ORIGINAL ARTICLE

UDC: 616-006:616.351-08-036
https://doi.org/10.2298/VSP160721382P

Complete histopathological regression in rectal cancer after neoadjuvant chemoradiotherapy and sphincter preserving surgical treatment

Kompletna patohistološka regresija karcinoma rektuma nakon neoadjuvantne radiohemioterapije i sfinkter prezervirajućih operacija

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Abstract

Background/Aim. Multimodal approach to locally advanced rectal cancer treatment results in better disease outcome. Preoperative chemoradiotherapy improves disease local control, reduces risk of local recurrence and in the majority of patients with complete or substantial regression of the tumors significantly improves survival rates. According to the literature data, approximately 20% of patients had achieved complete histopathological response (pCR) after neoadjuvant chemoradiation therapy. The aim of this study was to evaluate overall survival in rectal cancer patients treated with preoperative chemoradiotherapy and sphincter preserving surgery. **Methods.** This retrospective study included 191 patients. Patients received preoperative radiation therapy and chemotherapy-chemoradiation therapy (CRT) followed by operation that favorized sphincter preservation with total mesorectal excision (TME) from June 2000 until December 2010. Diagnosis was established according to the following algorithm: patient history, digital rectal examiantion, colonoscopy with biopsy and histopathology verification, and preoperative clinical staging. Patients with tumors located below promontorium were included in the study and patients with metastatic disease and local recurrence were excluded from the study. For tumors located below the promontorium preoperative radiotherapy was used with total dose of 50.4 Gy, divided into daily doses of 1.8 Gy, during 28 days. Chemotherapy followed radiotherapy with 5-fluorouracil and folic acid (Leucovorin®) on days 1, 2, 10, 11, 20 and 21. Six to ten weeks after neoadjuvant therapy, magnetic resonance imaging (MRI) to restage tumors and operation were performed. **Results.** Of all patients that received preopertive chemoradiation, 163 had radical sphincter preservig surgery and 28 patients had paliative operations. Histopathological examination of the specimens showed that the complete histopathological regression was achieved in 21.4% of the patients, downstaged was found in 63.2% of them and unchanged stage was found in 15.3% of the patients. The five-year survival rate was 63.3% and 50.5 % in the patients with pCR and patients with incomplete histopathological regression, respectively. Survival rates between two groups were not statistically significant ($p > 0.05$). **Conclusion.** The preoperative chemoradiotherapy is very important in achieving optimal clinical care for patients with locally advanced rectal cancer.

Key words:
rectal neoplasms; carcinoma; digestive surgical procedures; chemoradiotherapy; neoadjuvant therapy; prognosis.

Apstrakt

Uvod/Cilj. Multimodalni pristup u lečenju lokalno uznapredovalog karcinoma rektuma rezultira boljom prognozom bolesti. Preoperativnom primenom kombinovane radioterapije i hemioterapije-radiohemioterapije (RHT) poboljšava se lokalna kontrola bolesti, smanjuje rizik od pojave lokalnih recidiva i vodi boljem preživljavanju kod većine bolesnika kod kojih je postignuta kompletna ili nekompletna histološka regresija tumora.

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Oko 20% bolesnika nakon neoadjuvantne terapije ima potpunu patohistološku regresiju tumora. Cilj ovog istraživanja je bio evaluacija preživljavanja bolesnika nakon neoadjuvantne terapije i sfinkter prezervirajućih operacija. **Metode.** Retrospektivnom studijom obuhvaćen je 191 bolesnik. Bolesnici su primili neoadjuvantnu radiohemioterapiju a nakon toga su operisani u periodu od juna 2000. do decembra 2010. godine. Dijagnostika je izvođena prema sledećem algoritmu: anamneza, digito-rektalni tuše, kolonoskopija sa biopsijom i patohistološkom verifikacijom. U studiju su uključeni samo bolesnici sa tumorima lokalizovanim ispod promontorijuma. Iz studije su isključeni bolesnici sa udaljenim metastazama i sa reicidivima. Ukupna doza zračenja od 50.4 Gy je bila podeljena u dnevne doze od 1.8 Gy. Hemioterapija [5-fluorouracil i folna kiselina (Leucovorin®)] je pratila radioterapiju 1. 2. 10. 11. 20. i 21. dana. Šest do osam nedelja nakon ove terapije urađen je pregled male karlice magnetnom rezonancom (MR) radi novog stejdžinga. Bolesnici su operisani u periodu od 8 do 12 nedelja po završetku hemioiradijacije. **Rezultati.** Od svih bolesnika koji su primili neoadjuvantnu terapiju, kod 163 je urađena sfinkter prezervirajuća operacija sa totalnom mezorektalnom ekscizijom. Kod 28 bolesnika izvedena je palijativna operacija. Patohistološkim nalazom je utvrđeno da 21,4% bolesnika ima kompletnu histološku regresiju tumora, 63,2% nekompletnu, dok je 15,3% bolesnika bilo nepromenjenog statusa. Petogodišnje preživljavanje kod bolesnika sa kompletnom histološkom regresijom bilo je 63,3%, kod onih sa nekompletnom histološkom regresijom 50,5%. Razlika u preživljavanju između ove dve grupe bolesnika nije bila statistički značajna ($p > 0,05$). **Zaključak.** Preoperativna radiohemioterapija obezbeđuje optimalno kliničko zbrinjavanje bolesnika sa lokalno uznapredovalim karcinomom rektuma.

Ključne reči:
rektum, neoplazme; karcinomi; hirurgija digestivnog sistema, procedure; radiohemioterapija; lečenje, neoadjuvantno; prognoza.

Introduction

The managment of rectal cancer has changed over the last twenty years, due to improvement of surgical techinques and introduction of neoadjuvant radiation therapy and chemotherapy-chemoradiation therapy (CRT).

Multimodal approach to locally advanced rectal cancer treatment results in better disease outcome. Preoperative CRT improves local disease control and reduces risk of local recurrence. Some patients respond to neoadjuvant CRT with pathological complete response (pCR) in approximately 20% of casses [1]. Multimodal treatment for rectal cancer includes: introducing effective surgery (total mesorectal excision), neoadjuvant radiotherapy, and modern cytotoxic chemotherapy [2].

Preoperative chemotherapy and/or radiotherapy followed by surgery currently represents the standard approach for locally advanced rectal cancer, providing survival benefit for the patients compared to surgery alone. The most of the patients with complete or substantial regression of the tumors showed improved survival rates [3–8].

After preoperative CRT significant tumor downstaging and downsizing, greater rates of sphincter preservation surgery and better functional results have been reported [9].

Tumor response to neoadjuvant CRT is not consistent. It is connected with many factors such as specific treatment regimens, timing of surgery after CRT completion, tumor/patient characteristics and tumor biology [10].

Two most frequent regimens used in the preoperative treatment of patients with resectable clinical T3-T4 rectal cancers are fractionated long-course CRT followed by surgery after 6–8 weeks or pelvic short-course irradiation with 25 Gy in five fractions followed by immediate surgery [10].

The study of Maas et al. [11] showed that patients who achieved the pCR after neoadjuvant CRT had outcomes similar to those who underwent surgery. This fact was used for introduction of a concept based on "wait and see policy" instead of surgical treatment.

The aim of this study was to evaluate overall survival in patients after preoperative CRT and sphincter preserving surgical treatment.

Methods

This was a retrospective study which included 191 patients: 134 males and 57 females, (mean age 65.10 years; range 32–81 years). Patients received preoperative chemoradiation followed by operation that favorized sphincter preservation with a total mesorectal excision from June 2000 until December 2010. Diagnosis was established according to the following algorithm: patient history, digital rectal examiantion, colonoscopy with biopsy and histopathology verification, and nuclear magnetic resonance (NMR) of pelvis. Only the patients with tumors below the promontorium were included in evaluation, patients with metastatic disease and local recurrence were exluded from the study.

The radiation therapy regimen: total dose of 50.4 Gy was divided into daily doses of 1.8 Gy, during 28 days. Chemotherapy followed radiotherapy with 5-fluorouracil and folic acid (Leucovorin®) on days 1, 2, 10, 11, 20 and 21. Six to ten weeks after neoadjuvant therapy, magnetic resonance imaging (MRI) was performed in order to restage the tumor. Prior to surgery, complete blood count and biochemical analysis were performed as well as liver ultrasonograpahy.

Histopathological analysis of surgical specimen was used to determine the patients with pCR and incomplete pathological regression. The patients with metastatic disease and local recurrence were excluded from the study. The resected specimens were fixed in 4% formaldehyde overnight. After a specimen had been opened, the tumourous or fibrotic area was identified and described macroscopically. For an obvious residual primary tumor, a minimum of four paraffin blocks were processed. If no tumor was visible, the whole area suggestive of disease was sliced and embedded. Hematoxylin-eosin-stained sections were reviewed, and proximal, distal, and circumferential resection

margins were evaluated. All lymph node that was found was sampled and microscopically examined.

Histopathological assessment was performed according to the Rectal Cancer Regression Grade (RCRG), which classifies tumor regression into three levels: RCRG 1 – the tumour is either sterilised or only microscopic foci of adenocarcinoma remain; RCRG 2 – marked fibrosis with macroscopic tumour still present; RCRG 3 – little or no fibrosis in the presence of abundant macroscopic tumour. RCRG 1 and 2 were considered to represent significant tumour regression [12]. In cases where only acellular pools of residual mucin were noted, the response was considered to be complete.

For statistical analysis and survival rates both the patients with complete and incomplete histopathological regression were included. Software SPSS v17 was used for statistical analysis.

Results

Among 191 patients that had were examined, male predominated, and male:female ratio was 1.42 : 1. All patients received preoperative CRT, and 163 of them underwent sphincter preserving operations with total mesorectal exscision (TME). In 28 patients only palliative operation was possible (Table 1).

Table 1

Clinical characteristics of patients

Patient characteristics	Value
Mean age range (years)	65.1 (32–81)
Gender M/F, ratio	134/57 (1.42:1)
Type of surgery, n (%)	
sphincter preserving	163(85.4)
paliative	28 (14.6)
Preoperative CRT, n (%)	191(100)
HP finding, n (%)	
complete HP regression	35 (21.4)
incomplete HP regression	103 (63.2)
without change	25 (15.3)
Clinical T stage, n (%)	
cT3	155 (81)
cT4	36 (19)
Clinical N stage, n (%)	
cN(-)	123 (64.2)
cN(+)	68 (35.8)
Histology, n (%)	
well/moderately diferentiated	122 (63.8)
poorly diferentiated	69 (36.2)
Lymphovascular invasion, n (%)	43 (22.4)

M/F – male/female; CRT – chemoradiation therapy; HP – histopathological.

Figure 1 shows preoperative chemoradiated patients and types of operations (radical or palliative) practiced in our department over the years in the patients with locally advanced rectal cancers.

Histopathological examination of the operative specimen showed that 35 out of 163 (21.4%) patients treated with neoadjuvant treatment and sphincter preserving surgery with TME, achieved pCR (Figure 2); 103 (63.2%) were downstaged and only in 25 (15.3%) patients no change in tumor stage could be detected (Figure 3). The patients with pCR were younger compared to the patients with incomplete tumor regression (Spearman`s rho test; $p = 0.03$). There were no correlation between pCR or incomplete tumor regression with other clinical parameters such as gender, histology, lymphovascular invasion, initial (before preop-CRT) clinical T and N stages (Spearman`s rho test, $p > 0.05$).

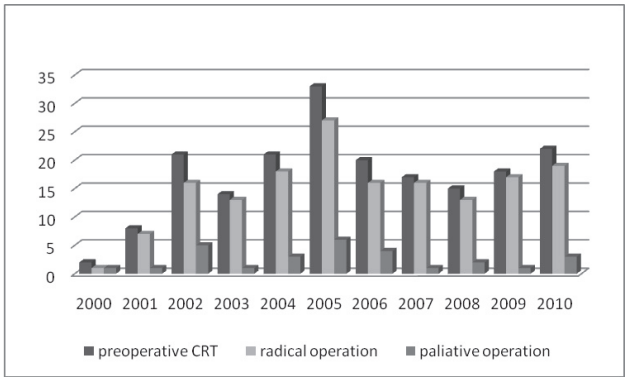
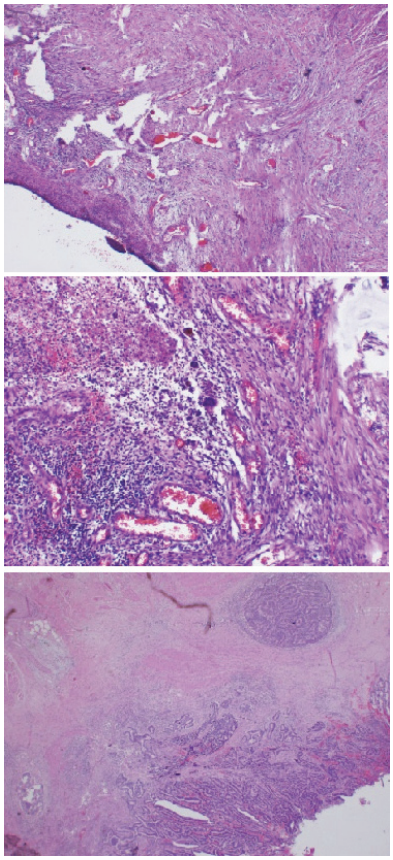


Fig. 1 – Preoperative chemoradiated patients and types of operations (radical or palliative) practiced in our department by year in the patients with locally advanced rectal cancers.



A)

B)

C)

Fig. 2 – Therapy response grade: A) complete therapy response with marked fibrosis without cancer tissue; B) near complete therapy response with few tumour cells outgrown by fibrosis and inflammation; C) poor therapy response showed residual cancer outgrowing fibrosis characterized by a scant presence of regressive changes (H&E, ×40).

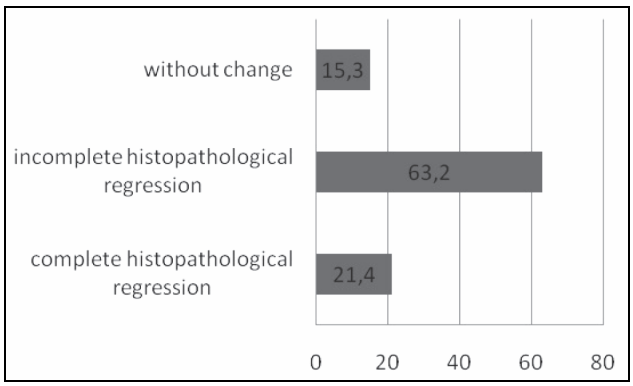


Fig. 3 – Histopathological examination of the operative specimen.

The five-year survival of patients with pCR was 63.3% while survival rate of the patients with incomplete histopathological regression was 50.5% (Figure 4). There were no statistical significance between survival rates of the pCR patients and patients with incomplete histopathological regression ($p > 0.05$).

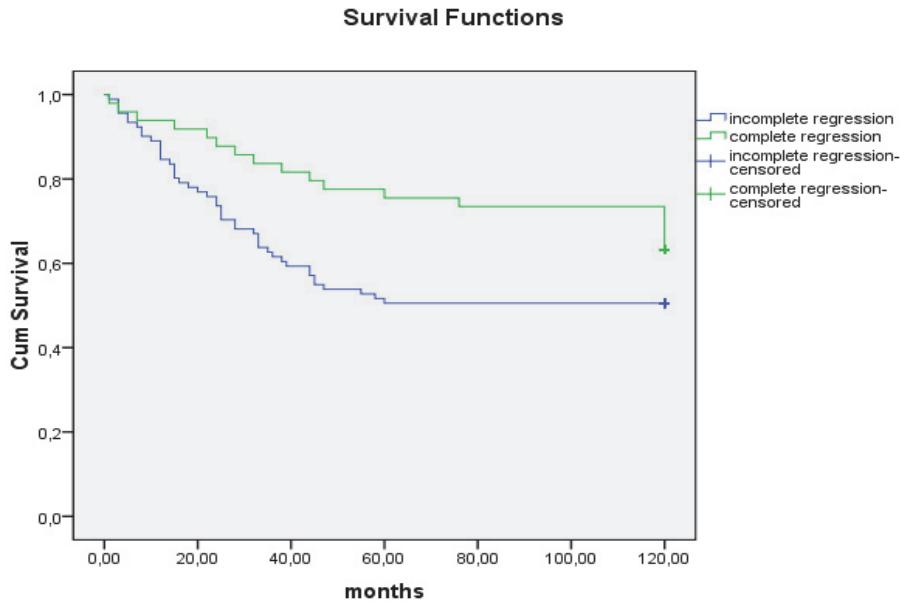


Fig. 4 – Patient survival in relation to histopathological tumor regression ($p > 0.05$).

Discussion

Modern concepts of treatment for locally advanced rectal cancer include preoperative chemoradiation followed by surgery. A large number of studies have demonstrated that preopearative chemoradiation for locally advanced rectal cancer can lead to tumor regression [13]. It is also shown that such treatment could reduce local recurrence rates and increase number of sphincter preserving operations, and, also increase patients' survival and thier quality of life [8, 14].

Complete pathological response appears in 10%–30% of patients who were treated with chemoradiotherapy.

The patients with pCR have better survival compared to patients with incomplete histopathological regression [9, 15].

In our study, among 163 patients who underwent sphincter preserving operations after preoperative chemoradiotherapy, pCR was found in 21.4% of the patients while incomplete histopathological regression in 63.2% of them. Cases with complete regression or RCRG 1 showed an absence of histologically identifiable residual cancer with predominant fibrosis extending through the different layers of the rectal wall or there were only microscopic foci of small cluster or individual tumor cells. Cases with RCRG2 or partial regression were characterized by presence of residual cancer tissue which was still outgrown by fibrosis. In grade 3 (poor regression) there were huge areas of residual cancer outgrowing fibrosis characterized by a scant presence or the complete absence of regressive changes.

Shivnani et al. [13] reported similar results. Their study included 100 patients, 25% with pCR and 60% without pCR. Our results are similar to data presented by Onaitis et al. [14] who analyzed 146 patients with locally advanced rectal cancer after preoperative chemoradiotherapy and surgery. They found 20% of patients with pCR and 57 % without pCR. In the study of Garcia-Aguilar et al. [15], among 168 patients who received preoperative chemoradiation therapy, only 13% were with pCR and 55.4% of them with incomplete histopathological regression.

Our study showed that five-year survival rate (63.3%) was better in patients with pCR compared to those with in-

complete histopathological regression (50.5%). However, the survival rate of our patients, regadless the HP outcome, were smaller compared to the reported data [14, 16, 17]. Stipa et al. [17] showed that five-year survival in patients with complete and incomplete histopathological regression was 90% and 68%, respectively. Similar results reported Garcia-Aguilar et al. [15], i.e., five-year survival in patients with pCR was 95.2%, while in patients with incomplete histopathological regression it was 55.4%. Shivnani et al. [15] showed that five-year survival in patients with pCR was 89% and 75% of the ones with incomplete regression.

Although tumor regression grade basically scores the ratio of residual cancer cell to radiation-induced fibrosis, a standard method for scoring tumor regression grade still does not exist. This is important because documentation of tumor regression grade (TRG) can be different depending on the methods used to prepare slides, the number of slides reviewed per tumor, staining and the experience of the reviewers. There are several grading systems for TRG. Some of them such as Mandard et al. [18] Dworak et al. [19], and Ruo et al. [20] proposed fivepoint grading systems while Rodel et al. [9] and Wheeler et al. [12] advocated three-point grading systems. Comparative studies showed that although prognostic impact might be the same, the three-point TRG was better with respect to intra- and inter-observer agreement [21, 22]. The three-point grade has the advantage of better reproducibility, with similar prognostic significance. Thus, we used the three-point grading system according to RCRG [12]. TRG was uniformly found by univariate analysis to get a prognostic value for survival and recurrence in rectal cancer after irradiation [14, 18]. Most series, however, failed to establish TRG as an independent prognostic factor stronger than ypT or ypN [23, 24].

New studies with “wait and see policy” were initiated. This concept is based on omitting surgery in patients with pCR after chemoradiation therapy. After a mean follow-up of 60 months, the results for the ”wait and see group” were impressive, with a five-year survival of 93% [25]. However complete response of the primary tumor cannot predict response in regional lymph nodes which were involved in 7%–17% of patients who have pCR of the primary tumor [26, 27]. So this concept has to be proved in randomized trials.

Conclusion

Complete histopathological response is now accepted as an independent predictor of long-term outcomes following neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Further work is needed to determine the clinical importance of lesser degree of pathological regression. A robust and internationally accepted system for the grading of tumour regression in rectal cancer following neoadjuvant chemoradiotherapy is currently required. Such consistency will help with clinical decision-making and will influence surgical strategies, postoperative adjuvant therapy and surveillance intensity.

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Received on July 21, 2015.
Revised on October 12, 2016.
Accepted on November 10, 2016.
Online First December, 2016.