The Influence of Neoadjuvant Treatment on the Number of Lymph Nodes on the Surgical Specimen in Mid and Low Rectal Cancer - A Retrospective Single-Centre Study

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Rezumat

Influenţa tratamentului neoadjuvant asupra numărului ganglionilor limfatici de pe piesa chirurgicală în cancerul rectal mijlociu şi inferior – un studiu retrospectiv realizat într-un singur centru

Introducere: În acest studiu, ne propunem să identificăm efectul radioterapiei neoadjuvante asupra numărului de ganglioni limfatici totali recoltaţi şi pozitivi în piesa operatorie. În plus, am încercat să identificăm impactul chimioterapiei asociate cu radioterapia asupra structurilor menţionate.

Pacienţi şi metodă: În cadrul studiului am inclus pacienţi trataţi pentru cancer rectal într-o singură unitate chirurgicală oncologică care deserveşte partea nord-estică a României, pe o perioadă de 5 ani şi jumătate, între mai 2013 şi aprilie 2018. În primul rând, am comparat stadializarea anatomopatologică a ganglionilor limfatici cu stadializarea preterapeutică. În al doilea rând, am comparat valorile ganglionilor limfatici în raport cu schema de tratament.

Rezultate: În total, 498 de pacienţi au fost trataţi radical prin intervenţii chirurgicale deschise pentru cancer rectal mediu şi inferior. Am observat o scădere a stadializării N în 218 cazuri, 65 rămânând staţionare şi în 10 crescând stadiul ganglionar pe specimenul chirurgical. Am identificat diferenţe semnificative în numărul total de ganglioni (17.4 vs 24.2, $p < 0.001$), numărul de ganglioni pozitivi (1.4 vs 3.4, $p < 0.001$) şi raportul între numărul de

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gaglioni pozitivi și totali (0.08 vs 0.14, $p < 0.001$), în pacienți cu, respectiv fără tratament neoadjuvant. Cu toate acestea, nu s-a identificat o diferență semnificativă statistic între pacienții cu și fără chimioterapie asociată radioterapiei neoadjuvante ($p = 0.539$, $p = 0.58$, $p = 0.575$).

Concluzie: Acest studiu arată că există variații semnificative în funcție de aplicarea tratamentului neoadjuvant, între numărul de ganglioni limfatici pozitivi și totali, precum și raportul pozitivi / totali al ganglionilor limfatici.

Cuvinte cheie: cancer rectal, ganglioni limfatici, tratament neoadjuvant

Abstract

Introduction: In this study, we aim to identify the impact of neoadjuvant radiation treatment upon the number of harvested and positive lymph nodes in the surgical specimen; in addition, we tried to identify the impact of chemotherapy in association with radiotherapy on said structures.

Patients and methods: In the study we included patients treated for rectal cancer within a single oncologic surgical Unit serving the north-eastern part of Romania, over a period of 5 and a half years, between May 2013 and April 2018. Firstly, we compared pathologic lymph node status to pretherapeutic staging. Secondly, we compared lymph node values in relation to the treatment scheme.

Results: There was a total of 498 patients treated radically through open surgery for low and mid rectal cancer. We saw a decrease in N staging in 218 cases, 65 remaining stationary and 10 increasing their lymph node staging on the surgical specimen. We identified significant differences between the total number of lymph nodes (17.4 vs 24.2, $p < 0.001$), the number of positive lymph nodes (1.4 vs 3.4, $p < 0.001$) and the ratio between positive and total lymph nodes (0.08 vs 0.14, $p < 0.001$) in patients with and without neoadjuvant treatment respectively. However, there was no statistical difference between patients with and without chemotherapy associated to radiotherapy in the neoadjuvant treatment plan ($p = 0.539$, $p = 0.58$, $p = 0.575$).

Conclusion: This study shows there are significant variations according to the application of neoadjuvant treatment, between the numbers of positive and total lymph nodes, as well as the positive/total lymph node ratio.

Key words: rectal cancer, lymph nodes, neoadjuvant treatment

Introduction

Rectal cancer is an important public health issue, not only through its high morbidity and mortality, but also because of its invalidating treatment that has an important impact on the patient's quality of life. However, the therapy of rectal cancer patients has seen important improvement in the last couple of decades, since the emergence of the concept of total mesorectal excision (1) and the demonstration of the effectiveness of neoadjuvant radiation therapy (2,3).

Colorectal cancer is among the leading types of cancer, being the world's third most common neoplasia in males and second in women (746000 cases – 10% of total, respectively 614000 cases – 9.2% of total), according to the Globocan study(4). In Romania, the issue is even more important, due to the lack of a national colorectal cancer screening programme.

The existence of a multimodal approach within a multidisciplinary team is essential for the treatment of rectal cancer to be effective. This approach to neoplastic rectal pathology is

one of the reasons of the improvement in survival in rectal cancer over the last decade (5). There are several major issues that the multidisciplinary team has to approach in rectal cancer, such as treatment of incipient neoplasia, indication of neoadjuvant treatment, quality of life and local recurrence.

Neoadjuvant treatment is an important part of multimodal therapy used in rectal cancer. This may be short-term or long-term radiotherapy (RT) or radiochemotherapy (CRT). Amongst the purposes of neoadjuvant treatment are the downsizing and downstaging of the rectal cancer, in order to improve resectability and reduce the risk of local recurrence. According to the European Society of Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines (6, 7), the indication for neoadjuvant treatment are locally advanced Stage II (cT3 or cT4, cN0) or Stage III (any T, cN1 or 2) tumors where the risk of local recurrence after surgical treatment is high because of the possibility of positive resection margins, or tumors in which a better local control can be achieved through neoadjuvant treatment followed by radical surgery.

The effect of preoperative RT or CRT is the reduction of the local recurrence rate, without the improvement of OS (8-10), but with an important impact on intestinal, urinary and sexual functions after surgery (6). Therefore, the indication of neoadjuvant RT or RCT must be thoroughly calculated within the multidisciplinary cancer treatment team, so as to reduce the risk of local recurrence, but, withal take into consideration the important secondary effects of RT on the patient's bowel, urinary and sexual functions.

On the other hand, the quality control of the surgical act is an important predictive factor and should follow the guidelines of the Royal College of Pathologists (11) in order to perform an adequate evaluation of the surgical specimen (12).

In accordance with the above-mentioned guidelines, a minimum of 12 locoregional lymph nodes must be examined in order to perform an adequate pathological assessment

of the surgical specimen (6, 7). Moreover, in a recently published article, Wu et al. imagine a statistical instrument by which they determine the minimum number of lymph nodes that need to be examined in order to obtain an accurate staging, that varies in accordance with the stage of the tumor: 5, 9 and 29 lymph nodes for a 90% accuracy for T1, T2 and T3 tumors respectively (13).

It is important to mention that the lymph node yield varies according to several factors, among which we can enumerate the quality of the surgical act, the availability of the pathologist to identify lymph nodes, patient-related factors, tumor characteristics, or neoadjuvant treatment (14).

In this study, we aimed to observe the variations in lymph node yield in accordance to the treatment scheme in a group of patients with radical treatment for rectal cancer. The objectives of this study were to make a comparison between patients with rectal cancer with and without neoadjuvant (chemo)radiotherapy in matter of positive lymph nodes and total lymph nodes on the resection specimen.

Patients and Methods

Patients

In the study we included patients treated for rectal cancer within the First Surgical Unit of the Iasi Regional Institute of Oncology over a period of 5 and a half years, between May 2013 and April 2018.

We considered the following inclusion criteria: patients with rectal cancer receiving curative treatment, with adequate documentation of the treatment plan, full medical records of the pathology report. Exclusion criteria were: localization of the tumor at the level (or higher than) the upper rectal ampulla (12 cm from the anal verge / above the peritoneal reflection), patients with incomplete medical records.

There was a total of 498 patients treated radically for mid and low rectal cancer that were considered for this study, according to the flowchart depicted in *Fig.1*.

Figure 1. Patient flowchart

Reviewed Patient Data

Clinical data was retrieved retrospectively from medical records.

Medical records were reviewed to obtain the following information: age, gender, type and localization of rectal neoplasia, clinical and pathological tumor staging using the American Joint Committee on Cancer TNM Staging(15), total number of harvested lymph nodes on surgical specimen, number of positive lymph nodes on surgical specimen, existence and type of neoadjuvant treatment, type of surgery.

Pre-therapeutic staging was performed through pelvic MRI in 84.5% of the cases (421 patients) and through pelvic CT scan in 19.6% of the cases (98 patients), where pelvic MRI was not possible due to patient-related factors (overweight, metal implants) or hospital-related factors. In all cases, we performed a pre-therapeutic abdominal ultrasonography

and chest X-ray. Metastases were documented through CT scan in all cases.

All patients who benefitted from neoadjuvant treatment were reevaluated through pelvic MRI or pelvic CT scan, in accordance to the above-mentioned particularities.

In order to analyze differences in lymph node numbers, in addition to the number of positive lymph nodes and the total number of harvested lymph nodes on the surgical specimen, we have also calculated the ratio between the two values (for ease of expression, we have named it PTLR – positive-to-total lymph node ratio).

Neoadjuvant Treatment

Neoadjuvant treatment was decided upon in accordance to the above-mentioned NCCN and ESMO guidelines, within the multidisciplinary rectal cancer treatment team.

The neoadjuvant treatment consisted of

long-term radiotherapy in 287 cases (57.6%), of which 214 (representing 74.6% of all patients with long-term radiotherapy) received associated chemotherapy. Thus, 73 patients (25.4%) received standalone radiotherapy. Two patients (0.4%) received short-term neoadjuvant radiotherapy. In addition, 4 patients (0.8%) benefited from neoadjuvant chemotherapy, all of whom were patients with multiple hepatic metastases with uncomplicated rectal tumors.

The long-course treatment plan consisted of a total dose of 50.4 Gray administered in 28 fractions, during a 5-week and a half treatment period. Short-course treatment consisted of a total dose of 25 Gray in 5 days. Capecitabine was associated as chemotherapy to long-course treatment with the purpose of increasing susceptibility of tumor cells to radiation.

Surgical Intervention

Out of a total of 498 patients with radical treatment for mid and low rectal cancer, in 185 cases (37.1%) the surgical intervention consisted of an extralevator abdominoperineal excision of the rectum, in 169 cases (33.9%) of a very low anterior resection of the rectum with total mesorectal excision, and 144 patients (28.9%) benefited from an extended Hartmann's operation with total mesorectal excision.

In all cases, the pelvic dissection respected the principles set by Heald in 1982 when he described the concept of total mesorectal excision (1). Moreover, the ligation of the inferior mesenteric artery was performed immediately below the emergence of the left colic artery in all cases.

Pathology Assessment

The pathological evaluation was performed within the hospital's Pathology Unit in a standardized manner. Lymph node identification and evaluation was performed by the Unit's pathologists.

Pathological staging was performed using

the American Joint Committee on Cancer TNM Staging (15).

Statistical Analysis

Statistical data processing was performed in SPSS v.25 (IBM SPSS Statistics). Non-parametric tests (Chi-square test, McNemar Chi-square or Fisher's exact test) were used to analyze the degree of association between categorical variables and parametric tests for the comparative analysis of continuous variables (Student's t test, Mann-Whitney test). The reference level for the significance of the test (p-value) was considered 0.05. Continuous variables were expressed as mean $\pm$ standard deviation.

Results

There was a total of 498 patients treated radically for low and mid rectal cancer, of which the majority were males, mostly in the 7th decade of life (*Table 1*).

All 498 patients were diagnosed with rectal adenocarcinoma.

A number of 293 patients received neoadjuvant treatment, whereas 205 patients were subjected to upfront surgery. Of the 293 patients with neoadjuvant treatment, 214 received a combined treatment consisting of radiation and chemotherapy.

A comparison between pre-therapeutic staging and pathological staging reveals an overall moderately-good response of the rectal neoplasm to neoadjuvant treatment. Thus, in 17 cases there was a pathological complete response to neoadjuvant treatment and there was an important reduction in the number of stage III cases (from 72.3% to 30.9%), with an increase in the number of stage-I and II cases (from 5.8 to 22.7, respectively from 7.4 to 26.1) (*Table 1, Fig. 2*). In addition, when comparing the initial TNM staging and the pathology result, we have observed that in 132 cases there was a decrease in the tumor stage, in 147 cases it was stationary, and in 14 cases it saw an increase; on the other hand, the lymph nodes had a more dynamic evolution, with a decrease

Table 1. Baseline patient details

Baseline data	Total N=498
Age (years) [†]	63.2±12.4
Gender (male:female)	327:171 (65.7: 34.3)
Clinical T stage	
cT1	9 (1.8)
cT2	52 (10.4)
cT3	342 (68.7)
cT4	95 (19.1)
Clinical N stage	
cN0	70 (14.1)
cN1	181 (36.3)
cN2	246 (49.4)
cN+	1 (0.2)
Initial clinical M stage	
cM0	426 (85.5)
cM1	72 (14.5)
Clinical TNM stage	
I	29 (5.8)
II	37 (7.4)
III	360 (72.3)
IV	72 (14.5)
Neoadjuvant radiotherapy	
Yes	289 (58.0)
No	209 (42.0)
Neoadjuvant chemotherapy	
Yes	218 (43.8)
No	280 (56.2)
Surgical procedure	
Abdominoperineal excision	185 (37.2)
Low anterior resection	169 (33.9)
Extended Hartmann's operation with TME	144 (28.9)
Pathological T stage	
pT0	18 (3.6)
pTis	8 (1.6)
pT1	16 (3.2)
pT2	113 (22.7)
pT3	290 (58.2)
pT4	53 (10.6)
Pathological N stage	
pN0	278 (55.8)
pN1	134 (26.9)
pN2	86 (17.3)
Postoperative cM stage	
cM0	421 (84.5)
cM1	77 (15.5)
Pathological TNM stage	
pCR	17 (3.4)
0	8 (1.6)
I	113 (22.7)
II	130 (26.1)
III	154 (30.9)
IV	76 (15.3)
Interval (days) [†] neoadjuvant therapy – surgical sequence	80.7±29.9

[†]Continuous variables were expressed as: mean ± standard deviation; categorical variables: number (%). Kruskal-Wallis for continuous variables; (*) Marked effects are significant at $p < 0.05$. Chi-square test (McNemar or Yates Chi-square) or Fisher's exact test; pTis, pathological tumor in situ; pCR, pathological complete response

Figure 2. Comparison between pretherapeutic and pathological staging in cases with neoadjuvant treatment for rectal cancer

in N staging in 218 cases, 65 remaining stationary and 10 increasing their lymph node staging on the surgical specimen.

The surgical intervention was performed at a mean distance of 80.7 ± 29.9 days from the end of the neoadjuvant treatment period.

In comparison between the values of positive lymph nodes and total harvested lymph nodes, in accordance to the presence or absence of neoadjuvant treatment, as depicted in *Table 2*, there have been statistically significant differences, with higher values in patients without neoadjuvant treatment. Moreover, the PTLR showed significantly higher values ($p < 0.001$) in patients without neoadjuvant treatment. Differences in lymph node numbers based on neoadjuvant treatment are depicted in *Fig. 3*.

On the other hand, we did not notice any statistically significant difference between evaluated lymph node values in accordance to the addition of chemotherapy within the treatment plan for neoadjuvant treated patients (*Table 3*).

Discussions

We have managed through this study to demonstrate that the number of harvested

Table 2. Statistic comparison between patients with neoadjuvant treatment, on the one hand and upfront surgery, on the other, in matter of total lymph nodes, positive lymph nodes and ratio between positive and total lymph nodes

Neoadjuvant treatment	Total lymph nodes		p-value*	Positive lymph nodes		p-value*	Positive lymph nodes/ total lymph nodes		p-value*
	Yes	No		Yes	No		Yes	No	
value [†]	17.4±9.9	24.2±11.9	<0.001	1.4±3	3.4±6.8	<0.001	0.08±0.16	0.14±0.23	<0.001

[†]mean±standard deviation

* Mann-Whitney test or t-test; statistically significant results for p < 0.05

Figure 3. The differences in total number of lymph nodes and in positive lymph nodes according to the presence or absence of neoadjuvant treatment

lymph nodes and the number of positive lymph nodes have shown to be negatively influenced by the presence of neoadjuvant radiotherapy in the treatment regimen. This result is consistent with the outcomes of other studies on this matter (16).

The particularity of this paper consists, on the one hand, on the high number of cases over a relatively short period of time and on the other hand on the consistency of radiochemotherapy throughout the study period, which increases the strength of the results. There were a

Figure 4. The differences in total number of lymph nodes and in positive lymph nodes in accordance with the association of chemotherapy in the neoadjuvant treatment plan

number of 76 patients with metastatic disease that underwent radical surgical resection that was decided upon within the multidisciplinary tumor board, in accordance with the principles and guidelines set by the ESMO consensus for the management of patients with metastatic colorectal cancer (17). These patients were included in the study, because all of these patients benefitted from a radical resection of the rectal tumor, with a total mesorectal

Table 3. Statistic comparison between patients with and without chemotherapy associated to neoadjuvant radiotherapy, in matter of total lymph nodes, positive lymph nodes and ratio between positive and total lymph nodes.

Chemotherapy associated to radiation therapy	Total lymph nodes		p-value*	Positive lymph nodes		p-value*	Positive lymph nodes/ total lymph nodes		p-value*
	Yes	No		Yes	No		Yes	No	
value [†]	17.2±10	18±9.6	0.5392	1.4±3.2	1.2±2.5	0.5803	0.079±0.16	0.074±0.14	0.575

[†]mean±standard deviation; *Mann-Whitney test or t-test; statistically significant results for p < 0.05

excision and we considered that metastatic disease does not directly influence lymph node status of the patient.

Radiotherapy may influence the number of lymph nodes through multiple mechanisms, such as destruction or fibrosis, which causes a more difficult dissection by the pathologist (18). The fact that, along with the decrease in the numbers of lymph nodes (positive and total), there was a decrease in the PTLR ratio as well, denotes the fact that neoadjuvant treatment, especially radiotherapy, influences the outcome of the lymph node status of the patient, by destruction of the tumor cells within said lymph nodes. Thus, there was a good response to an efficient neoadjuvant treatment in the studied batch of patients. On the other hand, had it not been a significant decrease in the PTLR, or had it even been an increase in its value, we would have had to raise the question if neoadjuvant treatment really is efficient on the patient's lymph nodes. This ratio may be considered a more exact prognostic factor than the number of positive lymph nodes that are evaluated on the surgical specimen.

The fact that chemotherapy was not significantly associated with lymph node status is interesting as well. This may be explained by the fact that chemotherapy does not have the same effect on lymph node structures as radiotherapy. However, the main purpose of the association of chemotherapy within neoadjuvant treatment is to sensitize tumor cells to radiation, thus its impact on lymph node numbers is undetectable.

The main limit of this study is the fact that there was no comparison regarding lymph node numbers between types of surgery. However, this was not the purpose of this study and may be addressed in a later study. In addition, we could not take into consideration the bias introduced by the fact that surgical specimens were analyzed by more than one (up to five) examiner within the pathology department; on the other hand, the fact that procedures are standardized within this department reduces the possible error introduced by this fact.

Variations in TNM staging are an interesting

issue and a comparison between pretherapeutic, post-neoadjuvant and pathological staging would be an interesting subject for a further study. However, as variations in lymph node staging were not a subject of this study, this aspect was not addressed in this paper.

Conclusion

We have shown a significant variation in the number of lymph nodes (both total examined and positive) in relation to the presence or absence of neoadjuvant treatment in patients with radical treatment for mid and low rectal cancer. In addition, the ratio between the two values varies significantly, with higher values in patients without neoadjuvant treatment. Through these findings, we reiterate the importance of this ratio in the prognostic of rectal cancer.

Compliance with Ethical Standards

This study was approved by the ethics board of the Regional Institute of Oncology and the University of Medicine and Pharmacy "Grigore T Popa" Iasi.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Conflict of Interest

The authors declare no conflict of interest.

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