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Preoperative Short-Course Chemoradiotherapy (SC CRT) with Delayed Surgery for Locally Advanced Rectal Cancer: A Single Center experience

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1. Abstract

1.1. Purpose: To evaluate tolerability and efficacy of preoperative SC CRT in patients with locally advanced rectal cancer.

1.2. Materials and Methods: 94 patients with locally advanced rectal cancer were included in the study. The patients were treated with SC CRT: conformal radiotherapy with a total dose of 25 Gy in five fractions and chemotherapy (5-fluorouracil or capecitabine administered on the day of radiotherapy), followed at 11 weeks (average delay time) by surgery and adjuvant chemotherapy (5-fluorouracil or capecitabine). Effects of therapy were followed by 3-year disease-free survival (DFS) and overall survival (OS) rates.

1.3. Results: The 3-year DFS was found to be 78.4% and 3-year OS was 93.4%.Pathologiccomplete response (ypCR) was observed in14% of patients. The size of tumor on completion of SC CRT was found to be a strong prognostic indicator of recurrence (AUC = 0.67; 95% CI 0.54-0.78; p=0.004; Cut off > 4cm).

1.4. Conclusion: This study concludes that SC CRT with delayed surgery has comparable efficacy to LC CRT in the treatment of locally advanced rectal cancer when ypCR, DFS and OS indicators from previously published studies are compared.

2. Introduction

Historically the high recurrence rate of tumors in locally advanced rectal cancer – up to 50% more frequent than the occurrence of distant metastases–has inspired major investigative studies in to the efficacy of postoperative RT and adjuvant fluoropyrimidines chemotherapy [1].As a result of these studies consensus on the use of trimodal treatment (surgery, chemotherapy and radiotherapy) for advanced rectal cancer was reached in 1990 [2]. Trimodal therapy has reduced local recurrence rates to 5-6 % [3], but the rate of metastatic disease has however remained at 25% [4], and is currently the leading cause of death in patients presenting with rectal cancer. Fisher et al, [5]. Performed a study in1988 that showed postoperative radiotherapy is efficient in reducing the recurrence rate [5]. A large German trial on 823 randomized patients with locally advanced rectal cancer concluded that the local recurrence rate was significantly reduced in the preoperative group of patients (6% *vs* 13%; p=0.006), whilst toxicity was lower and the patients receiving neoadjuvant chemotherapy had better quality of life. However, no difference in overall survival rates have been observed [6,7]. The NSABP R-03 study demonstrated the benefits of neoadjuvant chemoradiotherapy, but also showed a trend toward improved OS [7]. Obviously, there are questions related to the differences between SCRT and LCRT in terms of their respective benefits. Bujko et al, [8]. Showed that when comparing local control of disease, overall survival and the sphincter preservation rate, there is no statistically significant difference between SCRT and immediate surgery, and LCRT with 5-fluorouracil (5Fu) and Leucovorin, and delayed surgery. The difference was found in the overall response rate (0.7% in SCRT *vs* 16% in LCRT) [9,10]. The Trans-Tasman

Radiation Oncology Group (TROG) 01.04 trial confirmed the results obtained in an earlier Polish study [8]. All these studies have shown that SCRT has lower overall response rate and lower rate of serious side effects, but there is no significant difference in local control of the disease, DFS and OS [8-10]. The only study showing benefits in terms of OS and PFS for LCRT in combination with chemotherapy *vs* SCRT, was presented by Kairevice et al, [11]. As already mentioned, the generally low pathologic complete response rate (ypCR) is the main drawback of SCRT, which is not entirely surprising when viewed against immediate surgical treatment. Potential benefits of downsizing the tumor are an increase in sphincter preservation rate and improved local control of disease [12-14]. The Stockholm III study investigated the effects of SCRT with immediate surgery and SCRT with delayed surgery [15]. The higher complete response rate was found in the group treated by SCRT and delayed surgery (11.8%) in comparison with SCRT and immediate surgery (1.7%) [16]. The Lithuanian study investigated SCRT *vs* LCRT with the same surgery delay. Preliminary data suggested better response rates in LCRT, but further analysis has not confirmed any statistical significance (P=0.11) [17]. In 2017 the results of the Stockholm III study with 840 patients were published; 385 in three arm randomization (129 SCRT, 128 SCRT and delayed surgery, 128 LCRT) and 455 in two arm randomization (228 SCRT, 227 SCRT and delayed surgery). It shows that delayed surgery after SCRT gives similar oncological results as SCRT and immediate surgery. The LCRT shows results similar to the both SCRT results, but prolongs duration of the therapy [18]. All these studies demonstrate improvement in the control of the local disease, but significant problems still remain in relation to distant metastases [1]. A review of data taken from the National Comprehensive Cancer Network (NCCN) database shows that patients that receive neoadjuvant therapy exhibit significantly lower rates of micro metastatic disease [19]. With this in mind, new studies are directed towards researching systematic therapies in neoadjuvant settings with the aim of reducing the incidence of metastases [1]. In 2017, Chung et al, [20] published a study in which SCRT and LCRT with chemotherapy and delayed surgery, were comparedfor the first time[20]. It concludes that preoperative SC CRT is an efficient and safe treatment modality, with results comparable toLC CRTthat is presently used as the standard treatment.

3. Materials and Methods

The study involved 94 patients diagnosed with rectal cancer. The 3-year disease-free survival (DFS) and overall survival (OS) metrics were followed, and patients were treated from June 2009 through to May 2014. All patients were assessed by colonoscopy, measuring the distance of the tumor from the anocutaneous line (ACL), and by staging the cancer based on abdominal and pelvic CT scans. Clinical and pathological stages were determined according to the American Joint Committee on Cancer Staging, 7th edition. Patients received conformal radiotherapy in the tumor area and lymph drainage area with overall tumor dose of 25 Gy in five fractions together with chemotherapy (5-fluorouracil500mg/m^2, iv bolus, half an hour before RT, or capecitabine 1000mg /m^2 twice a day). Collection of data included data on presence of blood in stool and diarrhea, complete blood counts, tumor markers CEA and Ca 19-9, all of which were collected before the treatment, again 6 weeks after administration of the treatment and after surgical procedure. In order to evaluate tumor response, control colonoscopy was performed 6 weeks after administration of therapy. Surgical procedures were planned to take place 8 weeks after administration of RT. Data on tumor size, lymph node involvement, tumor grading and the presence of lymph or perivascular invasion were collected from histopathological examination. Relevant data on the chemotherapy, time to progression of disease and overall survival of patients were collected from the patients' medical history data at the Department of Oncology at the Clinical Medical Center Osijek (KBC Osijek).

4. Statistical Methods

Categorical data are presented by absolute and relative frequencies. The differences between categorical variables were evaluated by χ^2 test. The differences in the frequency of bowel movements and blood in stool, before and after therapy, were tested by McNemar's test. The normality of numerical variables distribution was evaluated by Shapiro-Wilk's test. Numerical data are described by the median value and interquartile range. The differences in numerical variables between two independent groups were tested by Mann-Whitney U test, and the differences in values obtained before and after therapy by Wilcoxon's test.The Kaplan-Meier survival rate curves were compared between the groups with a log-rank test.Cox's regression analysis was used to predict probability of recurrence, and was expressed as odd's ratio (OR) and the 95% confidence interval (95% CI). The ROC (Receiver Operating Characteristic) analysis was applied for determination of optimal cut-off values, area under the ROC curve (AUC), specificity, tumor size sensitivity after radiotherapy in relation to recurrence. All *p*-values were two-sided. Significance level was set to Alpha = 0.05. Statistical analysis was performed using the MedCalc Statistical Software version 19.0.5 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2019) and SPSS (IBM Corp. released 2013 IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

5. Results

The study involved 94 patients of which 61(65%) were male and 33(35%) female. Average age of patients was 63 years (IQR from 54 to 71 years) ranging from 26 to 83 years. Measuring from the anocutaneous line (ACL), low rectal cancer (up to 5 cm) was identified in 44 patients (47%). Average size of tumor determined by colonoscopy was 5 cm (IQR from 4.6 cm to 8 cm), which was reduced after radiotherapy to 3 cm (IQR from 2 cm to 4.5 cm). In

13 patients (14%) the complete pathologic response was observed. Perineural invasion was observed in 9 patients (10 %) and perivascular invasion in 11 patients (12%). Adjuvant therapy was administered to 69 patients (76%), which most often was 5-fluorouracil, administered to 50 patients (73%). The5-fluorouracil therapy was administered to 6 out of 50 patients (12%) in less than 6 cycles, and capecitabine therapy in less than 8 cycles to 4 out of 19 patients (21%), (Table 1). In 53 patients (80%) blood in stool was noticed prior to the surgery, and after radiotherapy there was a significant reduction to only 5 patients (8%) (McNemar's test, $P < 0.001$). As for the frequency of stools, before therapy 30 patients (65%) had frequent stools, and after therapy the number was significantly reduced to 10 patients (22%), (McNemar's test,$p < 0.001$). Out of 44 patients (48%) with low rectal cancer 16 patients (33%) had *resectio recti anterior*, and of 48 patients (52%) with high rectal cancer 15 patients (35%) had abdominoperineal resection (χ^2 test, $p= 0.003$). The median CEA value before therapy was 8.8 (IQR 3.4 to 23.7) which was significantly reduced to median value 4 (IQR 1.8 from to 16) at follow-up assessment (Wilcox test, $p< 0.001$). In patients without recurrence or without metastases the elapsed time from radiotherapy to surgery is somewhat longer (one week longer), without significant difference compared to patients who experienced recurrence or metastases (Table 2). Regression analysis was used to evaluate the effect of different factors on the probability of recurrence. The model is based on four independent variables (tumor size after RT, time elapsed from diagnosis to RT, time elapsed from RT to surgery, number of positive lymph nodes), with tumor size after SC CRT identified as a significant predictor of recurrence (OR = 2.7, 95% CI 1.1 to 6.4) with $p= 0.03$) (Table 3). The ROCcurve method was chosen as a simple method for evaluation of recurrence indicators between the groups of patients, and is based on specificity and sensitivity. In order to evaluate the validity of a predictor (tumor size after SC CRT), identified by logistic regression as a significant contributor of recurrence, a ROC method with gradual change of values which separate patients with and without recurrence was applied. By changing the cut-off point for a group of patients, and analyzing the respective ROC curve, it is possible to objectively determine the cut-off value that differentiates the groups in anoptimal way. From this data set, tumor size after SC CRT in relation to recurrence, is seen to be a significant diagnostic predictor of recurrence (AUC = 0.67; 95% CI 0.54 to 0.78; sensitivity =54.5; specificity = 70.4; p=0.004; Cut off > 4) (Figure 1). The 2-year DFS of patients with recurrence and/or metastases was 83.2% and the 3-year DFS 78.4% (Figure 2).

The 2-year OS was 96.5%, and the 3-year OS was 93.4% (Figure 3). There is no statistically significant difference in the 3-year survival of patients without adjuvant therapy (95.7%) in comparison with patients with adjuvant therapy whose survival was 92.8% (Log-rank test,$p= 0.72$) (Figure 4).

Table 1: Basic characteristics of patients.

Distance from ACL [cm] [median (25%-75%)]	6 (3.3 – 8.8)
Grouped by distance from ACL[n (%)]	
Low (<5 cm)	44 (47)
High (>5 cm)	48 (51)
Tumor sizebefore RT[cm] [Median (25%-75%)]	5 (4.6 – 8)
Tumor size after RT [cm] [Median (25%-75%)]	3 (2 – 4.5)
Tumor size after OP pT[n (%)]	
T0	13 (14)
T1	1 (1)
T2	41 (44)
T3	36 (38)
T4	3 (3)
N rupture[n (%)]	1 (1)
Perineural invasion [n (%)]	9 (10)
Perivascular invasion [n (%)]	11 (12)
Grade [n (%)]	
I	17 (18)
II	37 (39)
III	2 (2)
Received adjuvant therapy[n (%)]	69 (73)
Type of adjuvant Th[n (%)]	
5FU	50 (73)
Capecitabine	19 (23)
Number of cycles of adjuvant Th [Median (25%-75%)]	
5FU (ranging from 1 to 12)	6 (6 – 6)
capecitabine (ranging from 2 to 8)	8 (7.25 – 8)

Table 2: Values of elapsed time (weeks) from radiotherapy to surgery in relation to recurrence or metastases.

		Median (25%-75%) [weeks] elapsed time from radiotherapy to surgery	P*
Recurrence	No	11 (9 – 13)	0.30
	Yes	10 (8 – 12)	
Metastases	No	11 (9 – 13)	0.58
	Yes	10 (9 – 12)	

*Mann Whitney U test

Table 3: Prediction of the probability of recurrence (Cox's regression).

Predictor	β	Standard error	Wald	*p*	Odds ratio (Exp β)	95% CI for Exp β
Tumor size after RT	0.985	0.44	4.85	**0.03**	2.7	1.1 – 6.4
Time elapsed from diagnosis to RT	0.118	0.08	1.99	0.16	1.1	0.96 – 1.32
Time elapsed from RT to surgery	-0.070	0.12	0.37	0.54	0.93	0.74 – 1.17
Number of positive N	0.055	0.16	0.12	0.73	1.1	0.77 – 1.45

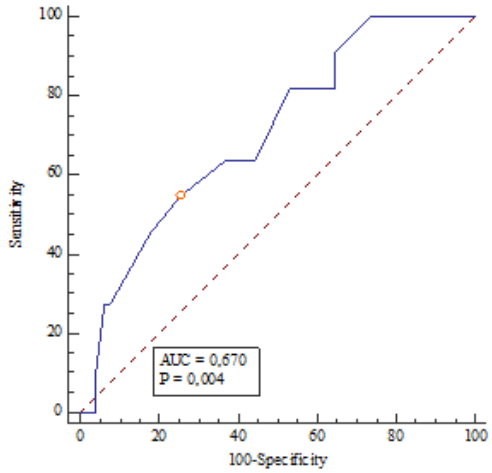

Figure : ROC analysis of sensitivity, specificity and tumor size values after radiotherapy in relation to recurrence (AUC=0.670; *p*= 0.004).

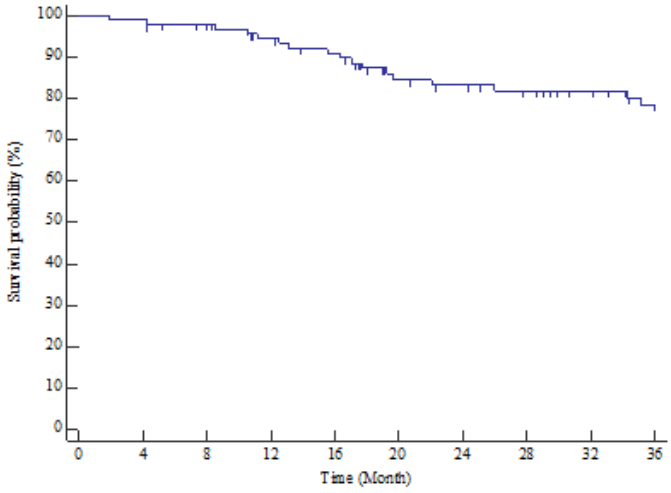

Figure 2: The 3-year DFS of patients with recurrence and/or metastases.

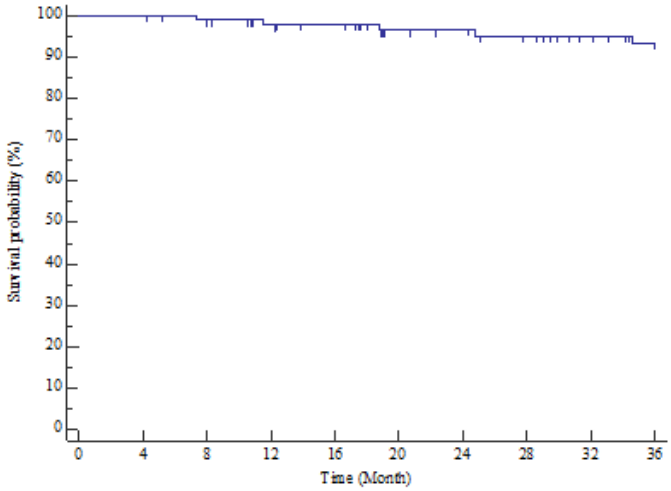

Figure 3: The 3-year overall survival of patients.

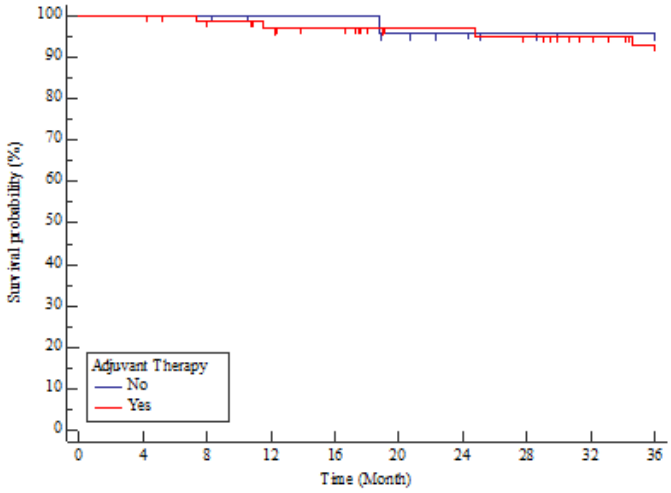

Figure 4: The 3-year survival of patients in relation to adjuvant therapy.

6. Discussion

Since the adoption of neoadjuvant approaches in the treatment of rectal cancer there has long been an interest in tackling the question of which RT treatment is better, LCRT or SCRT. The clinical effect of administering chemotherapy together with LCRT has therefore been investigated in several meta-studies where this method has been compared with SCRT [11-13].Another question that arises is whether the efficacy of SCRT can be improved when combined with chemotherapy, and what level of toxicity can be expected. Thanks to a combination of pressure on staff time and a lack of RT equipment at our center, we had to investigate the use neoadjuvant SCRT. At the same time however, we wanted to improve patients' outcomes and to decrease recurrence rates and the development of metastases. As such, we introduced additional chemotherapy together with radiotherapy, SC CRT, with control of toxicity effects. The first positive results in terms of good tolerability were encouraging and we continued with SC CRT treatments and monitored the effects. Clearly the main limitation of this study is the lack of a control group with either LC CRT or SCRT. This is why we have compared the results obtained under this work with pre-existing published results from similar studies. The pathologic complete response values obtained in the Stockholm III study for patients randomized in the SC RT and delayed surgery arm was 11.8%, in comparison with the 14% we report here for SC CRT and delayed surgery [18]. The Stockholm III study had a period of 5.7 years of follow-up There were significantly lower tumour stages after SC RT with delay, and pathological complete response was associated with superior survival [21]. We followed DFS and OS over 3-years.In the study by Kaireviče et al, [11]. Patients randomized to the SCRT arm achieved an ypCR of 4.4%, and patients randomized to the LC CRT with delayed surgery arm had an ypCR of 11%. In our study, a group of patients treated by SC CRT and delayed surgery obtained a pathologic complete response of 14%. The 3-year OS for LC CRT and SCRT in the Kaireviče study were 85% and 74% respectively compared with 93.4% for SC CRT obtained in our study. The 3-year DFS for LC CRT and SC RT were 73 % and 57 %, respectively, whilst the 3-year DFS reported here for SC CRT is 78.4%.A Korean study [22] from 2013 was unable to demonstrate clinical benefit after treatment with 5Fu for 5 days of RT with delayed surgery, where only one complete response was observed and down stating occurred in 28% of patients. In terms of study design and the number of patients enrolled, our study is most similar to the Korean study published by M. J. Chung *et al*. where ypCR was reported to be 13.2 % for patients in the LC CRT group, and 21.1% in the SC CRT group.[20] The value of 21.1 % for ypCRmay have arisen as a result of the small number of patients (4/19) in the SC CRT group. However, comparing it with our result of 14 % for ypCR (13 of 94 patients), it appears that our study broadly supports their results. It shows that SC CRT is not an inferior treatment option in comparison with LC CRT. In comparing our 2-year OS of 96.5 % for the SC CRT group with the Korean results, where the2-year OS was 90% for the SC CRT group and 91% for the LC CRT group, we may reasonably conclude that these results are similar. The main difference in treatment protocol between the studies is in the chemotherapy administration dynamics: our patients were administered5-fluorouracil or capecitabine (iv bolus) each of five days of RT and received no further chemotherapy prior to surgery. However, patients in the Chung *et al*. study were administered chemotherapy only on the 1st and the 2nd day of RT, as well as a further 3 cycles of chemotherapy before surgery. Our protocol does not involve multiple visits to the hospital after completion of SC CRT, which is both beneficial to patients and at the same time reduces the workload on the hospital day care unit. A further beneficial reduction in workload on medical staff was achieved when capecitabine was approved as a prescription drug. As evident from the follow-up, this protocol is effective and well tolerated by patients. In the group of patients with low rectal cancer, 33% had preserved sphincter function. In the group of patients with high rectal cancer, 35% required rectum amputation. These figures largely arose as a result of differences in the working protocols and surgical approaches taken by the hos-

pitals and clinics from which patients were originally referred to our center for neoadjuvant treatment. It was found in our study that 6-weekspost SC CRT, our patients had normalized stool without blood, and their CEA was statistically significantly reduced. All of which contributes to the improved physiological and physical state of patients prior to surgical treatment. Our initial plan was to perform surgical procedure 8 weeks after administration of radiotherapy. Due to organizational difficulties outside of our control, the average elapsed time from RT to surgical treatment was 11 weeks. However, the 11 week delay from RT to surgical treatment did not adversely affect results when compared against data from previously published studies. The group of patients who had recurrence and/or metastases had on average one week shorter delay period from RT to surgery (10 weeks) in comparison with patients who were recurrence and/or metastases free (11 weeks). This finding is without statistical significance. The size of remaining tumor larger than 4 cm at the time of surgery after completion of neoadjuvant SCCRT, has been found to be a statistically significant risk factor for recurrence. This possibly results from the chemoradioresistency of such tumors, indicating a need for more aggressive neoadjuvant chemotherapy, possibly by addition of oxaliplatin according to FOLFOX or CAPOX protocols. Also, during the course of this study we noticed that additional organizational efforts are needed to reduce elapsed time from diagnosis to start of RT, as well as greater unification across institutions of the surgical protocols implemented in the treatment of rectal cancer.

7. Conclusion

This study demonstrates that SC CRT with delayed surgery is an excellent choice for treating rectal cancer with data compared with published results from other centers. The technique has been found to be as equally effective as LC CRTonypCR, DFS and OS-metrics.SC CRT is well tolerated by patients and was found to relieve symptoms quickly, e.g. bleeding and other problems with stool. The therapy is also shorter and thus better received by patients, and at the same time may contribute to reduced workload on overstretched hospital day care units and the many demands on radiotherapy equipment. Remaining tumor size in excess of 4 cm has been identified as a statistically significant risk factor for recurrence development. This poses the question of whether more aggressive neoadjuvant chemotherapy might benefit this particular patient group. A further prospective study on this subject is needed to give a definite answer to the question. This work was supported by the Josip Juraj Strossmayer University of Osijek – Faculty of Medicine in Osijekunder grant number VIF2018-MEFOS-14 which is gratefully acknowledged.

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