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Upper Rectal Cancer: Benefit After Preoperative Chemoradiation Versus Upfront Surgery?

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1. Summary

1.1 Purpose: Upper rectal cancer management is controversial. The present series reports the outcomes of treatment comparing neoadjuvant chemoradiation (NCRT) versus upfront surgery.

1.2. Methods and materials: In this retrospective study we enrolled patients with upper rectal or sigmoid junction locally advanced tumors (stages II-III). At the first Institution patients received NCRT followed by surgery (study group); at the second Institution patients were referred to upfront surgery (control group). Overall survival was the main endpoint of the analysis. Local relapse and other clinical variables were also analyzed.

1.3. Results: Fifty patients in the study group and 32 patients in the control group were analyzed. In the NCRT group there were more N-positive patients ($p<0.001$); T-stage was similar for both groups. All surgical procedures were performed with R0 margins. Among NCRT patients, in seven cases (14%) complete pathologic response was found. In 27 cases (54%) downstaging in T-stage was achieved. Comparing OS between NCRT and control group there was no significant difference at five years: 84% for NCRT group and 79% for control group (p 0.37). In univariate analysis, clinical T-stage had a statistically significant impact on survival. Patients with cT3 disease did better than patients with cT4 ($p = 0.014$). Two cases of G4 toxicity were observed and only one case of local relapse was observed in NCRT group.

1.4. Conclusion: NCRT achieved a high rate of downstaging alongside tolerable toxicity profile, but did not affect survival outcome in this selected group, as compared to surgery alone.

2. Introduction

Rectal adenocarcinoma is a leading cause of cancer death in developed countries1. In the last few decades, significant improvement has been achieved in patient outcome [2]. Preoperative radiation has resulted in improved local control and overall survival. Combined neoadjuvant radiotherapy with chemotherapy (NCRT) followed by Total Mesorectal Excision (TME) has been well evaluated in several landmark studies and this approach has been defined as the standard of care for the treatment of locally advanced rectal cancer [3-9].

This treatment schedule, however, has mainly been evaluated in lower and mid rectal tumors while studies include roughly 12-18% upper rectal tumors. Data currently available regarding preferable preoperative curative options for patients with adenocarcinoma located at the upper third of the rectum, rectosigmoid junction, or distal sigmoid colon are scarce [10, 44]. For these patient's different management approaches have been used [11]. For tumors confined within the narrow pelvis walls and neighboring organs, the achievement of clear recection margins (R0) is more difficult.

While the downsizing obtained after NCRT is critical for R0 surgery in low and mid rectal tumors, [2] this approach is not established in upper rectal tumors and most centers perform upfront surgery. In case of upper rectal T3 tumors R0 resection may be achieved without exposing the patient to radiation, but rendering a T4 tumor resectable may demand delivering NCRT or intraoperative radiotherapy [12, 13].

Strong level I evidence concerning management of upper rectal cancer is lacking. Retrospective series have shown that NCRT in upper rectal cancer may contribute to achieving R0 margin [14]. However, it is not clear whether applying NCRT may lead to enhanced survival for these patients [46].

The objective of the current study is to compare outcomes for NCRT versus upfront surgery in patients with upper rectal adenocarcinoma utilizing cohorts from two institutions.

3. Materials and Methods

3.1. Patient selection and staging

Patients from two Institutions were analyzed during a period a period ranging from 2008 to 2014. EC approved the clinical research of these patients.

The patients from the first Institution were treated with NCRT followed by surgery, and they represented the study arm. Patients from the second Institution did not received neoadjuvant chemoradiation (non-NCRT) and underwent only upfront surgery, and they represented the control arm. The decision for each approach was undertaken after discussion in multidisciplinary tumor board meetings in both institutions.

Staging procedures included colonoscopy with biopsy, pelvic margetic resonance imaging (MRI) for T- and N-stage evaluation, total body Computed Tomography (CT) for distant metastases exclusion, and additional imaging procedures for evaluation of liver findings if needed. Complete blood tests and serum tumor markers such as CarcinoEmbryonic Antigen (CEA) and carbohydrate antigen (CA 19-9) were also performed.

The inclusion criteria were biopsy proven upper rectal adenocarcinoma. All included patients were fitted for surgery. The standard TME technique was used for lower anterior resection of tumors in both centers. [15]

The tumor distance from anal verge was measured using a colonoscopy. As soon as a biopsy-proven malignant lesion was identified, an MRI was peformed using currently accepted protocol. Patients with tumor boundaries that exceded those defined by our study protocol were excluded from the study. If the upper boundary was higher than 16 cm, the patient was treated as a sigmoid-cancer case; whereas a tumor starting below 11 cm was considered as a mid-rectal cancer case and treated accordingly.

Patients referred to our centers for radiation therapy were diagnosed in different hospitals and MRI reports often didn't contain the information about tumor location with respect to peritoneal reflection. Given the retrospective nature of our current study we took the data "as is" at the decision making point.

Exclusion criteria included metastatic disease on presentation, patients not fitted for surgery, previous "short-course" radiotherapy (25Gy in 5 fractions), and tumor located below 11cm from the anal verge.

3.2. Simulation, Planning and Radiation Treatment

3D Simulation CT was performed in prone position on a belly board (Civco©) as the immobilization device, without intravenous (IV) contrast media injection and with comfortable full bladder. The MRI and CT simulation were co-registered for gross target volume (GTV) delineation with the assistance of an MRI radiologist. The clinical target volume (CTV) included GTV (tumor and enlarged lymph nodes) pelvic lymphatic drainage regions and mesorectum. In the case of T4 disease, CTV included adjacent involved organs and external iliac nodes. Planning target volume (PTV) was created from CTV with an isotropic expansion of 1 cm.

The 3D thechnique was 3 fields PA with 6MV photons and 2 laterals wedged fields (L&R) with 18MV photons. The prescribed dose was 45-50.4 Gy in 25-28 fractions, five days a week. The PTVs were retrieved from Eclypse treatment planning system database. Organs at risk (small bowel, bladder walls and femoral heads) were defined for further dosimetry in order to not exceed the normal tissue tolerance thresholds. For the first group, further analysis was performed to describe influence of tumor size and planning target volume (PTV) on pathological complete response (pCR) and on overall survival (OS).

3.3. Concomitant Chemotherapy

The concomitant chemotherapy (fluorouracil-5-FU infusion 1000 mg/m2/day IV days 1-5 for 5 weeks or oral capecitabine 825 mg/m2 BID for five weeks, five days a week) were prescribed in accordance to indication and patient preference.

3.4. Surgery

Lower anterior resection (TME techniques) was performed after of 6-8 weeks of radiation completion. In case of adjacent organ invasion, an additional resection was performed at the surgeon's discretion at the same time.

4. Adjuvant Chemotherapy

Adjuvant chemotherapy was applied in accordance with ESTRO-ESMO guidelines for the treatment of rectal cancer patients and according to institutional policy.

4.1. Follow-up

Patients were followed with CT scan and blood samples including tumoral markers every five months for the first five years and annually thereafter up to 10 years. Colonoscopy was included at first, fifth and tenth year of the follow-up. Common Terminology Criteria for Adverse Events v4.0 (CTCAE v4) was used for toxicity evaluation.

4.2. Toxicity

The toxicity data collection was made on weekly physician examination at radiation oncology unit starting from day 1 of chemoradiation and finishing a day before surgery.

4.3. Statistical Analysis

For statistical analysis, descriptive and t-test for independent samples were used. In order to assess discrepancies between the groups, Propensity Score Matching (PSM) algorithm was used [16]. This algorithm was performed using tumor level in rectum, gender, age, clinical T- and N-stage as independent factors. Radiotherapy was determined as a factor influencing survival (outcome). Life tables method for examining of distribution of the treatment-to-death interval was used. Cumulative 3- and 5-year survival curves were obtained using Kaplan–Meier method. The proportional hazards model (Cox regression) was used to describe influencing survival covariates. As covariates for Cox regression, gender, age, smoking, tumor location and volume, stage, diagnosis-surgery time, PTV value, and down staging were used. For statistical analysis the IBM SPSS v25 software (SPSS, Chicago, IL, USA) was used. For PSM analysis R-statistics (R version 3.6.2 (2019-12-12,) © 2019 was used.

5. Results

This retrospective study collected data from patients with locally advanced rectal cancer patients treated at two different hospitals from 2008 to 2014. The first group database query provided 375 patients with locally advanced rectal cancer; among them 53 (14%) had tumors in an upper rectal location. From the list, patients who had been treated with 25 Gy in 5 fractions and those with synchronous metastatic disease were excluded. The final first group cohort included 50 patients (24 males and 26 female) with clinical stage II-III diseases (study group), with a median age of 64 years (range 37-80 years). In the second group, of 436 patients were referred to upfront surgery, 32 (7.3%) (17 males and 15 females) met the inclusion criteria (control group), with a median age of 65 years (range 43-86 years). Median follow-up time for alive patients was 6.4 years (range 0.4-11.2 years) in the first group, and 6.9 years (range 0.22-13.79 years) in the second group.

Comparing clinical T- and N-stage between both groups, T-stage was similar for both groups while the study group contained significantly more clinical N-positive tumors ($p<.001$).

In the first group, four patients were T2 (8%), 40 patients were staged as T3 (80%), and 6 patients were T4 (12%). Forty-seven patients (94%) had clinical positive nodes seen on MRI. Forty-nine patients received NCRT and one patient (2%) was treated with radiotherapy alone due to severe underlying cardiovascular disease. Forty-eight (96%) patients were treated with 45 Gy in 25 fractions as prescribed, one patient received 43.2Gy and one was treated with additional boost to cumulative dose of 50.4 Gy (median 45.07±0.8Gy). Forty-nine patients (98%) were assigned to concomitant 5FU or capecitabine protocol. Adjuvant chemotherapy was not applied to 12 patients (24%) due to either complete pathological response in seven cases (14%), contraindication in one (2%), or slow recovery after previous treatment in four cases (8%).

All surgical procedures were performed with R0 margins. Among 50 enrolled first group patients, in seven cases (14%) complete pathologic response was achieved. In 27 cases (54%) downstaging in T-stage was achieved. Of 47 patients with clinically positive lymph nodes, ypN0 was achieved in 30 cases (78.7%)

With a median follow-up of 6.4 years (0.3 to 10.4), median survival time was not reached and OS was 84% at 5 years. Six patients (12%) developed distant metastases. One patient (2%) had a local relapse. Four of them had died of disease and two remained alive with disease.

In the second group (control group) there were 32 patients with proven stage II-III disease. In this arm, T2 tumor was seen in two cases (6.5%), T3 in 28 (87.1%), and T4 in two (6.5%); node positive disease was registered in 12 patients (38.7%). Four pathological stage III patients (12.5%) were treated with adjuvant 5-FU chemoradiation. Two patients (6.2%) developed distant metastases. With a median follow up of 6.9 years, median survival time was not reached and OS was 79% (IC 95% 64-94%) at five years. No local relapses were observed. Differences in OS between study group and control group were not significant at 5 years ($p= 0.87$) (see Figure 1).

The two different centers have a different policy to approach patients with this specific tumor location. The second Institution policy is upfront surgery in case of upper rectum or distal sigmoid tumor location, whereas the first Institution multidisciplinary tumor board meeting has a different protocol, allowing neoadjuvant treatment delivery for upper rectum.

In (Table 1) the clinical data are presented, inference about more advanced disease and greater number of lymph-node involvement was made based on clinical imaging studies, which can be prone to interinvestigator uncertainty. Comparing patients on a clinical N-stage basis may increase the amount of bias, which is inherent to retrospective studies.

In univariate analysis clinical T-stage had a significant impact on survival in the NCRT group. Overall survival (OS) for patients with T3 was 90% (IC 95% 81%-99%) and for patients with T4 was 50% (IC 95% 10%-90%) (p 0.014) (see Figure 2). However, no differences in OS associated with node status were observed in spite of only three patients with N0.

Neither gender, nor tumor location had statistically significant influence on OS.

Interestingly, PTV value (1439.3±342.6 cc) did influence OS but in inverse correlation ($p<.046$) with improved OS in the NCRT group (less PTV implied better OS).

Response to NCRT did not influence OS. Distance from anal margin to tumor also did not affect OS. In the control group, no differences in OS were seen between T3 and T4 or node status. After using PSM, good matching was showed for all factors besides tumor level in the rectum and clinical N-stage. Using genetic matching the groups were well balanced besides clinical N-stage where t-test p-value remained <.0001. Comparing the two groups, more patients with stage III disease were significantly observed in the first group (p<.003). After stratification by gender or accordingly to disease stage OS remained equivalent. Only 2% of patients in the study group relapsed locally. In the control group no local relapses were observed.

Gastrointestinal (GI) and genitourinary (GU) toxicity are displayed in (Table 2). In the perioperative period, one patient (2%) had anastomotic leakage (grade 4) and required second surgery, and one patient (2%), with cT4 bladder involvement, developed bladder fistula that required surgical repair as well (grade 4).

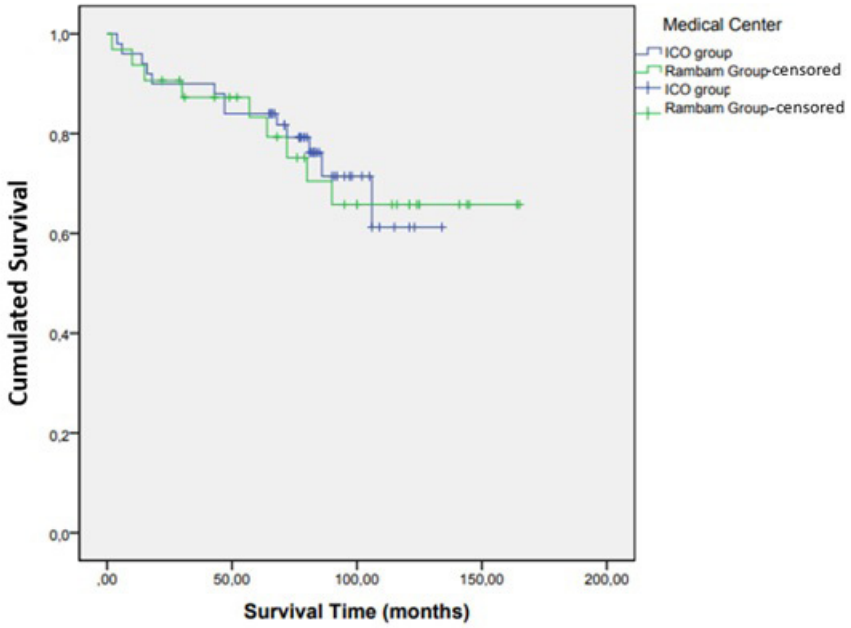

Figure 1: Overall survival of both groups (neoadjunat treatment vs. direct surgery) in patients with upper rectal cancer (p 0.869)

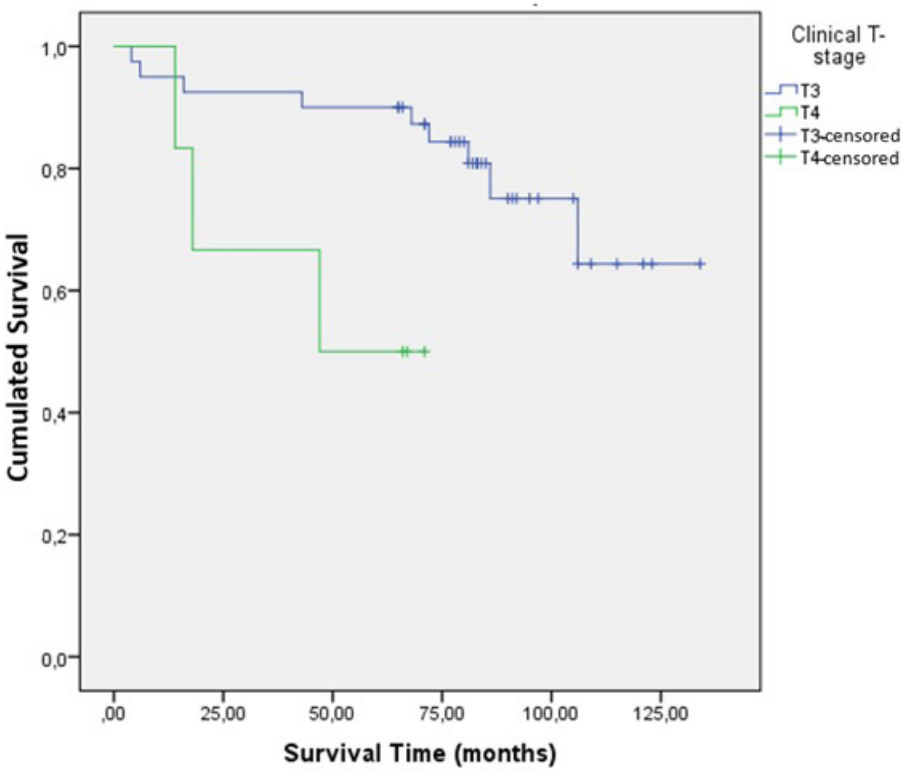

Figure 2: Overall survival curve comparing T3 vs. T4 upper rectal cancer (p<.014)

Table 1: Clinical and pathologic characteristics of ICO (study) and Ram bam (control) groups.

Characteristic	ICO (Badalona)	Rambam (Haifa)	Statistical significance
gender			NS
Male	24	17	
female	26	15	
Mean Age (±SD)	64.02 ±1.5	64.8±2.2	NS
Stage			
T stage			NS
T2	4 (8%)	2 (6.3%)	
T3	40 (80%)	28 (87.6%)	
T4	6 (12%)	2 (6.3%)	
N-stage			p<.001
N0	3 (6%)	20 (62.5%)	
N1	20 (40%)	9 (28.1%)	
N2	27 (54%)	3 (9.4)	
Clinical stage grouping			P<.001
II (cT3-4, cN0, cM0)	3 (6)	20 (62,6)	
III (cTany, cN+, cM0)	47 (94%)	12 (37.4)	
Pathology data			NA
Pathologic complete response, n (%)	7 (14%)	0	
T-Downstaging	27 (54%)		
N-Downstaging			
ypN0	30 (78.7%) of 47 N+		
Median Follow-up	6,4	6,9	NS
Distant relapse	4	2	
Local relapse	1 (2%)	0	
Median time	6±0.3	6.6±0.3	NS

6. Discussion

The three parts of the rectum, or the upper, middle and lower rectum, have been defined in several studies and national projects concluding that the uppermost boundary is at the level of 16 cm from the anal verge as measured by colonoscopy [21, 22, 23, 24]. Currently MRI is known to be a more reliable procedure to evaluate tumor location. [17, 18, 19, 11, 20]. Since MRI is widely accepted for both description and numeric measurement of upper rectal tumors, we have accepted for this study to set the upper part of rectum starting at 11 cm from the anal verge and to consider tumors lying within 11 - 16 cm from the anal verge [11, 25, 26]

The benefit and input of a multidisciplinary evaluation and treatment of patients with lower and mid rectal cancer tumor currently is the standard approach. [27, 21, 28, 29, 30] However, there is a paucity of data about the role of NCRT in upper rectal or distal sigmoid colon cancer. [26, 31, 45], leading to the current summary and evaluation of our experience with NCRT patients with upper rectal and sigmoid cancer. The main focus of our study was to analyze OS and influencing factors. Toxicity profile allowed us to evaluate patient safety. Time frames of patient management were appropriate and met ESMO/ESTRO guidelines for treatment of rectal cancer patients. For all the patients, a resection with pathologically proven R0 margin status was performed. Analyzing the results in terms of an efficiency, the study showed a portion of complete pathological response (14%) after delivering NCRT treatment which is within the reported range among patients with lower and mid rectal cancer [1, 7, 32-36]. The surgical aspect of the treatment protocol was not a part of the study. Total mesorectal excision is a standard surgical approach that was adopted in both our centers. Pathological report on resectional margins was sufficient to assess the response to neoadjuvant chemoradiation.

Given the bicentric retrospective character of the present study, there was an attempt made at pseudo-randomizing the patients using a PSM approach. The PSM results showed well balanced groups by all parameters except for clinical N-stage. The difference was clear in t-test results and remained a non-removable confounder.

Evaluating OS within this group of patients, it is important to note that median survival in both NCRT and surgery groups were not reached, and a five years OS around 80% is a good integrative indicator of effectiveness and safety of this approach.

PTV was a factor having inverse impact on NCRT probability of

response (larger volume correlated with worse response). In our consideration, the larger volumes were derived to cover larger volumes so PTV has been used as a surrogate for larger tumor volume and its lymphatic spread.

As in the lower and mid rectum, tumors located in the upper part of rectum follow the well-known rule that T – stage is a more important prognostic factor for OS than N – stage. [37] Patients with T3 did better than T4 in terms of OS.

Evaluation of toxicity profile was performed based on CTCAE v4. To estimate type and severity of acute and late toxicity, published materials on approaches to upper rectal cancer patients were used for references [31, 38, 39]. Assessing the results of our study we should note that the treatment was delivered with no significant GU toxicity, although grade 4 toxicity was found in two patients (Table 2). GI grade 1-2 toxicity with high incidence is partly explained by the chemotherapy agent and would not be fully attributed to RT. We made an additional t-test calculation and did not find the correlation between PTV volume and high/low grade toxicity ($p>0.5$) (results not showed). We can note that we used modern treatment technique, and our paramount concern was not to exceed the normal tissue tolerance, especially for small bowel wall [7].

In second group 15 (46.9%) patients and in the first group 12 patients (24%) did not receive adjuvant chemotherapy. In recent publications there is increasing support for a "watch-and-wait" treatment strategy after complete pathologic response [35, 40-43].

We understand that the study has several weak points such as its retrospective nature, it rereflects independent experience of two institutions, and the number of enrolled patients is relatively small.

Nevertheless, our results show that this retrospective study has been performed in two centers with a high volume of patients with rectal cancer and highly skilled radiation oncology, medical oncology and surgical oncology teams. All patients were treated accordingly to up-to-date guidelines and using modern treatment techniques.

The small number of patients is explained by a non-standard situation when most of tumor mass is located at the rectosigmoid junction, laying above and below the anterior peritoneal reflection, which makes assigning a patient to a rectal or sigmoid cancer cohort equivocal. Decision were made on multidicsiplinary tumor borads after achieving a consensus whenever a patient was referred to neoadjuvant chemoradiation.

Due to that the lack of observed differences in terms of OS and local relapse between the study group and control group the benefit of adding neoadjuvant treatment to these patients is questionable. However, in the study group patients had more locally advanced tumors and more nodes affected. As a consequence, the fact that OS is very similar between the two groups it can be speculated that neoadjuvant treatment may be beneficial to these patients in terms of downsizing either for T (54%) or for N (79%) stage.

Table 2: Neoadjuvant chemoradiation toxicity profile, ICO group.

Grade	Signs and Symptoms	Events/%
Grade 1-2	Abdominal pain	3/2.7
	Anal pain	2/1.8
	Anemia	1/0.9
	Anorexia	3/2.7
	Anxiety	1/0.9
	Constipation	2/1.8
	Non-infectious Cystitis	15/13.6
	Dermatitis radiation	14/12.7
	Diarrhea	24/21.8
	Disseminated intravascular coagulation	1/0.9
	Erectile dysfunction	5/4.5
	Fatigue	1/0.9
	Fecal incontinence	6/5.5
	Fever	2/1.8
	Flatulence	2/1.8
	Hematuria	1/0.9
	Lip infection	1/0.9
	Pain in extremity	1/0.9
	Rash maculopapular	1/0.9
	Rectal anastomotic leak	1/0.9
	Rectal hemorrhage	7/6.4
	Rectal mucositis	1/0.9
	Renal and urinary disorders	1/0.9
	Skin hyperpigmentation	1/0.9
	Thromboembolic event	1/0.9
	Urinary incontinence	1/0.9
	Urinary urgency	3/2.7
	Vomiting	1/0.9
	Total Grage 1-2	103/93.6
Grade 3 - 4	Abdominal pain	2/1.8
	Anemia	1/0.9
	Constipation	1/0.9
	Rectal mucositis	1/0.9
	Surgical and medical procedures	1/0.9
	Wound dehiscence	1/0.9
	Total Grade 3-4	7/6.4

7. Conclusion

The results of this analysis demonstrated a high five-year OS, with an excellent toxicity profile, suggesting that the NCRT is safe and efficient for upper rectal cancer patients. However, the delivery of NCRT for unselected patients with upper rectal tumors did not provide an OS advantage in our series.

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