka. *Tyrimo tikslas.* Pagal TNM sistemos reikalavimus, norint nustatyti tikslią N stadiją, reikia ištirti bent 12 limfmazgių pašalintame preparate. Įvertinome ikioperacinio chemospindulinio gydymo įtaką limfmazgių skaičiui pašalintame tiesiosios žarnos preparate.

Metodai. 138 ligonių, operuotų dėl II–III stadijos tiesiosios žarnos vėžio (2004–2006), retrospektyvieji duomenys (kontrolinė grupė) lyginti su prospektyviaisiais duomenimis 38 ligonių, kuriems (2007–2008) taikytas ikioperacinis chemospindulinis gydymas (tiriamoji grupė). Lygintas metastazinių limfmazgių skaičius, limfmazgių skaičius pašalintame preparate, metastazinių limfmazgių skaičius preparate, naviko dydis.

Rezultatai. Metastazinių limfmazgių rasta 88 (64 proc.) kontrolinės grupės ligoniams lyginant su 9 (21 proc.) tiriamosios grupės ($p < 0,05$). Vidutinis limfmazgių, rastų pašalintame preparate, skaičius buvo 13,5 kontrolinėje grupėje ir 6,29 – tiriamojoje ($p < 0,05$). Statistiškai reikšmingas skirtumas rastas vertinant metastazinių limfmazgių skaičių preparate (5,12 – kontrolinėje grupėje palyginti su 2,11 tiriamojoje, $p < 0,05$). Vidutinis naviko dydis buvo 4,37 cm kontrolinėje grupėje ir 2,45 cm tiriamojoje grupėje ($p < 0,01$).

Išvados. Ikioperacinis chemospindulinis gydymas taikytas ligoniams, kuriems nustatytas progresuojantis tiesiosios žarnos vėžys, sumažina limfmazgių skaičių pašalintame tiesiosios žarnos preparate. Taip pat mažiau metastazinių limfmazgių rasta preparate ir III (N+) stadijos ligonių. Ikioperacinis gydymas gali sumažinti piktybinio naviko dydį ir stadiją, bet reikėtų atkreipti dėmesį į operacijos ir patologinio tyrimo kokybę siekiant išvengti neadekvataus vėžio stadijų nustatymo.

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Received 10 November 2009, accepted 7 May 2010
 Straipsnis gautas 2009 11 10, priimtas 2010 05 07