ORIGINAL ARTICLE

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Outcome and Survival in Patients with Stage II/III Sigmoid, Rectosigmoid and Upper Third Rectal Cancer Treated with Upfront Surgery

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Abstract

Objective: Rectosigmoid junction is hard to define clinically. Its clinicopathological features seem different when compared to the ones of the sigmoid and upper rectal cancer. This study investigated the outcome and survival in patients with postoperative stage II/III sigmoid, rectosigmoid and upper third rectal cancer treated with upfront surgery.

Methods: Patients with sigmoid, rectosigmoid junction and upper rectal cancer underwent upfront curative surgery in the period (2016-2022) in tertiary institutions are retrospectively examined. Patient, tumor and follow-up data divided into three groups were retrospectively reviewed and compared for outcome and overall survival.

Results: Of a total number of 76 patients, 32 had rectosigmoid junction cancer, followed by sigmoid and upper third rectal cancer (in 27 and 17 patients, respectively). Most of the patients (63) presented with postoperative stage III. The mean follow-up period was 34.22 months. Patients with positive lymph nodes had worse survival (p=0.016). Perineural invasion affected the survival significantly (p=0.022). Rectosigmoid junction cancer showed the worst survival in comparison with sigmoid and upper rectal cancer (p=0.041).

Conclusion: Rectosigmoid junction cancer had the worst overall survival between the investigated groups. Perineural invasion presented as an independent factor for survival. The clinical behavior of the rectosigmoid junction cancer differs from the other cancers of the "terminal colon".

Keywords: Rectosigmoid junction cancer, sigmoid colon cancer, upper third rectal cancer, survival, outcome

INTRODUCTION

This retrospective single-center study aimed to evaluate and compare the clinicopathological features, postoperative outcome and overall survival (OS) of patients operated for sigmoid, rectosigmoid junction (RSJ) and upper third rectal cancer (URC) (all with postoperative stage II and III).

The difference in treatment between sigmoid colon cancer (SCC) and URC is clearly defined (1). When RSJ cancer is added "between", certain dilemmas are imposed. Namely, the precise preoperative localization of the RSJ itself is a diagnostic challenge (2,3). Eventual misclassification of the tumor localization (whether is rectal or sigmoid) can lead to inadequate type of surgery, possible different functional outcomes and additional overtreatment or under treatment with neoadjuvant radiotherapy (1). The RSJ is added in the International Classification of Diseases in 2014 (4). Current recommendations for RSJ cancer treatment consist of oncologic rectosigmoid resection (open or minimally invasive) with the addition of adjuvant chemotherapy for stage III and high-risk stage II addressing on the unresected micrometastases (5). The treatment of URC is depended on the preoperative stage in terms of whether neoadjuvant chemoradiation will be applied

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(6). Few studies addressing on the comparison of outcome, OS and clinicopathological features of sigmoid, RSJ and URC are present in the relevant literature (7-9).

METHODS

Patients with stages I and IV were excluded. Patient data were extracted from an electronic medical data system for the period (2016-2021). All the patients were treated with upfront surgery according to the decision of the gastrointestinal and colorectal oncologic board of the clinic.

The patients were assessed preoperatively with colonoscopy, abdominal computed tomography and magnetic resonance imaging (MRI) scans. Tumor location was determined with combined use of endoscopy, computerized tomography (CT) and MRI scan simultaneously in order to define its precise preoperative position. URC location was determined with colonoscopy and rectum MRI. Additional intraoperative assessment defined the localization for URC (above the peritoneal reflexion) and for the RSJ cancer (absence of colonic taenia). All the findings were reviewed on the clinic multidisciplinary oncologic board before surgery for proper tumor localization and oncologic protocol.

Six colorectal surgeons performed all the operations resulting with R0 resection. Standard laparoscopic and open approaches were used. High ligation of the inferior mesenteric artery was mandatory. Splenic flexure mobilization was not routinely performed and it depended on the colon length. Sigmoid resection was performed without TME. For RSJ and URC, PME or TME were performed (10). All the colo-rectal anastomoses were stapled with a circular stapler (no. 29, 31 and 33) by using the double-stapled technique. Fast-track feeding protocol was used in the postoperative period (11).

Patient characteristics, surgery and tumor data and follow-up period in months were collected. Demographic patient data used for statistical analysis were age, gender and American Society for Anesthesiologists (ASA) score.

Tumor data referred to localization, distal resection margin, postoperative tumor stage, number of retrieved lymph nodes per procedure, lymph node involvement with metastases grade and the presence of lymphovascular (LVI) and perineural invasion (PNI). The patients were divided in three groups according to tumor location for statistical analysis (sigmoid, rectosigmoid and upper rectum). Survival analysis was performed between the three groups in terms of OS and additional ones according to the presence of lymph node metastases, LVI and PNI.

Statistical Analysis

Statistical analysis was performed using the SPSS v. 18.0.0 (IBM Corp., Armonk, NY, USA) software. Numeric variables are presented as mean and compared with Student's t-test or the Mann-Whitney U test. Categorical variables are presented as numbers and compared with the chi-square test. OS was estimated by the Kaplan-Meier method and the log rank test was used to compare differences between the groups. Statistical significance was set for a p value of ≤0.05. The study was approved by the Local Ethical Committee of the University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital, clinic, no. E-48670771-514.99, issue: 49.

RESULTS

A total number of 76 patients were operated, with the most frequent localization of tumor in the RSJ 32), followed by the sigmoid (27) and upper third rectum (17). Fifty patients were males, and the rest (26) were females. Mean age of patients was 63.3 years and no statistical difference was noted on the different tumor localization on age, gender and ASA score. Postoperative stage II was confirmed in 13 patients and the rest 63 were diagnosed with stage III. Number of patients presented with stage II for the sigmoid colon, rectosigmoid colon and upper rectum were 4,4,5 and the number of patients with stage III were 23,28,12 respectively. There was no statistical difference according to localization between each group (p=0.303). There was no statistical difference between stages II and stage III in terms of survival (p=0.551). Mean distal resection margin was 5.8 cm. The total mean number of harvested lymph nodes was 26.6. Lymph node metastases were present in 42 patients, half of them in patients with RSJ cancer. No statistical difference was seen between the groups (p=0.151). LVI invasion was present in 40 patients. More than half of them (21) were patients with RSJ cancer. There was no statistical difference between the groups (p=0.150). Of total number of 35 patients with PNI, the predominant cancer location was again the RSJ (17), followed equally by sigmoid and upper rectal cancer (9). The analysis of three different tumor localizations and its association with lymph node metastases, LVI and PNI revealed no statistical difference (Table 1).

There was no statistical difference in estimated survival according to age, gender, postoperative tumor stage, ASA score and LVI presence.

Estimated three-year survival rate for patients with metastases in lymph nodes was 66.7% (SE: 19.2), and in lymph node negative patients it was 96.6% (SE: 3.4), p=0.016, (Figure 1).

OS rate for the presence of PNI during follow-up period was 67.2% (SE: 8.3) and the patients without PNI had an OS rate of 93.2% (SE: 4.79). The long-rank test of equality of survival for patients with present PNI presented with statistical significance (p=0.022), therefore, confirming the PNI to be an independent factor for survival (Figure 2).

Overall three years survival rate was 81.6% for all tumor locations. Patients with SCC had the best OS rate of 96.3% (SE: 3.9), for RSJ cancer location 62.5% (SE: 9.6) and for patients with URC OS rate was 94.1% (SE: 6.4). Log-rank test for survival distribution according to tumor localization presented with significance meaning that the RJC cancer showed worst survival (p=0.041), (Figure 3).

The Cox regression analysis of different factors affecting survival showed that only the PNI is the independent prognostic factor in the survival (p=0.008), (Table 2).

DISCUSSION

The debate of proper cancer treatment of the terminal colon variously described as "rectosigmoid", "upper rectum", or "lower sigmoid" is old and still unanswered (12). Doubts exist on the RSJ

Table 1. Patient and tumor data

	Total n=76 (%)	Sigmoid colon (%)	Rectosigmoid junction (%)	Upper rectum (%)	p value
Patient data					
Gender					
Male	50 (65.8)	18 (23.6)	18 (23.6)	14 (18.4)	0.185
Female	26 (34.2)	9 (11.8)	14 (18.4)	3 (3.9)	
Age mean; (range)	63.3; (42-85)				
ASA score ASA I ASA II ASA III ASA IV	 13 (17.1) 26 (34.2) 25 (32.8) 12 (15.7)	 4 7 11 5	 7 13 6 6	 2 6 8 1	0.362
Tumor data					
Tumor stage					
Stage II	(17.2)	4	4	5	0.302
Stage III	(82.8)	23	28	12	
Distal resection margin (mean)		7.78	5.82	3.14	**0.002**
Tumor differentiation					
Well	4 (5.2)				
Moderate	58 (76.3)				
Poor	5 (6.5)				
Mucinous	6 (7.8)				
Not available	3 (3.9)				
Lymph nodes extracted (mean)	26.6	22.04	30.47	26.59	**0.043**
pN0	35 (46)	16	11	8	0.155
pN1/N2	41 (54)	11	21	9	
LVI					
(-)	36 (47)	15	11	10	0.150
(+)	40 (53)	12	21	7	
PNI					
(-)	41 (54)	18	15	8	0.256
(+)	35 (46)	9	17	9	

LVI: Lymphovascular invasion, PNI: Perineural invasion, ASA: American Society for Anesthesiologists

anatomic location. Different definitions have been proposed according to its anatomy and physiology, but none of them is associated with the same anatomical area which can be confusing for the surgeon when dealing with malignancy in this part of the colon. Several proposed definitions in the literature are dependent on different specialty (radiology, endoscopy, surgery). Hence, from surgeons' aspect two anatomic landmarks have been proposed: the disappearance of taenia (end-point of the sigmoid of the colon) and the peritoneal reflection (bellow the upper rectum) (13). Precise location of the colorectal cancer is essential for appropriate treatment modality choice. Insufficiently accurate endoscopic arbitrary measurements (from the anal verge) were used for the preoperative marking of the RSJ (2). In the study of Moltzer et al. (14) endoscopy failed to distinguish distal sigmoid carcinomas from rectal carcinomas in one out of 10 patients. Therefore, they recommend combining endoscopy and MRI/CT scans and underlay the importance of a multidisciplinary approach. Recently, after the Delphi consensus, the "sigmoid take-off" alternative landmark was implemented (15). It defines the transition from the rectum to the sigmoid with the beginning of the sigmoid mesocolon (2). A recent Dutch survey was conducted on the implemented Delphi consensus in the Dutch national guidelines. According to the results, although not yet been implemented in all multidisciplinary meetings, the new definition of the rectum improved the sensitivity and the negative predictive value. However, due to the small number of tumors in the area of the sigmoid take-off (only three cases), the authors concluded that the implementation of such a landmark should be accompanied with adequate training in order to ensure proper assessment (16). In the study of Hui et al. (17), patients were included with primary tumors located 9-20 cm from the anal verge on staging CT, MRI, or colonoscopy In this study, a combination of endoscopy, CT and MRI marking of the RSJ tumors was used for more precise accuracy.

Table 2. Multivariate analysis of different factors affecting survival (Cox regression)

		95.0% CI for Exp (B)		
	HR	Lower	Upper	p
LVI	0.672	0.173	2.606	0.566
PNI	0.120	0.025	0.578	0.008
Tumor localization	1.266	0.591	2.711	0.545
Met. lymph node	0.991	0.911	3.598	0.830
ASA score	1.811	0.917	1.072	0.090

LVI: Lymphovascular invasion, PNI: Perineural invasion, ASA: American Society for Anaesthesiologists, HR: Hazard ratio, CI: Confidence interval

The dilemma for the optimal management of patients with locally advanced RSJ cancer is unclear. Pros and cons exist whether upfront surgery or neoadjuvant chemoradiation should be implemented for the RSJ cancer on regard of OS (18-20). In their retrospective study, Venigalla et al. (21) suggest the use of neoadjuvant chemoradiation in patients with

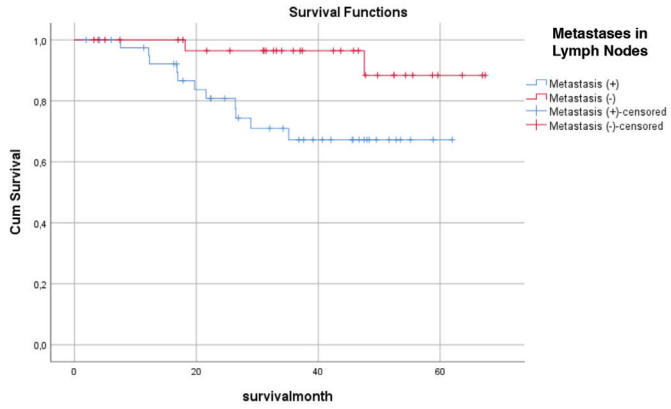

Figure 1. Kaplan-Meier curve on the survival distributions according to metastases presence in lymph nodes

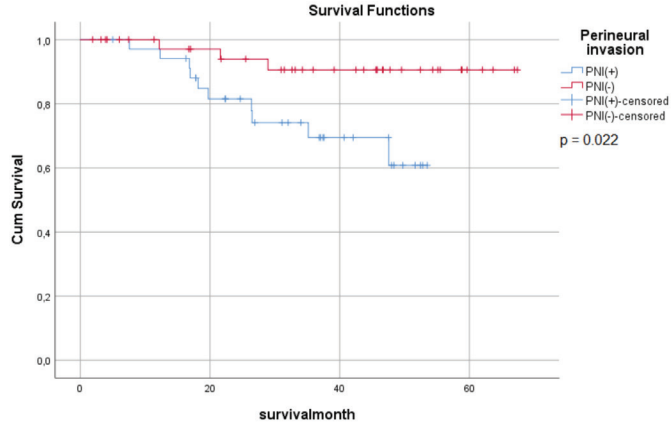

Figure 2. Kaplan-Meier curve on the survival distributions according to perineural invasion presence

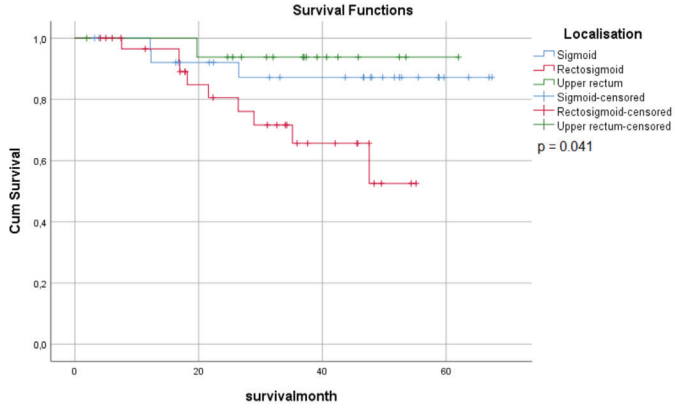

Figure 3. Kaplan-Meier curve on the overall survival distributions according to tumor localization

locally advanced RSJ cancer instead of upfront surgery use due to OS improvement. They reported 24% decreased hazard of death associated in neoadjuvant chemoradiation recipients (21). Hui et al. (17) found no statistical difference in the 2-year OS between the group of patients treated with upfront surgery and the one treated with neoadjuvant therapy. The Dutch rectal cancer study showed no improvement in local disease control with neoadjuvant radiotherapy use for tumors located 10.1-15 cm from the anal verge in comparison to more distal tumors (22). Contrary, the MRC CR07 and NCIC-CTG C016 trial revealed advantages of preoperative radiotherapy for tumor location >10-15 cm from the anus with a 3-year local recurrence rate of 1.2% in opposition to 6.2% recurrence rate for patients with the conduction of selective post-operative chemoradiation (23).

The proportion of lymph node metastases is reported to be different for cancers of the sigmoid, RSJ and upper rectum. Park et al. (9) reported significantly increased presence of pararectal lymph node metastases with exclusion of patients who underwent preoperative chemoradiotherapy. They emphasis different patterns of lymphatic spread in RSJ cancer, as a possible reason for the raised frequency of lymph node metastases (9). Falch et al. (7) reported significantly more frequent presence of four and more lymph node metastases (pN2;) in RSJ cancer in comparison to sigmoid and rectal one. Hui et al. (17) reported lymph node metastases presence in 54.7% (pN1) and in 25% (pN2) in his group of 64 patients treated with upfront surgery for RSJ cancer. In this study the most predominant cancer in terms of lymph node metastases appearance was also the one in RSJ, but without statistical significance.

Reports on the LVI and PNI are heterogeneous in terms of their rate in the RSJ cancer. Falch et al. (7) reported significantly higher rates of LVI in RSJ tumor location and no difference in terms of PNI. In the study of Park et al. (9) neither LVI, nor the PNI presented statistical difference between the three groups of patients. In this study LVI and PNI were predominant in about half of the RSJ cancers without statistical significance. Still, it was proven that the PNI is independent factor that affects the OS in all patients.

The most complex analysis of survival is reported by Mukai et al. (8). They found no statistical difference on the 5-year OS in patients with colon cancer, RSJ and rectal stage II cancer. However, in patients with stage III, patients with rectal cancer had the worst prognosis (significant differences were found for colon cancer vs. RSJ, and RSJ vs. rectal cancer (8). Park et al. (9) found his oncologic results on the RSJ cancer slightly unfavorable to SCC without difference in OS regarding tumor location. Falch identified the RSJ to be the risk factor for a worse OS. He pointed on the RSJ cancer to be with the worse five-year OS in comparison to patients with SCC and rectal cancer (44.6%, 70.9% and 70.2%, respectively) (7). In this study the RSJ cancer presented with the worst OS according to the long-rank test. However, in the Cox regression analysis tumor localization did not affect survival. Further analyses with large series are needed to clarify the importance of tumor localization in the RSJ and its influence on survival.

Study Limitations

This is retrospective study with small number of patients. Metastatic lymph nodes were not divided according to N stage into subgroups (N1 and N2). The follow-up period is relatively short.

CONCLUSION

The results from this study showed that RSJ cancer has significantly worse OS in comparison to SCC and URC in patients with stage II and III treated with upfront surgery. The presence of PNI represents an independent factor that affects survival in all three groups of patients. Therefore, we can conclude that RSJ cancer's clinical behavior is different from another adenocarcinoma appearing in the sigmoid colon and upper rectum. Certainly, more large comparative studies are needed for this conclusion to be confirmed.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethical Committee of the University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital, clinic, no. E-48670771-514.99, issue: 49.

Informed Consent: Retrospective study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.U., A.N., Concept: C.U., A.N., Design: C.U., A.N., Data Collection or Processing: C.U., Analysis or Interpretation: C.U., A.N., Literature Search: C.U., A.N., Writing: C.U., A.N.

Conflict of Interest: No conflict of interest was declared by the authors.

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