MARMARA
MEDICAL JOURNAL

Original Article

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The oncological outcomes of postoperative radiotherapy in patients with stage II and III upper rectal cancer

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Submitted: 22.11.2021 **Accepted:** 11.04.2022

ABSTRACT

Objective: We assessed the oncological outcomes of postoperative radiotherapy and chemotherapy in patients with stage II or III upper rectal cancer who had undergone curative surgery.

Patients and Methods: We retrospectively investigated 133 patients who underwent primary curative resection of stage II or III upper rectal cancer. The median age was 62 years (range 30–82 years). Among these patients, 48% were stage II and 52% stage III. All received postoperative radiotherapy, and most received adjuvant 5-fluorouracil-based chemotherapy for 6 months after radiotherapy ceased. Survival curves were plotted using the Kaplan–Meier method, and survival was compared using the log-rank test.

Results: The median follow-up was 71.4 months. The 5-year local recurrence-free survival, cancer specific survival, and overall survival (OS) rates were 91.6%, 80.6%, and 75.4%, respectively. Nodal stage 2 ($p = 0.02$, $p = 0.05$) was a significant predictor of poor local recurrence-free survival and cancer specific survival rates. In the multivariate analysis, older age ($p = 0.01$) and a higher N stage ($p = 0.01$) were independent risk factors for poor OS.

Conclusion: The nodal state was predictive of all endpoints in patients with upper rectal stage II or III cancer.

Keywords: Upper rectal cancer, Postoperative radiotherapy, Outcomes

1. INTRODUCTION

Colorectal cancer is the fourth most common cancer worldwide [1]. Management of locally advanced rectal cancer is multimodal, consisting of radiotherapy (RT), chemotherapy, and total or partial mesorectal excision [2-4]. Although, management for advanced low and middle rectal cancers is now well-standardized, the optimal management for upper rectal cancer is less clear. Most studies on colorectal carcinomas do not evaluate the rectosigmoid junction alone, but together with the rectum [5-7] or colon [8]. Only a few have analyzed adenocarcinoma of the rectosigmoid junction [9-12]. Here, we present our long-term results on prognostic factors in patients with upper rectal cancers. The literature on postoperative RT is sparse.

2. PATIENTS and METHODS

Marmara University Ethics Committee approved the study (approval no. 09.2021.211). We evaluated 133 patients treated between July 1997 and December 2015. Table I summarizes their demographic and pathological characteristics. Before treatment, all patients underwent physical examination, colonoscopy, tumor biopsy, abdominal computed tomography or pelvic magnetic resonance imaging, and routine laboratory tests. Masses of 10–15, 15–20, and > 20 cm from the anal verge were considered to be in the upper rectum, rectosigmoid region, and sigmoid region, respectively. Tumor stage was classified in accordance with the seventh edition of the American Joint Committee on Cancer staging manual and handbook [13]. All patients had stage II or III disease. All received a median of 50.4 Gy (range 45–59.4 Gy) in 25–33 fractions of megavoltage external beam RT to the entire pelvis, delivered in the three-dimensional conformal mode in 82% of patients and in the intensity-modulated or volumetric arc mode in 18%. All but six patients received concurrent 5-fluorouracil (5-FU)-based

How to cite this article: Alsan Cetin I, Akay SU. The oncological outcomes of postoperative radiotherapy in patients with stage II and III upper rectal cancer. Marmara Med J 2022; 2; 35(2):225-229. doi: 10.5472/marumj.1121383

ISSN: 1309-9469

http://doi.org/10.5472/marumj.1121383
Marmara Med J 2022;35(2): 225-229

chemotherapy, and all but five an additional 6 months of adjuvant chemotherapy.

One of the following three regimens was prescribed to all patients undergoing RT: (1) intravenous bolus of 5-FU (400 mg/m2/day) and leucovorin (20–25 mg/m2/day) during the first and last weeks of RT, (2) continuous infusion of 5-FU (225 mg/m2/day), or (3) oral capecitabine (825 mg/m2 b.i.d.) on days 1–5. All patients were examined at 3-month intervals for 2 years, at 6-month intervals for the next 2–5 years, and annually thereafter.

Overall survival (OS) was defined as the time from cancer diagnosis to the end of follow-up or the date of death from any cause. Cancer-specific survival (CSS) was defined as the time from cancer diagnosis to the end of follow-up or cancer-related death. The local control time was defined as the time from surgery to pelvic cavity relapse.

Statistical Analysis

Survival curves were obtained by the Kaplan–Meier method, and the survival curves were compared using the log-rank test. Univariate and multivariate Cox regression models were employed to estimate hazard rates (HRs) with precise 95% confidence intervals (CIs). All statistical tests were two-sided. A p-value ≤ 0.05 was considered to reflect statistical significance. SPSS ver. 22 software (IBM, Armonk, NY, USA) was used for all statistical analyses.

3. RESULTS

The median follow-up time was 71.4 months (6–274 months). Although, distant metastasis (DM) constituted the dominant failure pattern (n = 26, 19.5%), locoregional recurrence (LRR) occurred in 14 patients (10%). Most recurrent lesions developed in patients with pT3 or T4 tumors (25 with DM, 13 with LRR). LRR developed within the radiotherapy field in 12 patients (9%). Half of the DM lesions were multiorgan in nature, occurring most commonly in the liver and lungs (n = 11). The most common acute gastrointestinal side effects were not observed in 35.3% of patients, but 22.6%, 36.8%, and 5.3% of patients exhibited grade 1, 2, and 3 side effects, respectively. In terms of chronic gastrointestinal side effects, 88% of patients were not affected, whereas 6% and 4.5% of patients had grade 1 and 2 side effects, respectively; only one patient had grade 3 side effects. Grade 4–5 acute or late toxicity was not observed. The OS, CSS, and local recurrence-free survival rates at the 5-year follow-up were 75.4%, 80.6%, and 91.6%, respectively. The respective survival rates of patients with nodal stage 2 (N2) tumors were 50%, 57%, and 88%. On univariate analysis, age ≥ 64 years (p = 0.04), stage III disease (p = 0.04), and N2 (p = 0.01) were significantly associated with poor OS. N2 (p = 0.02, p = 0.049) was also significantly associated with poor CSS and local recurrence-free survival rates (Table I). On multivariate analysis, N2 [SE (Standard Error) = 0.3, HR = 2.6, 95% CI (1.2–5.6), p = 0.012] and age ≥ 64 years [SE = 0.2, HR = 1.9, 95% CI (1.1–3.5), p = 0.017] were significantly and independently predictive of poor OS (Figure 1).

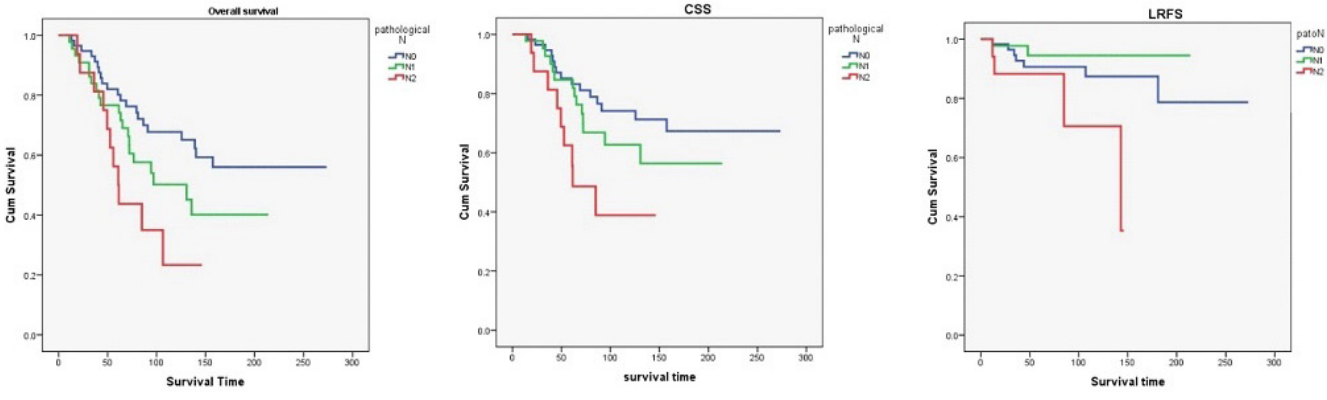

Figure 1. *Overall survival, cancer-specific survival, and local recurrence-free survival in terms of the nodal state*

http://doi.org/10.5472/marumj.1121383
Marmara Med J 2022;35(2): 225-229

***Table I**: Demographic and pathological characteristics of the patients and univariate analysis results for overall survival, cancer-specific survival, local recurrence-free survival.*

	Number of patients (N=133) (%)	OS	CSS	LRFS
		P value	P value	P value
Age		**0.04**	0.2	0.8
Median	62 (30-82)			
<64	79 (59.4)			
≥64	54 (40.6)			
Gender		0.2	0.8	0.9
Male	74 (55.6)			
Female	59 (44.4)			
AJCC stage		**0.04**	0.06	0.8
II	64 (48.1)			
III	69 (51.9)			
AJCC T stage		0.9	0.5	0.07
T1/T2	7 (5.3)			
T3/T4	126 (94.7)			
AJCC N stage		**0.01**	**0.02**	**0.049**
N0	63 (47.5)			
N1	50 (37.5)			
N2	20 (15)			
Grade		0.6	0.1	0.2
I	10 (7.5)			
II	101 (76)			
III	16 (12)			
Unknown	6 (4.5)			
The number of lymph nodes		0.4	0.8	0.4
<11	53 (40)			
≥11	73 (55)			
Unknown	7 (5)			
Tumor size(cm)		0.2	0.3	0.6
≤4	48 (36)			
>4	76 (57)			
Unknown	9 (7)			
Surgical border		0.7	0.8	0.07
Negative	125 (94)			
Positive	8 (6)			
Localization		0.5	0.6	0.9
Upper rectum	52 (39)			
Rectosigmoid	56 (42)			
Sigmoid	25 (19)			
RT dose		0.9	0.6	0.1
<50 Gy	16 (12)			
≥50Gy	117 (88)			
RT technic		0.2	0.1	0.3
3CRT	109 (82)			
VMAT	24 (18)			

OS=Overall survival, CSS=Cancer specific survival, LRFS=Local recurrence-free survival, RT=Radiotherapy, 3CRT= 3D conformal RT, VMAT=Volumetric arc therapy

http://doi.org/10.5472/marumj.1121383
Marmara Med J 2022;35(2): 225-229

4. DISCUSSION

In our study, N2 stage was found as a significant predictor of poor local recurrence-free survival and cancer specific survival rates. In the multivariate analysis, older age and a higher N stage were independent risk factors for poor OS.

Although, adjuvant RT has been suggested as inappropriate because the upper rectum is covered with peritoneum, postoperative chemoradiotherapy increased the local control and survival of patients with stage II and III upper rectal cancer in some studies [14,15]. Some studies found that if tumors are located ≤ 12 cm from the anal verge, lymph node involvement and pelvic recurrence are more common than DM, whereas the reverse is true for more distant tumors (45% of recurrent lesions develop in the liver) [16-20]. As locally advanced upper rectal cancer is assumed to be a systemic disease, adjuvant pelvic RT may be beneficial. Sauer et al., showed that, as was true for middle and lower rectal cancers, adjuvant chemoradiotherapy (CRT) reduced local upper rectal cancer recurrence [21]. The 5-year local recurrence rate was also low (8.4%) in our study. The DM rate was higher and independent of the upper rectal tumor stage, which also did not affect the rate of OS or local recurrence. Lymph node metastasis was an important independent risk factor for local recurrence and survival in many studies [22-25]. We found that N2 stage independently predicted poor outcomes. Vigliotti et al., suggested that postoperative adjuvant radiotherapy was useful for reducing the local recurrence of rectal and rectosigmoid adenocarcinomas. A total dose > 50 Gy to the entire target volume is often used to minimize the relapse rate (< 10%) [26]. We found that postoperative RT reduced local recurrence of upper rectal cancer. Moreover, although statistical significance was not attained, local recurrence was prevented by RT > 50 Gy (5-year local recurrence-free rate: 85.7% vs. 92.4%). Tabchouri et al., found that neoadjuvant CRT did not improve the long-term oncological outcomes of patients with locally advanced upper rectal adenocarcinoma and, in fact, increased postoperative complications [27]. Our postoperative CRT complication rates were very low. Acute gastrointestinal side effects were observed in only 5.3% of patients and grade 3 chronic gastrointestinal side effects in only one patient.

In summary, in this retrospective study, we found that local recurrence of stage II/III upper rectal cancer decreased with postoperative RT, and that N2 was negatively associated with all endpoints. A prospective randomized trial is needed to confirm our findings.

Compliance with the Ethical Standards

Ethical Approval: Marmara University Ethics Committee approved the study (approval no. 09.2021.211).

Financial Support: The authors have no relevant financial information to close.

Conflict of Interest: The authors have no potential conflicts of interest to disclose.

Author Contribution: Both authors participated equally in the idea, concept, design, data collecting and processing, literature review, writing article, and analysis of the paper.

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