Neoadjuvant Radiotherapy in Rectal Cancer: A Single Center Experience

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ABSTRACT

Neoadjuvant chemoradiotherapy (CRT) followed by surgical resection is the standard treatment for locally advanced rectal adenocarcinoma. In this study we evaluate our treatment results in patients treated with neoadjuvant radiotherapy (RT). Medical records of 144 patients treated between January 2009 and February 2019 were retrospectively evaluated. Most of the patients had (76%) MRI as a part of initial staging. Patients received either short course (25 Gy/5 fractions) (8%) or long course RT (92%) (median 50.4 Gy/28 fractions) ± chemotherapy (ChT). Median age was 56 years (range, 24-90 years) and 131 patients received CRT. Most common concomitant ChT regime was oral capecitabine (48%). 26 patients refused the surgery. For rest of the patients, median time to surgery was 8 weeks. Sphincter was preserved in 19 patients (38%) who underwent surgery for distal tumors. With a median follow-up of 28 months, 19 patients had local recurrence and 30 patients had distant metastases. Two and five year estimated overall survival (OS), locoregional control (LRC) and distant metastases free survival (DMFS) rates were 88-67%, 78-62% and 74-57%, respectively. Presence of surgery significantly affect OS (HR= 0.147, 95% CI: 0.67-0.32, p< 0.001) , LRC (HR= 0.10, 95% CI: 0.05-0.2, p< 0.001) and DMFS (HR= 0.25, 95% CI: 0.13-0.49). Patients tolerated the treatment well with no grade 3 acute or late gastrointestinal and genitourinary system toxicities. Regardless of the schema neoadjuvant RT seems to be an efficient and safe treatment for patients with rectal adenocarcinoma. We found that surgery is the sole prognostic factor for better OS, LC and DMFS.

Keywords: Radiotherapy, Rectal cancer, Surgery, Neoadjuvant radiotherapy, Chemotherapy

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in the Western World and cancers of the rectum and rectosigmoid junction account for 30% of all CRC cases.[1] Rectal cancer is defined as tumours arising within 15 cm of the anal verge. Neoadjuvant treatment followed by surgical resection is the standard treatment for locally advanced rectal adenocarcinoma.[2] Neoadjuvant therapy may comprise of either radiotherapy (RT) alone or in combination with chemotherapy (ChT). It is well known that RT can reduce local recurrence (LR) when used combined with surgical resection and can enhance survival when used in multidisciplinary treatment (MDT).[3] In case of anal sphincter involvement neoadjuvant therapy can downsize the tumour and allow for preservation of the anal sphincters and maintaining anal continence.[4]

The RT can be delivered either in short-course with high dose per fraction or long-course with conventional fractional dose concomitant with ChT. A recent meta-analysis comparing short-course with long-course preoperative neoadjuvant therapy for rectal cancer showed no significant difference in treatment outcomes.[5]

However most of the centers still prefer to use long-course concomitant chemoradiation (CRT) in patients with locally advanced rectal cancer.

In this study we evaluate treatment results at a tertiary cancer center in patients with rectal adenocarcinoma treated with RT plus/minus ChT in neoadjuvant intent.

MATERIALS AND METHODS

Patients

Medical records of 197 patients treated between January 2009 and February 2019 were retrospectively evaluated. All patients should be greater than 18 years-old with biopsy proven rectal adenocarcinoma and have good performance status (Karnosky score ≥70). Patients with prior non-rectal cancer (except noninvasive cervical carcinoma and skin cancer [excluding melanoma]), or who received prior pelvic radiation were excluded. Surgical data was available in 144 patients thus the analyses were restricted to patients who either did not have surgery or had surgical data.

Pretreatment evaluation included a complete history and physical examination, proctoscopy and/or colonoscopy with biopsy, complete blood counts (CBC) and biochemical profiles, and chest/abdominal/pelvic computerized tomography (CT). Magnetic resonance imaging (MRI) scan of the pelvis was optional however it became a standard of initial work-up in the last decade. Thus most of the patients (86%) had MRI as a part of initial staging.

Treatment Procedures

All patients were instructed to empty their bowel and bladder and drink 500 cc water 30 minutes before each treatment. Patients received either short-course or long-course RT with or without ChT. RT field includes the primary tumor within rectum plus mesorectum and pelvic lymphatics. Internal iliac, presacral, obturator lymph nodes (LNs) ± external iliac LNs (T4 disease) were involved in the lymphatic field. In long-course RT schema patients received concurrent ChT. Most commonly used ChT regimens were either infusional fluorouracil (FU; 1000 mg/m^2 daily for five days during the first and fifth weeks of RT) or capecitabine (825 mg/m^2 twice per day, without weekend breaks) was initiated on the first day of RT and was delivered concurrently with RT.

Total mesorectal excision (TME) was performed as the standard procedure, and the particular type of surgery was determined at the time of resection. All patients must sign the treatment specific informed consent. The analysis of the data was approved by the institutional Ethics Committee. Ethical approval for this retrospective study was obtained from the Institutional Review Board of Hacettepe University (December 26, 2019 - IRB Decision number: 2019/12-26).

Toxicity

Acute gastrointestinal (GI) and genitourinary (GU) toxicities were evaluated by using Common Criteria for Adverse Events (CTCAE) version 4.0 and late toxicities were evaluated by using RTOG/EORTC Late Radiation Morbiditiy Scoring Schema.

Statistical Analysis

Descriptive statistics were reported as counts and percentages where appropriate and Kaplan-Meier test was used to estimate survival probabilities and differences between groups were evaluated with log-rank test. Cox regression was used for hazard rates. The value of $p< 0.05$ was used to determine statistical significance. SPSS 21.0 (IBM Inc., Armonk, NY, USA) version was used for the statistical analysis.

RESULTS

Median age was 56 years (range, 24-90 years) and 59% of the patients were male. Most of the patients had stage III disease (77%) according to 8th version of AJCC staging system. Tumor was located in the distal one third of the rectum in 47% of cases. Patient and treatment characteristics are shown in Table 1. Short-course RT dose was 25 Gy in 5 fractions, long-course RT dose was median 50.4 Gy in 28 fractions (range, 45-60 Gy in 25-30 fractions). One-hundred-thirty-one patients received concom-

Table 1. Patients Characteristics (n= 144)

Characteristics	Number (%)
Gender	
Female	59 (41)
Male	85 (59)
Tumor location	
Proximal	26 (18)
Middle	51 (35)
Distal	67 (47)
Stage	
I	0 (0)
II	26 (18)
III	111 (77)
IV*	7 (5)
Radiotherapy	
Short course	12 (8)
Long course	132 (92)
Radiotherapy technique	
Conventional radiotherapy	17 (12)
3 dimensional radiotherapy	105 (73)
Intensity modulated radiotherapy	22 (15)
Concomitant chemotherapy	
Yes	131 (91)
No	13 (9)
Chemotherapy regime (n= 131)	
Oral Capecitabine	63 (48)
Continuous 5-FU infusion	57 (44)
Bolus 5-FU	11 (8)
Completion of concomitant chemotherapy	
Yes	124 (95)
No	7 (5)
Adjuvant chemotherapy	
Yes	97 (70)
No	28 (20)
Unknown	19 (10)
Surgery	
Yes	118 (82)
No	26 (18)

* Metastases confined to one organ or site

itant ChT with long-course RT. Most common concomitant ChT regime used was oral capecitabine (48%) and continuous FU infusion (44%). Ninety five percent of the patients completed the planned concomitant chemotherapy. Adjuvant ChT was received by 70% of the patients.

Table 2. Two and five year estimated overall survival (OS), locoregional control (LRC) and distant metastases free survival (DMFS) rates for the whole cohort and according to surgical status

	2 y	5 y	p value
Overall survival	88%	67%	
Surgery	94%	75.3%	
No Surgery	57%	21%	< 0.001
Locoregional control	78%	62%	
Surgery	90.3%	70.9%	
No surgery	21.3%	21.3%	< 0.001
DMFS	74%	57%	
Surgery	82%	64%	
No surgery	41.7%	31.3%	< 0.001

All patients were referred to surgery however twenty six patients did not have surgery due to medical comorbidities or patient refusual. Median time to surgery was eight weeks (1-12 week) and pCR rate was 16%. Early and late postoperative complication rates were 14.5% and 17%, respectively. Fifty patients with tumors located in distal rectum underwent surgery. Tumor was located median 3 cm (range, 0-5 cm) to anal canal and sphincter was preserved in 19 patients (38%). With a median follow-up of 28 months (range 2-116 mo), 19 patients had local recurrence and 30 patients had distant metastases. Two and five year estimated overall survival (OS), locoregional control (LRC) and distant metastases free survival (DMFS) rates are shown in Table 2.

We evaluated the effect of age (≤ 65 y vs > 65 y), gender, stage, tumor location (proximal vs mid vs distal rectum), RT schema (short-course vs long-course), RT technique (conventional 2 dimensional vs 3 dimensional vs intensity modulated RT), presence of surgery, time to surgery (≤ 8 weeks vs > 8 weeks), sphincter preservation, use of concomitant ChT, adjuvant ChT and pathological complete response (pCR) on treatment outcomes. On univariate analyses patients ≤ 65 years-old (p= 0.055), who had surgery (p< 0.001), and concomitant ChT (p= 0.09) had better OS; patients who had surgery (p< 0.001) and concomitant ChT had better LRC (p= 0.032) and patients who had surgery (p< 0.001) had better DMFS. Table 3 shows the results

Table 3. Factors affecting overall survival (OS), locoregional control (LRC) and distant metastases free survival (DMFS) rates in univariate analyses. Cox regression analysis was used for multivariate analysis.

	OS (HR [95% CI])	LRC (HR [95% CI])	DMFS (HR [95% CI])
Age (≤ 65 y vs >65 y)	1.39 (0.68-2.82, p= 0.055)	X	X
Presence of surgery	0.147 (0.067-0.32, p< 0.001)	0.10 (0.05-0.20, p< 0.001)	0.25 (0.13-0.49, p< 0.001)
Concomitant chemotherapy	0.57 (0.234-1.40, p= 0.093)	0.51 (0.22-1.19, p= 0.032)	X

Abreviations: *HR= Hazard ratio, CI= confidence interval*

of univariate analyses. On multivariate analyses only the presence of surgery significantly affect OS (HR= 0.147, 95%CI: 0.67-0.32, p< 0.001) , LRC (HR= 0.10, 95% CI: 0.05-0.2, p< 0.001) and DMFS (HR= 0.25, 95%CI: 0.13-0.49).

Non Operative Management:

Neoadjuvant RT or CRT followed by surgical resection is the standard treatment for locally advanced rectal adenocarcinoma. However in our cohort 26 patients either refused to go surgery or not suitable for surgery due to medical comorbidites. Characteristics of patients are shown in Table 4. Short-course RT was delivered to 15% of patients and long-course RT with or without ChT was delivered to 85% of patients. Twenty patients received concomitant ChT with long-course RT. Most common concomitant ChT regime used was oral capecitabine (70%) and continuous FU infusion (30%). Response to treatment was evaluated by digital rectal examination, endoscopy or radiological imaging. Six patients had endoscopy, however twenty patients did not accept any invasive examination. Twenty one patients had pelvic MRI for evaluation of treatment response.

With a median follow-up of 15 months (range 3-93 months), eight patients (30%) had recurrence of disease at the irradiated site. Median OS, LRC and DMFS rates were 26 months (95% CI: 18.4-33.9 months), 11.7 months (95% CI: 6-17.4 months) and 23.4 months (95% CI: 9.9-37 months), respectively. On univariate analyses; patients who were ≤ 65 years old (p= 0.054) and who received adjuvant chemotherapy (p= 0.006) had better OS. Patients who had received adjuvant ChT had better LRC (p= 0.043). Patients ≤ 65 years old (p= 0.033) and who had concomitant CRT had better DMFS (p= 0.054). On multivariate analyses; no significant difference was found for these parameters.

Toxicity: Patients tolerated the treatment well with no grade 3 acute or late gastrointestinal and genitourinary system toxicities. Acute Grade 1-2 GIS and GUS toxicity rates were 64% and 13%, respectively. Late Grade 1-2 GIS and GUS toxicity rates were 3.5% and 1.4%, respectively.

DISCUSSION

In this single center study we evaluated the role of neoadjuvant RT on treatment outcomes. Regardless of the schema neoadjuvant RT seems to be an efficient and safe treatment for patients with rectal adenocarcinoma. We found that presence of surgery is the sole prognostic factor for beter OS, LC and DMFS.

German Rectal Cancer Study Group trial randomly assigned 823 patients with clinically staged T3/4 or node-positive rectal cancer to either preoperative or postoperative RT (50.4 Gy/28 fractions ± boost of 5.4 Gy in postoperative cases) to the tumor and pelvic lymph nodes concurrent with infusional fluorouracil.[6] All patients underwent TME and four additional cycles of adjuvant single-agent FU. The five-year OS (76% vs 74%) and DFS rates (68% vs 65%) were similar for preoperative and postoperative therapy. However five-year cumulative incidence of local relapse was 6% for patients in the preoperative CRT and 13 % in the postoperative CRT group (p= 0.006). Grade 3 or 4 acute toxic effects occurred in 27% of the patients in the preoperative-treatment group, as compared with

Table 4. Characteristic of patients treated with non-operative management

Characteristics	Percentage (%)
Age (median, range)	62 (range 29-88 y)
Gender	
Female	58
Male	42
Tumor Location	
Proximal	24
Middle	20
Distal	56
Stage (AJCC 8th Ed.)	
II	15
III	66
IV	19

40% of the patients in the postoperative-treatment group (p= 0.001); the corresponding rates of long-term toxic effects were 14 percent and 24 percent, respectively (p= 0.01). Updated results of the study revealed that LRC difference still persisted at 11th year follow-up.[7] In current study our treatment outcomes are smilar to previously reported preoperative RT results.[5] Additionaly we have not had grade 3 or 4 toxicity, this might be related to use of 3D-CRT and IMRT in 88% of the cases. Data from retrospective series suggest good compliance and low acute GI toxicity rates after preoperative IMRT with concurrent fluoropyrimidine therapy.[8-10]

The optimal interval between completion of neoadjuvant long-course conventional CRT and surgery is not established; however most patients have surgical resection within 6 to 8 weeks following the completion of chemoradiotherapy.[11-13] A meta-analyses revealed that compared to a standard 6-8 week interval from completion of neoadjuvant RT to surgery, a minimum 8 week interval was associated with higher pCR (HR 1.41, 95% CI: 1.30-1.52) and tumor downstaging (mainly the T stage, HR 1.33, 95% CI: 1.04-1.72), but no differences in rates of complete resection, sphincter preservation, or treatment complication.[14] In our study median time to surgery was 8 weeks and pCR rate was 16%. Early and late postoperative complication rates were 14.5% and 17%, respectively. Our results indicate that 8 weeks seem to be a convenient time for optimum pCR and complication rates. Meta-analayses and retrospective series revealed that following neoadjuvant CRT 13.5-20% of patients have pCR and it is associated with fewer local recurrences, less distant metastases, and higher OS at 5 years.[15-17] We could not find a relationship between pCR and treatment response but it should be kept in mind that this is a retrospective study and full post-surgical pathological reports were not available in 34% of cases.

In the literature favorable results for NOM have led to question whether selected patients with complete clinical response (cCR) after neoadjuvant CRT might be able to avoid surgery. Currently there are no randomized trials that compares surgery or no surgery in patients with a cCR to neoadjuvant CRT. However long-term results of patients treated with NOM strategies seem to have promising results.[18-21] A meta-analyses showed that after identification of a cCR, 15.7% of patients managed with NOM developed an intraluminal local regrowth and 95.4% of these patients subsequently received salvage therapies. we found no significant differences in non-regrowth recurrence, cancer-specific mortality, or OS.20 However, patients with NOM have poorer disease-free survival than did those who underwent radical surgery with pCR.

An international multicentre registry study evaluated treatment results in 880 patients. With a median follow-up time of 3.3 years 2 year cumulative incidence of local regrowth was 25.2% (95% CI: 22.2-28.5%), 88% of all local regrowth was diagnosed in the first 2 years. Distant metastasis were diagnosed in 8% of patients and 5 year OS rate was 85% (95% CI: 80.9-87.7%).21 With careful endoscopic, clinical, and radiographic follow up this approach might avoid selected patients from surgical morbidities and life-long stomas. However prospective data with standardized definitions, diagnostic criteria, and management protocols are required. The results of the NCT02008656, NCT02514278, NCT02794520, NCT01047969, and NCT03426397 studies will be helpful for validation of NOM.

In current study 26 patients did not have surgery and it was found that patients who had surgery had better OS, LRC and DMFS. In our non-surgical

group median follow-up was 15 months and 5 year OS, LRC and DMFS rates were 21%, 21.3% and 31.3%, respectively. Our results seem to be inferior compared to previously reported NOM studies however it should be noted that these patients were all reffered to surgery. They were not put on a specific NOM programme thus they might not have initial cCR to treatment either. As their low OS shows most of them had medical comorbidities to surgery.

Our single center treatment results show that surgical resection should stil be the standard approach after neoadjuvant therapy for patients who are medically operable. RT seems to be an effective treatment with low toxicity rates.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68: 394-424, 2018.
2. Yamashita K, Matsuda T, Hasegawa H, et al. Recent advances of neoadjuvant chemoradiotherapy in rectal cancer: Future treatment perspectives. Ann Gastroenterol Surg 3: 24-33, 2018.
3. Kim JH. Controversial issues in radiotherapy for rectal cancer: a systematic review. Radiat Oncol J 35: 295-305, 2017.
4. Feeney G, Sehgal R, Sheehan M, et al. Neoadjuvant radiotherapy for rectal cancer management. World J Gastroenterol 25: 4850-4869, 2019.
5. Chen K, Xie G, Zhang Q, et al. Comparison of short-course with long-course preoperative neoadjuvant therapy for rectal cancer: A meta-analysis. J Cancer Res Ther 14 (Supplement): S224-S231, 2018.
6. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351: 1731-1740, 2004.
7. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 30:1926-1933, 2012.
8. Ashman JB, Zelefsky MJ, Hunt MS, Leibel SA, Fuks Z. Whole pelvic radiotherapy for prostate cancer using 3D conformal and intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 63: 765-771, 2005.
9. Dapper H, Rodríguez I, Münch S, et al. Impact of VMAT-IMRT compared to 3D conformal radiotherapy on anal sphincter dose distribution in neoadjuvant chemoradiation of rectal cancer. Radiat Oncol 13: 237, 2018.
10. Jabbour SK, Patel S, Herman JM, et al. Intensity-modulated radiation therapy for rectal carcinoma can reduce treatment breaks and emergency department visits. Int J Surg Oncol 2012: 891067, 2012.
11. Lefevre JH, Mineur L, Kotti S, et al. Effect of interval (7 or 11 weeks) between neoadjuvant radiochemotherapy and surgery on complete pathologic response in rectal cancer: A multicenter, randomized, controlled trial (GRECCAR-6). J Clin Oncol 34: 3773-3780, 2016.
12. Saglam S, Bugra D, Saglam EK, et al. Fourth versus eighth week surgery after neoadjuvant radiochemotherapy in T3-4/N0+ rectal cancer: Istanbul R-01 study. J Gastrointest Oncol 5: 9-17, 2014.
13. Akgun E, Caliskan C, Bozbiyik O, et al. Randomized clinical trial of short or long interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. Br J Surg 105: 1417-1425, 2018.
14. Ryan É J, O'Sullivan DP, Kelly ME, et al. Meta-analysis of the effect of extending the interval after long-course chemoradiotherapy before surgery in locally advanced rectal cancer. Br J Surg 106: 1298-1310, 2019.
15. Martin ST, Heneghan HM, Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. Br J Surg 99: 918-928, 2012.
16. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 11: 835-844, 2010.
17. Lorimer PD, Motz BM, Kirks RC, et al. Pathologic complete response rates after neoadjuvant treatment in rectal cancer: An analysis of the National Cancer Database. Ann Surg Oncol 24: 2095-2103, 2017.
18. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 240: 711-717, 2004.
19. Renehan AG, Malcomson L, Emsley R, et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol 17: 174-183, 2016.
20. Dossa F, Chesney TR, Acuna SA, Baxter NN. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2: 501-513, 2017.
21. van der Valk MJM, Hilling DE, Bastiaannet E, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet 391: 2537-2545, 2018.

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