Analysis of patients with complete histopathological tumour regression after neoadjuvant chemoradiotherapy for locally advanced rectal cancer

Tomislav Petrović[1], Zoran Radovanović[1], Bojana Bokorov[1], Ivan Nikolić[1], Slavica Knežević-Ušaj[1], Milenko Čanković[2]

SUMMARY

Background: *Our aim was to present the effect of the neoadjuvant chemoradiation therapy on the development of the complete histopathological tumour regression in patients with locally advanced rectal cancer and its influence on a five-year survival of these patients.*

Methods: *In total, 223 patients were included in the analysis; 109 patients had the locally advanced rectal cancer; 75 patients received the neoadjuvant chemoradiation therapy, which was later followed by surgery; 34 patients were treated with the surgery alone. The surgical procedure was done 6 to 8 weeks after the chemoradiation therapy and it was preceded by haematology and biochemical analyses. In addition, patients were examined by ultrasound and MRI imaging of liver to evaluate the effects of neoadjuvant chemoradiation therapy. Accordingly, we had two patient groups: patients with the complete histopathological tumour regression and patients with the incomplete or no regression. We performed the statistical analysis of all locally advanced rectal cancer patients and determined their survival.*

Results: *The complete histopathological tumour regression was found in 10.7% of 75 patients who were treated with preoperative chemoradiation. The down staging of the tumour appeared in 53.3% of patients. There were no stage changes in 21.3% of patients. The disease progressed into a more severe stage in 9.3% of patients, while the effects of the preoperative chemoradiation therapy could not be determined in 5.3% of patients. The survival of patients with the complete histopathological tumour regression was 70% in a five-year period, while it was 40% in patients with incomplete histopathological regression.*

Conclusion: *The preoperative chemoradiation therapy leads to complete histopathological tumour regression and increases a five-year survival (70%). It also leads to the increase of the number of patients who undergo radical surgery.*

KEY WORDS: *Rectal Neoplasms; Chemotherapy, Adjuvant; Radiotherapy, Adjuvant; Preoperative Period; Treatment Outcome*

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[1]Oncology Institute of Vojvodina, Sremska Kamenica, Serbia, [2]Institute of Cardiovascular Diseases Vojvodina, Sremska Kamenica, Serbia

Correspondence to:
Dr. Tomislav Petrović, Oncology Institute of Vojvodina, Institutski put 4, 21204 Sremska Kamenica, Serbia

petrovic.tomislav@onk.ns.ac.rs

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Abbreviations:
MRI – Magnetic resonance imaging, TME – Total mesorectal excision, TD – Total dose, MeV – Mega electrone volte, CT – Computorised tomography, PH – Pathohistology

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INTRODUCTION

Rectal cancer is one of the most frequent malignant cancers of the modern days. It is an insidious disease, which is in 90% of cases detected in the symptomatic phase of the disease when the possibility of its healing is drastically reduced in relation to the asymptomatic phase (1). The basic treatment principle is surgical procedure, which leads to healing in 50-60% of the cases.

The incidence of rectal cancer is significantly different among countries. It is the highest in the areas where the western way of living and nutrition is practiced. In 100,000 people, the incidence rate of this disease in Vojvodina is 24.7 for men and 16.1 for women. In 2007, there were 4,909 new male patients suffering from carcinoma and 259 of them (4.9%) had rectal cancer. There were 4,462 new female patients suffering from carcinoma and 165 of them (3.7%) had rectal cancer. The cumulative risk represents the probability of a disease appearance at a certain age. Under the condition that it does not come to death as an outcome of some other cause, the cumulative risk of rectal cancer is 1 of 64 in the male population and 1 of 112 in the female population (2). In our paper, a special attention was given to the patients with the locally advanced rectal cancer (T3-4, N1-2) who preoperatively received neoadjuvant chemoradiation therapy and had complete histological tumour regression. The aim of the combined chemo and radiation therapy is to improve the treatment results acting on several levels. The radiation therapy aims to improve the disease control and it functions as a radio-potentiator for the chemotherapy. Neoadjuvant chemoradiation therapy leads to the tumour regression, which is manifested by size reduction, down staging or even complete tumour disappearance. Tumour down staging contributes to the increase of the number of patients who undergo the radical surgery (3). It increases the number of sphincter-preservation interventions (4), improves the local disease control and affects the survival rate (5). However, the long-term oncologic results of the complete histopathological tumour regression are still controversial (6).

MATERIAL AND METHODS

The research was conducted as a retrospective study at the Oncology Institute of Vojvodina, Clinic for surgical oncology. The study group consisted of 223 patients who were treated for rectal cancer from 01.01.2000 to 31.12.2004. The patients were between 32 and 82 years of age. There were 338 patients that underwent surgery at the Clinic during that period but, due to lack of data, 115 patients could not be included into the study.

The rectal cancer diagnosis and the stage of the disease were determined preoperatively. Diagnostic algorithm included anamnesis, digitorectal examination, colonoscopy, biopsy, histopathological confirmation of adenocarcinoma, CT and/or MRI of small pelvis.

This study included all the patients who underwent surgery but who did not have stage IV of the diseases, i.e. who did not have any visible metastases prior to therapy.

A special attention was paid to the patients who had locally advanced disease (109). Thirty-four of them did not receive the preoperative chemoradiation therapy but only underwent surgery. There were 75 patients who received preoperative chemoradiation therapy.

The radiotherapy was performed on linear accelerator with the energies from 10 to 15 MeV. Following radiotherapy, the patients received the chemotherapy (5-FU and leucovorin) on day 1, 2, 10, 11, 20 and 21. At the protracted protocol, the preoperative radiation dosage was total dose 50.4 Gy fractionally divided into the equal daily dosages of 1.8 Gy. A daily dosage of TD to 2 Gy was allowed to be given, but not to be exceeded, because of the special sensitivity of the small intestine as well as the other, critical organs.

The MRI was performed and the restaging was determined 6-8 weeks after the chemoradiation therapy.

Before the surgical procedure, blood and biochemical analysis were performed as well as the liver ultrasound. Depending on the tumour spreading, either radical or palliative surgical procedure was done. The radical surgery implied the front lower rectal resection and the rectal amputation with the total mesorectal excision (TME). The palliative surgical procedures were the formation of the bipolar stomata or transanal tumour excision or just peritoneum biopsy in the case of carcinosis.

Disease stage was determined by histopathological analysis of surgical samples. Based on that, the two subgroups of patients were formed:

- Patients with the complete histological regression (tumour was not found at the removed part of the rectum with the mesorectum) and
- Patients with the tumour (there was no histological regression or it was incomplete).

We did the statistical overall analysis of patients with the locally advanced rectal cancer and determined their survival.

RESULTS

We examined 223 patients: 131 men with mean age of 63.65 years and 92 women with mean age of 63.82 years. The ratio was 1.42:1 in favour of men. There were 168 patients (75.3%) who underwent radical surgery and 5 patients (24.7%) who underwent palliative surgery (Table 1).

Radical surgery was done in 75.3% of patients and palliative surgery in 24.7% patients (Table 1).

The results of histopathological analysis of surgical samples regarding tumour regarding the TNM staging of patients are shown in Table 1.

The grouping according to the stage of the disease in relation to the clinical staging showed that 3.6% of patients had complete histopathological tumour regression; 16.1% of patients had the stage I of the disease; 22.9% of patients had stage II; 29.6% of patients had stage III; and 19.7% of patients had the stage IV. Due to the insufficient data from TNM classification, the stage of the disease could not be determined in 8.1% of patients (Table 1).

The patients who underwent surgery at the Clinic for surgical oncology were followed up for the evaluation of survival by the end of December 2009. Of 223 evaluated patients, 91 patients (40.8%) are alive and 132 patients (59.2 %) have died (Figure 1).

A five-year survival in evaluated group of patients was 50%.

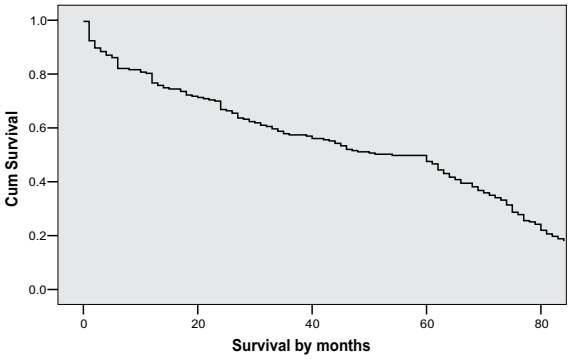

Figure 1. Survival in the evaluated group of patients

We determined the survival in relation to the type of surgery (Figure 2).

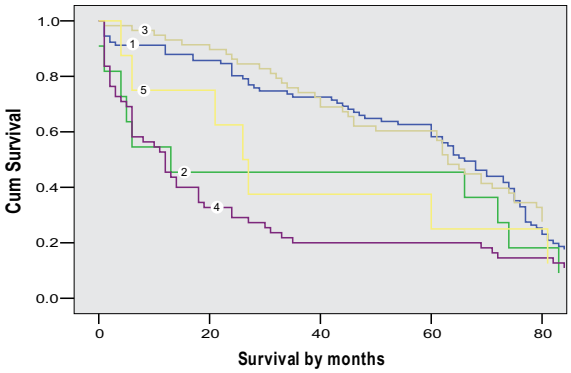

Figure 2. Patients' survival in relation to the type of surgery
1 – Low anterior, 2 – Hartmann, 3 – Miles, 4 – Palliative surgery – colostomy, 5 – Resectio rectosigmae

Figure 2 shows that the patients who underwent radical surgery (Dixon, Miles) have a five-year survival around 60%, which is higher than in patients who underwent palliative surgery and whose five-year survival rate is 20%.

Among the patients with locally advanced rectal cancer (109), 69.8% of patients received preoperative radiation therapy and 31.2% of patients did not (Table 1). Among patients who received the radiation therapy, 85.3% of patients underwent radical surgery, while 14.7% of patients underwent palliative surgery. In the group of patients with the locally advanced rectal cancer that had no preoperative radiation therapy, 76.5% of patients underwent radical surgery and 23.5% of patients underwent palliative surgery (Table 1).

We determined and compared the survival rates of patients with the locally advanced rectal cancer (Figure 3). We analyzed two groups:

- Patients who preoperatively received radiation therapy and
- Patients who did not preoperatively receive radiation therapy

We analysed the effect of radiation therapy, giving special attention on the occurrence of the complete histopathological rectal cancer regression. Seventy-five patients with the locally advanced rectal cancer received radiation therapy, and the complete histopathological tumour regression developed in 10.7% of these patients. From 75 patients who received the radiation therapy, 40% of patients are alive and 60% of patients have died. From the group of patients with the complete histopathological tumour regression, 37.5% of patients are alive and 62.5% of patients have died. There were 67 patients with the incomplete or no tumour regression; 40.3%

Table 1. Clinical characteristcs of patients with advanced rectal cancer

Gender	**No of patients / %**
Male	131
Female	92
TNM stage	**No of patients / %**
Stage 0	8 (3.6%)
Stage 1	36 (16.1%)
Stage 2	51 (22.9%)
Stage 3	66 (29.6%)
Stage 4	44 (19.7%)
Undetermined stage	18 (8.1%)
Total	223 (100%)
Type of surgery	
Miles	58 (26.0%)
Low anterior	91 (40.8%)
Hartmann	11 (4.9%)
Recto sigma resection	8 (3.6%)
Palliative surgery - colostomy	55 (24.7%)
Total	223 (100%)
Patients with locally advanced cancer	
With preoperative radiation therapy	75 (68.8%)
Without radiation therapy	34 (31.2%)
Total	109 (100%)
Patients with preoperative radiation therapy (type of surgery)	
Low anterior	31 (41.3%)
Miles	32 (42.7%)
Rectosigma resection	–
Hartmann	1 (1.3%)
Palliative surgery - colostomy	11 (14.7%)
Total	75 (100%)
PH finding	**Alive**
Complete regression	3 (37.5%)
Incomplete regression	27 (40.3%)
Patients without preoperative radiation therapy (type of surgery)	
Low anterior	12 (35.3%)
Miles	7 (20.6%)
Rectosigma resection	2 (5.9%)
Hartmann	5 (14.7%)
Palliative surgery - colostomy	8 (23.5%)
Total	34 (100%)
Died	
5 (62.5%)	8 (100%)
40 (59.7%)	67 (100%)
Evaluation of radiation therapy effects	**No (%)**
Complete pathohistological tumour regression	8 (10.7%)
Down-staging	40 (53.3%)
Without changes	16 (21.3%)
Progression	7 (9.3%)
Undefined effect	4 (5.3%)
Total	75 (100%)

of them are still alive, while 59.7% of them have died. Test of statistical significance did not show any significant statistical difference (p>0.05) (Table 1).

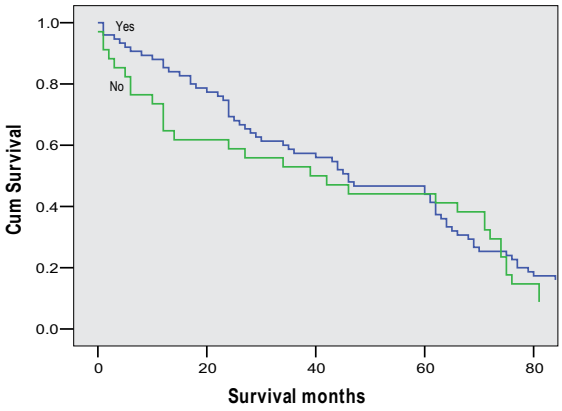

Figure 3. Patient survival according to preoperative radiation

Of 75 examined patients, 40% of patients are still alive, while 60% of patients have died. Of 8 patients (stage 0), 37.5% of patients are alive and 62.5% of patients have died; of 8 patients (stage I), 62.5% of patients are alive and 37.5% patients have died; of 16 patients (stage II), 50.0% are alive and 50.0% have died; of 32 (stage III patients), 40.6% are alive and 59.4% patients have died; of 7 patients (stage IV), 14.3% of patients are alive, while 85.7% of them have died. Because of the incomplete data from TNM classification, 4 patients were not included into this classification.

The evaluation of radiation therapy effects showed response in 64% of patients, 21.3% of patients had unchanged findings, and 9.3% of patients had disease progression (Table 1). We could not estimate the effect of the preoperative radiation therapy in 5.3% of patients due to insufficient data from the TNM classification.

We determined and compared the survival for two groups of patients with the locally advanced rectal cancer who were previously treated with the chemoradiation therapy. In patients with the complete histopathological tumour regression a five-year survival was 70% and in patients without the complete histopathological tumour regression it was 40% (Figure 4).

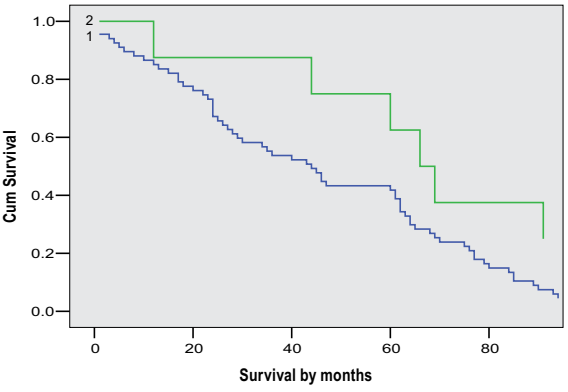

Figure 4. Survival in relation to histopathological tumour regression
1 – Without complete histological regression
2 – With complete histological regression

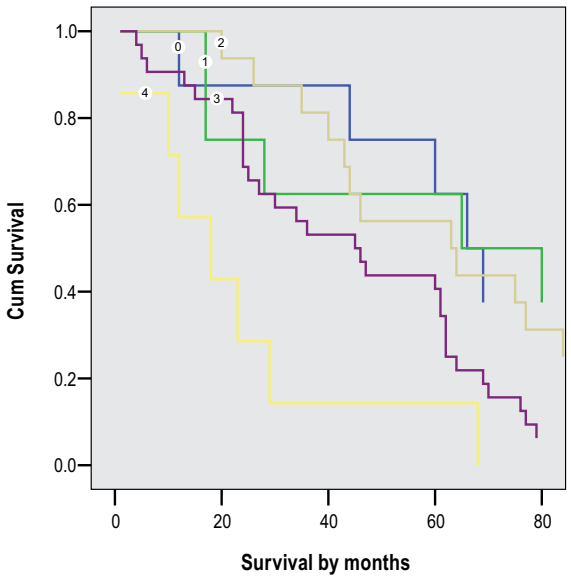

Figure 5. Patient survival according to stage of the disease (Stage 0-4)

We used the Kaplan-Maier method to present the survival in patients who were treated with the preoperative radiation therapy in relation to the clinical stage of the disease. We found that a five-year survival in patients with S_0 of disease was 70%, 65% in patients with S_1, 55% in patients with S_2, 45% in patients with S_3 stage, and 15% in patients with S_4 of disease (patients with distant metastases) (Figure 5).

One of the indicators of the combined therapy success was the presence of the local recurrence. In our study group, 8 patients from 64 patients that underwent radical surgery had the basic disease recurrence. After rectal resection, 3 patients developed the local recurrence and it developed in 5 patients that underwent rectal amputation. From these 8 patients, there were 5 men and 3 women. In 4 patients, the therapy for the local recurrence was the radiation therapy and the recurrence was surgically removed in 2 patients. The combination of surgery and radiation therapy was performed in one case. Nothing was done in one case.

DISCUSSION

Modern treatment of the rectal cancer is based on the determination of the stage of the disease. It gives insight in the prognostic factors as well as in the choice of therapy. For the classification of the stage of the disease, the TNM classification is used. It is clear that its precise determination is necessary. The chemoradiation therapy is used in the treatment of the locally advanced rectal cancer (T_{3-4} N_{1-2}). The numerous studies have shown that its preoperative use contributes to the tumour regression, which can be partial or complete. It also reduces the frequency of recurrence and increases the use of the radical surgery, especially sphincter-preservation procedures. It must not be forgotten that these patients have a larger number of postoperative complications in relation to the patients who did not receive this preoperative therapy. Patients with the complete histopathological tumour regression have a five-year survival of 70%, while the patients without the complete histopathological tumour regression have a significantly lower five-year survival of 40%.

Julio Garcia-Aguilar and associates published a paper, which included 168 patients that received preoperative radiation therapy. They reported that down staging was manifested in 58% of patients, including 13% of patients with the complete histopathological tumour regression. In this study, a five-year survival was 95.2% in patients with the complete histopathological tumour regression, while it was 55.4% in patients without the complete histopathological regression (7).

Francesco Stipa and associates published a paper, which analyzed 476 patients with the locally advanced rectal cancer who were treated with the preoperative radiation therapy. The complete histopathological regression developed in 12.6% of patients, while there was no down staging in 29.5% of patients. A five-year survival in patients with the complete histological tumour regression was 90%. The patients without the tumour down staging had a five-year survival of 68% (8).

If we compare the results of our study, it can be seen that the complete histopathological regression manifested in a small percent of patients (10.7%), while the survival of patients with the complete histopathological tumour regression was 70%, which was significantly lower in relation to the above-mentioned studies.

In their study, Hak-Mien Quah and associates presented the disease recurrence. Of 331 patients that were analyzed in the study, 22% developed recurrence. They analyzed the survival in relation to the stage of the disease. The survival of patients with the stage S_0 (the complete histopathological regression) was 90%; the patients with the stage S_1 had the survival of 85%; the survival of patients with the stage S_2 was 65% and it was 45% in patients with the stage S_3 (9).

In our study the local recurrence developed in 12.5% of patients in the group of 64 patients that underwent radical surgery. Patients with the S_0 stage had the survival of 70%. It was 65% in patients with the S_1 stage of the disease, while the survival of the patients with the S_2 stage was 55%. In patients with the S_3 stage of the disease, the survival was 45%. A five-year survival was 15% in patients with the S_4 stage (patients with the distant metastases).

For the time being, the study does not explain the mechanism of the complete histopathological tumour regression after the preoperative chemoradiation therapy that develops in some patients (it happens in 10%-30%). However, it can be noticed that these patients have a better survival in relation to the patients with the incomplete or no histopathological tumour regression.

The molecular studies try to discover the factors responsible for the development of the complete histopathological regression in some patients. This discovery would make the therapeutic treatment more efficient. Several studies have proven that the discovery of certain molecular biomarkers (PCNA index, p21 expression and p53 immunostaging) in the pre-radiation biopsy can predict the response of a tumour to the chemoradiation therapy (10).

We concluded that the preoperative chemoradiation therapy (neoadjuvant therapy) leads to:

- The complete histopathological tumour regression thus increasing a five-year survival (70%).
- The increase of the number of patients with radical surgery (85%) compared to the patients without preoperative radiation therapy (75%).

- The increase of the number of the sphincter-preservation interventions in relation to the amputation procedures. The previous relation was 70% to 30%, and now it is 50% to 50%.
- The reduction of the local recurrence from previous 39% to current 12.5%
- Because of the adoption of the TME and the introduction of the chemoradiation therapy, the percentage of the patients that underwent radical surgery was 80% in 2005. In 1985 it was 50% and in 1995, 61% (historical data).

Conflict of interest

We declare no conflicts of interest.

REFERENCE

1 Gerzić Z, Dragović B. Osnovi hirurgije. Beograd: Medicinska knjiga; 1994.
2 Miladinov-Mikov M, Gudurić B. Epidemiologija raka debelog creva i rektuma u Vojvodini. In: Gudurić B, Breberina M, Jovanović D, editors. Rak debelog creva u Vojvodini. Novi Sad: VANU, Institut za onkologiju Vojvodine; 2009. p. 9-18.
3 Chen ET, Mohiuddin M, Brodovsky H, Fishbein G, Marks G. Downstaging of advanced rectal cancer following combined preoperative chemotherapy and high dose radiation. *Int J Radiat Oncol Biol Phys*. 1994;30:169-75.
4 Rouanet P, Fabre JM, Dubois JB, Dravet F, Saint Aubert B, Pradel J, et al. Conservative surgery for low rectal carcinoma after high-dose radiation. Functional and oncologic results. *Ann Surg*. 1995;221:67–73.
5 Minsky BD, Cohen AM, Enker WE, Saltz L, Guillem JG, Paty PB, et al. Preoperative 5-FU, low-dose leucovorin, and radiation therapy for locally advanced and unresectable rectal cancer. *Int J Radiat Oncol Biol Phys*. 1997;37:289–95.
6 Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. Preoperative versuspostoperative chemoradiotherapy for rectal cancer. *N Engl J Med*. 2004;351:1731–40.
7 Garcia-Aguilar J, Hernandez de Anda E, Sirivongs P, Lee S-H, Madoff RD, Rothenberg DA. A pathologic complete response to preoperative chemoradiation is associated with lower local recurrence and improved suevival in local cancer patients treated by mesorectal excision. *Dis Colon Rectum*. 2002;46:298-304.
8 Stipa F, Chessin DB, Shia J, Paty PB, Weiser M, Temple LK, et al. A pathologic complete response of rectal cancer to preoperative combined-modality therapy results in improved oncological outcome compared with those who achieve no downstaging on the basis of preoperatice endorectal ultrasonography. *Ann Surg Oncol*. 2006;13(8):1047-53.
9 Quah HM, Chou JF, Gonen M, Shia J, Schrag D, Saltz LB, et al. Pathologic stage is most prognostic of disease-free survival in locally advanced rectal cancer patients after preoperative chemoradiation. *American Cancer Society*. 2008;113:57-64.
10 Fu CG, Tominaga O, Nagawa H, Nita ME, Masaki T, Ishimaru G, et al. Role of p53 and p21/WAF1 detection in patient selectoinfor preoperative radiotherapy in rectal cancer patients. *Dis Colon Rectum*. 1998;41:68-74.