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

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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 threedimensional 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

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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 \geq 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

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

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

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 \leq 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).

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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.

REFERENCES

- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66:7-30. doi: 10.3322/caac.21332. Epub 2016 Jan 7.
- [2] Cedermark B, Dahlberg M, Glimelius B, Påhlman L, Rutqvist LE, Wilking N. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 1997;336: 980-7. doi: 10.1056/NEJM199.704.033361402.
- [3] Kapiteijn E, Marijnen CA, Nagtegaal ID, et al; Dutch Colorectal Cancer Group: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345: 638-46. doi: 10.1056/NEJMoa010580.
- [4] Zaborowski A, Stakelum A, Winter DC. Systematic review of outcomes after total neoadjuvant therapy for locally advanced rectal cancer. Br J Surg 2019;106: 979-87. doi: 10.1002/ bjs.11171.
- [5] Yamamoto S, Watanabe M, Hasegawa H, Kitajima M. Prospective evaluation of laparoscopic surgery for rectosigmoidal and rectal carcinoma. Dis Colon Rectum 2002; 45:1648e54. doi: 10.1097/01.DCR.000.003.4514. 34747.80.
- [6] Ponz de Leon M, Marino M, Benatti P, et al. Trend of incidence, subsite distribution and staging of colorectal neoplasms in the 15-year experience of a specialised cancer registry. Ann Oncol 2004; 15:940e6. doi: 10.1093/annonc/mdh224.
- [7] Kaser SA, Froelicher J, Li Q, et al. Adenocarcinomas of the upper third of the rectum and the rectosigmoid junction seem to have similar prognosis as colon cancers even without radiotherapy, SAKK 40/87. Langenbeck's Arch Surg 2015;400:675e82. doi:10.1007/s00423.014.1243-1.
- [8] Suttie SA, Shaikh I, Mullen R, Amin AI, Daniel T, Yalamarthi S. Outcome of right – and left-sided colonic and rectal cancer following surgical resection. Colorectal Dis 2011; 13:884-9. doi:10.1111/j.1463-1318.2010.02356.x.
- [9] Guan X, Jiang Z, Ma T, et al. Radiotherapy dose led to a substantial prolongation of survival in patients with locally advanced rectosigmoid junction cancer: a large population based study. Oncotarget 2016; 7:28408e19. doi: 10.18632/ oncotarget.8630.
- [10] Burton S, Brown G, Daniels I, et al. MRI identified prognostic features of tumors in distal sigmoid, rectosigmoid, and upper rectum: treatment with radiotherapy and chemotherapy. Int J Radiat Oncol Biol Phys 2006;65: 445e51. doi: 10.1016/j. ijrobp.2005.12.027.
- [11] Bussotti C, Burattini MF, Ricci E, Giuliani N, Bufalari A, Servoli A, et al. Rectosigmoid junction neoplasms: our experience. Geka Chiryo 2003; 24:409e12.
- [12] Moutinho-Ribeiro M, de Sousa JP. 81 cancers of the rectosigmoid junction. Colonic or rectal neoplasms? Acta Med Port 1993; 6:443e7.

- [13] Greene FL. AJCC cancer staging manual. 7th ed. New York: Springer-Verlag; 2010.
- [14] Song C, Song S, Kim JS, et al. Impact of postoperative chemoradiotherapy versus chemotherapy alone on recurrence and survival in patients with stage II and III upper rectal cancer: A propensity score-matched analysis. PLoS One 2015;22;10: e0123657. doi: 10.1371/journal.pone.0123657.
- [15] Kang BM, Baek JH, Park SJ, et al. Impact of adjuvant therapy type on survival in stage II/III rectal cancer without preoperative chemoradiation: A Korean multicenter retrospective study. Ann Coloproctol 2018; 34: 144-51. doi:10.3393/ac.2017.09.26.1.
- [16] Pilipshen SJ, Heilweil M, Quan SH, Sternberg SS, Enker WE. Patterns of pelvic recurrence following definitive resections of rectal cancer. Cancer 1984; 53: 1354-62. doi: 10.1002/1097-0142(19840315)53:6<1354::aidcncr282.053.0623>3.0.co;2-j.
- [17] Polk HC, Spratt JS. Recurrent colorectal carcinoma: Detection, treatment, and other considerations. Surgery 1971; 69:9-23.
- [18] Welch JP, Donaldson GA. The clinical correlation of an autopsy study of recurrent colorectal cancer. Ann Surg 1979; 189:496-502. doi: 10.1097/00000.658.197904000-00027.
- [19] Vassilopoulos PP, Yoon JM, Ledesma EJ, Mittelman A. Treatment of recurrence of adenocarcinoma of the colon and rectum at the anastomotic site. Surg Gynecol Obstet 1981; I52:777-80.
- [20] Mittelman AM, Knowlton AH, Weiland L. Phase Ill study of adjuvant therapy of surgically operable rectal carcinoma, Stages B2 and C. Proceedings Gastrointestinal Tumor Study Group, National Cancer Institute, 1975.

- [21] Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004; 351: 1731-40. doi: 10.1056/NEJMoa040694
- [22] Valentini V, van Stiphout RG, Lammering G, MC, et al. Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. J Clin Oncol 2011; 29:3163-72. doi: 10.1200/ JCO.2010.33.1595
- [23] Gunderson LL, Sargent DJ, Tepper JE, et al. Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: a pooled analysis. J Clin Oncol 2004; 22:1785-96. doi: 10.1200/JCO.2004.08.173. Epub 2004 Apr 5.
- [24] Quirke P, Steele R, Monson J, et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. Lancet 2009; 373:821-8. doi: 10.1016/S0140-6736(09)60485-2.
- [25] Hu S, Li S, Teng D, et al. Analysis of risk factors and prognosis of 253 lymph node metastasis in colorectal cancer patients. BMC Surg . 2021;21:280. doi: 10.1186/s12893.021.01276-2.
- [26] Vigliotti A, Rich TA, Romsdahl MM, Withers HR, Oswald MJ. Postoperative adjuvant radiotherapy for adenocarcinoma of the rectum and rectosigmoid. Int J Radiat Oncol Biol Phys 1987;13:999-1006. doi: 10.1016/0360-3016(87)90037-x.
- [27] Tabchouri N, Eid Y, Manceau G, et al. Neoadjuvant treatment in upper rectal cancer does not improve oncologic outcomes but increases postoperative morbidity. Anticancer Res 2020 ;40:3579-87. doi:10.21873/anticanres.14348.