Initial Results of Treatment of Rectal Cancer using the Neoadjuvant Treatment

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ABSTRACT:

Introduction. Treatment of rectal cancer needs additional preoperative improvements that would decrease tumor volume and move away the lower edge of the tumor from a dentate line, allowing a higher percentage of operability and higher percentage of AR for APR and sterilize potential locoregional tumor deposits. Surgery can accomplish these improvements by using radio and chemotherapy.

Patients and Methods. From September, 2011 to September, 2013, 153 patients with rectal cancer were treated. Neoadjuvant radio and chemotherapy by the Swedish protocol were applied in 20 patients (13.07%) with T 2-4 stages. There were fifteen men (75%) and five women (25%), average age was 59.28 years. Long course therapy occurred in fifteen (75%) and short course in five patients (25%).

When compared to the previous two-year period, the percentage of inoperable cancers was decreased by 0.9% ($p = 0.61$) during the period of application of neoadjuvant therapy. There were also some other differences: a number of APR was 19, i.e. decreased by 3.85% ($p = 0.83$) or for 10 patients when compared to the previous two-year period, when there was 29 APR.

Conclusion. Neoadjuvant therapy may convert up to 60% (3 of 5) of inoperable patients into an operable group. The percentage of APR is lower by 3.5% ($p = 0.83$), i.e. 10 patients when compared to the previous two-year period and neoadjuvant radio and chemotherapy does not affect the anastomosis healing process and / or the occurrence of fistula and / or abdominal collection.

KEY WORDS:

cancer, rectum, surgery, neoadjuvant treatment

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Introduction

Colorectal cancer is the most common abdominal neoplasm with an average prevalence of 13.2 / 100 000 population / year in Greece, to 30.6 in Italy.¹ Banja Luka has about 20 new cases . Five-year survival is still unsatisfactory, with 50-90% in stage II or 30-60% in stage III.² Local recurrence in patients who are not included in radiotherapy is 15-45%,³ (usually around 27%), and in case of the operated patients with radiotherapy, local recurrence is below 10%.⁴ Operability , the choice of the abdominal rectal re-

section (AR) or abdominoperineal resection of the rectum (APR), the reduction of local recurrence and extension of Progression free survival (PFS) and / or overall survival (OS) are the tasks of treatment in which surgery alone can not give better results than achieved. Local tumor severity defines operability, i.e. the ability of the tumor resection. Distance of the lower border of the tumor from a dentate line of rectum limits the possibility of making colorectal anastomosis instead of definitive colostomy . Standards of operability of the tumor and AR or APR are intraoperative

constants that can no longer be affected by achieved levels of operative techniques. Surgery needs additional preoperative improvements that would:

- 1) decrease tumor volume and move away the lower edge of the tumor from a dentate line, allowing a higher percentage of operability and higher percentage of AR for APR and
- 2) sterilize potential locoregional tumor deposits. Surgery can accomplish this improvements by using radio and chemotherapy. During the last 20 years, different studies have been conducted, with the use of neoadjuvant therapy according to different protocols, and the most utilized are short term protocol (Swedish study) with five doses of 5 Gy irradiation, and long term protocol (American study) with twenty eight doses of 2 Gy irradiation together with chemotherapy in the first and last week of treatment.^{4,8,18}

Objective

- 1) To show the extent and level (short or long course) use of neoadjuvant radio and chemotherapy,
- 2) To establish if neoadjuvant therapy increases the percentage of operability of rectal cancer,
- 3) To define if this treatment affects the reduction of abdominoperineal resection of the rectum and definite colostomy and
- 4) To establish if it affects negatively (fistula, stenosis) on the healing of colo-rectal anastomosis.

Patients and Methods

From September, 2011 to September, 2013, 153 patients with rectal cancer were treated. Neoadjuvant radio and chemotherapy by the Swedish protocol were applied in 20 patients (13.07%) with T 2-4 stages. There were fifteen men (75%) and five women (25%), average age was 59.28 years. Long course therapy occurred in fifteen (75%) and short course in five patients (25%). Radical surgery was done in 18 patients (ten AR, four APR, one Transanal Endoscopic Microsurgery (TEM) and three Transanal excisions) and two patients underwent a definitive colostomy. (Table 1.)

Table 1. Operative procedures after neoadjuvant therapy

Operations	No.	%
Low anterior resection	10	50
Abdominoperineal resection	4	20
TEM or transanal excisions	4	20
Inoperable	2	10
In total	20	100

Resection margin was in all patients with anterior resection, even in cases where the resection margin was <10 mm distant from the lower edge of tumors.

Results

We used Ryan's classification for assessing the response of tumor tissue to neoadjuvant therapy: 0-complete response = one patient, 1-moderate response = fifteen, 2-minimal answer= two, and 3-unanswered tumor tissue = two patients.

When compared to the previous two-year period, the percentage of inoperable cancers was decreased by 0.9% ($p = 0.61$) during the period of application of neoadjuvant therapy. There were also some other differences: a number of APR was 19, i.e. decreased by 3.85% ($p = 0.83$) or for 10 patients when compared to the previous two-year period, when there was 29 APR. (Table 2.)

Thanks to the good tumor response, three (60%) out of five patients were moved to the operable group. Although the sample of patients with rectal cancer was lower for 26 patients when compared to the previous two-year period, the number of inoperable carcinoma of the rectum after the application of neoadjuvant therapy decreased by 0.9% ($p = 0.61$). There was only one patient with local recurrence (5.5%).

There was not any postoperative complications in terms of recto-vaginal fistula and / or abdominal collections. Interference by incontinence and bowel mucosal secretions occurred in one patient, while there was no bleeding after irradiation.

Table 2. Results of application of neoadjuvant therapy

Operations	September, 2009 - August, 2011		September, 2011 - August, 2013	
	No.	%	No.	%
Low anterior resections	132	73.69	120	78.44
Abdominoperineal resection	29	16.26	19	12.41
Inoperable	18	10.5	14	9.15
In total	179	100	153	100

Period of two years is short for follow up: PFS and / or overall survival. It is worth mentioning that all patients who underwent radical procedure (18 patients) are alive and that only one of them has a local recurrence. The majority of surgically treated patients (14 of 18 patients) have a good quality of life, due to the lack of definitive colostomy and the absence of serious complications. The study will be continued. Accordingly, we will check whether neoadjuvant radio and chemotherapy affect survival. The authors state that this therapy does not affect overall survival.

Discussion

A local severity of rectal cancer (bulky tumors) is one of the most common factors of inoperability. In 133 patients without neoadjuvant therapy, the percentage of inoperable rectal cancer was 9.15% (14 patients). Stabilization of the disease and the reduction of the tumor volumes, (Fig. 1. and 2.) with respect to operative techniques, provide a greater ability to convert initial inoperable tumor into a group of operable. The effect of this treatment is also expected in recurrent and / or bulky tumors. Thanks to long course therapy, three (60%) out of five patients became operable due to the significant downsizing.

Figures 1. and 2. Downsizing of rectal cancer after neoadjuvant therapy

Local recurrence of rectal cancer is an ongoing concern, especially in conditions when the radiation therapy (pre and / or post-operative) is uncertain or absent. Rectal cancer patients, where surgery is applied with chemotherapy, have a local recurrence of 15-45%.³ The percentage of local recurrence is less than 10% and preferably about 8% in the group of patients where neo and / or adjuvant therapy is

applied.⁹ 15 years ago, we had a percentage of local recurrence in T3 and T4 stages up to 25%.¹⁰ With the neoadjuvant therapy, the percentage of local recurrence was 5.5% (one patient), mainly due to neoadjuvant therapy.¹⁴

Improvement of operative techniques by applying new technologies (primarily stapling and "ligasure" technology) allows operability and preservation of the anal sphincter in only a number of the tumors, while the others need downsizing for better results.

The percentage of definitive colostomy in middle and lower thirds of the rectum in a well-organized surgery is up to 20%.¹¹⁻¹³ In the last 15 years, the percentage of these operations in our clinic was very high and was up to 45%.¹⁰ Increase of the distance of the lower edge of the tumors to dentate line can only be achieved by downsizing of the tumors. In 18 patients (80%), we had the downsizing of the tumor, thanks to which we made 10 AR and four transanal wedge excisions and / or TEM procedures. Five years ago, all of these patients would have had APR of rectum or definitive colostomy. It is known that a low colo-rectal anastomosis (within 5 cm. from dentate line) have a dehiscence of 3-25%, the protection of the anastomosis are done routinely.¹⁵⁻¹⁷

Conclusion

1. The percentage of 13.7% of patients with rectal cancer in which we apply neoadjuvant therapy is unsatisfactory and does not correspond to real conditions;
2. Neoadjuvant therapy may convert up to 60% (3 of 5) of inoperable patients into an operable group;
3. The percentage of APR is lower by 3.5% ($p = 0.83$), i.e. 10 patients when compared to the previous two-year period;
4. Neoadjuvant radio and chemotherapy does not affect the anastomosis healing process and / or the occurrence of fistula and / or abdominal collection.

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Početni rezultati liječenja carcinoma rektuma primjenom neoadjuvantne terapije

APSTRAKT

Uvod. Hirurškom liječenju karcinoma rektuma su potrebna dodatna preoperativna poboljšanja koja bi, smanjila volumen tumora i udaljila donju ivicu tumora od ore serate rektuma omogućujući veći procenat operabilnosti, odnosno veći procenat APR, "sterilizovala" potencijalne lokoregionalne tumorske depozite. Ova preoperativna (neoadjuvantna) terapijska poboljšanja, hirurgija može dobiti sa radio i hemoterapijom.

Ispitanici i metode. Od septembra 2011. do septembra 2013. liječili smo 153 pacijenta oboljela od rektalnog karcinoma. Neoadjuvantnu radio i hemio terapiju primijenili smo kod 20 (13,07%) bolesnika stadija T 2-4. Muškaraca je bilo petnaest (75%), a žena pet (25%), prosječne životne dobi 59.28 godina. Petnaest bolesnika (75%) bilo je na terapiji po dugom protokolu, a pet bolesnika (25%) na terapiji po kratkom protokolu.

Procenati neoperabilnih karcinoma u periodu primjene neoadjuvantne terapije je manji za 0,9% ($p=0,61$) u poređenju sa prethodnim dvogodišnjim periodom, a broj APR je 19, odnosno manji je za 3,85% ($p=0,83$), odnosno za 10 bolesnika u odnosu na prethodni dvogodišnji period kad smo imali 29 APR.

Zaključak. Neoadjuvantnom terapijom može se prevesti do 60% (3 od 5) inoperabilnih bolesnika u grupu operabilnih. Procenat APR je manji je za 3,5% ($p=0,83$) odnosno za 10 bolesnika u poređenju sa prethodnim dvogodišnjem periodom i neoadjuvantna radio i hemoterapija ne utiču na process zarastanja anastomoza i/ili pojavu fistula i/ili abdominalnih kolekcija.

KLJUČNE RIJEČI:

karcinom, rektum, hirurgija, neoadjuvantna terapija