RESEARCH ARTICLE

Appropriate Timing of Surgery after Neoadjuvant Chemo-Radiation Therapy for Locally Advanced Rectal Cancer

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Abstract

Background: Surgery is the corner stone for the management of rectal cancer. The purpose of this study was to demonstrate the optimal time of surgical resection after the completion of neoadjuvant chemo-radiotherapy (CRT) in treatment of locally advanced rectal cancer. Materials and Methods: This study compared 2 groups of patients with locally advanced rectal cancer, treated with neoadjuvant CRT followed by surgical resection either 6-8 weeks or 9-14 weeks after the completion of chemo-radiotherapy. The impact of delaying surgery was tested in comparison to early surgical resection after completion of chemo-radiotherapy. Results: The total significant response rate that could result in functional preservation was estimated to be 3.85% in group I and 15.4% in group II. Some 9.62% of our patients had residual malignant cells at one cm surgical margin. All those patients with positive margins at one cm were in group I (19.23%). There was less operative time in group II, but the difference between both groups was statistically insignificant (P=0.845). The difference between both groups regarding operative blood loss and intra operative blood transfusion was significantly less in group II (P=0.044). There was no statistically significant difference between both groups regarding the intra operative complications (P=0.609). The current study showed significantly less post-operative hospital stay period, and less post-operative wound infection in group II (P=0.012 and 0.017). The current study showed more tumor regression and necrosis in group II with a highly significant main effect of time F=61.7 (P<0.001). Pathological TN stage indicated better pathological tumor response in group II (P=0.04). The current study showed recurrence free survival for all cases at 18 months of 84.2%. In group I, survival rate at the same duration was 73.8%, however none of group II cases had local recurrence (censored) (P=0.031). Disease free survival (DFS) during the same duration (18 months) was 69.4 % for patients in group I and 82.3% for group II (P=0.429). Conclusions: Surgical resection delay up to 9-14 weeks after chemo-radiation was associated with better outcome and better recurrence free survival.

Keywords: Rectal cancer - timing of surgery - neoadjuvnat chemo-radiation therapy

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Introduction

Surgery is the corner stone for the management of rectal cancer, with the majority of patients treated with abdominoperineal resection (APR) for low rectal lesions (4-6 cm from the anal verge) or by low anterior resection (LAR) for higher lesions (Heeney et al., 2012).

In low rectal tumors, surgery alone has 30% overall survival, with a local failure rate of about 55%-65%, and disease free survival (DFS) of 30%-35%, 70% of local and systemic failures occur within the first 2 years after surgery. Total mesorectal excision (TME) in low and mid rectal cancers improved local control (LC) (Giraudo and Morino, 2005).

Superior results of either pre or post-operative radiation and TME compared to surgery alone (TME) have been reported (Volk et al., 2000).

Different trials were performed comparing pre versus post-operative chemo-radiation. In addition to the advantages of tumor down staging, increase tumor resectability with sphincter saving procedures (SSP) and less toxicity in favor of pre-operative treatment, these trials reported improvement of LC (Hess et al., 2004; Martling et al., 2015), DFS and/or overall survival (OS) (Allegra et al., 2009). Both improved survivals and SSP carries a great hope to improve the quality of life especially for young patients with controlled disease.

In low rectal cancer, there is no serous coat acts as a barrier that prevents tumor extension to pelvic tissues. The possibility of the presence of residual microscopic disease after neoadjuvant chemo-radiation especially in advanced tumors should be excluded.

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An unsolved aspect of neoadjuvant chemo-radiation is the appropriate timing of surgery after completion of neoadjuvant chemo-radiation.

The time interval between completion of chemo-radiation and surgical resection is broadly accepted as 4-6 weeks. However, there has been other data as to whether further delaying surgery beyond 6-8 weeks would result in further tumor "down staging" or "downsizing" without oncologic or safety compromise (Hochhaus et al., 2007). Further downsizing was observed in patients in whom surgery was delayed up to 14 weeks, and adopted a delay of 10-14 weeks for patients with bulky tumors (Holt et al., 2006).

To date, there has been little more than anecdotal evidence that patients had more tumor shrinkage when surgery was deferred for a few more weeks, up to 14 weeks after completion of neoadjuvant chemo-radiation.

Aim: This study aimed to compare the response and the outcome of performance of surgical resection 6-8 weeks versus surgical delay up to 9-14 weeks, after completion of neoadjuvant chemo-radiation for patients with locally advanced rectal cancer.

Materials and Methods

This prospective interventional study was carried out from May 2011 to September 2015. 52 patients with locally advanced (T3-4, N-/+ and M0) rectal carcinoma were included and were treated by pre-operative concurrent chemo-radiation followed by surgery.

All patients were subjected to full history and general examination, routine laboratory investigation, CEA and CA19.9 tumour markers detection (base line and follow up), radiological and colonoscopic examinations, and biopsy for histopathological examination of tumour type and grade. Staging was performed according to the 1992 American Joint Committee of Cancer (AJCC).

Methodology:

Radiotherapy was given to all patients through box technique aiming at delivery of 45Gy/25 fractions/5weeks to the true pelvis and 5.4Gy/3fractions as tumor boost. Concomitant xeloda was given at a dose of 825 mg/m^2 twice daily during radiotherapy days.

Evaluation of the response 5-6 weeks after the end of treatment was done through clinical evaluation, MRI pelvis and transrectal ultrasound (TRUS), complete laboratory investigations and tumour markers.

The patients were randomized into two groups according to time of surgery after the end of neoadjuvant chemo-radiotherapy

Group 1 (26 patients); surgery was performed 6-8 weeks after the end of chemo-radiation. Group 2 (26 patients); surgery was performed 9-14 weeks after the end of chemo-radiation. Type of surgery was determined according to post treatment disease status, in the form of APR or LAR with preservation of the anal sphincter.

Comparing between both groups was done as regards; types of performed surgery, types of surgical approaches, operative time, intra-operative, operative and post-operative complications. Pathological examination of the surgical specimens (post chemo-radiation) was done.

Postoperative chemotherapy was given when indicated according to pre-treatment disease stage, in the term of: 5-FU (425 to 450 mg/m^2) and Leucovorin (20 mg/m^2) from day 1 to 5 and to be repeated every 21-28 days for 6 months.

Follow-up:

Clinical examination every 2 months for the first 6 months and then every three months for 18-24 months, CEA and CA19.9 every 3 months, chest x-ray, CT and MRI abdomen and pelvis every three months, and colonoscopic examination if applicable.

Statistical Methods

Data was analysed using SPSS version 20. Numerical data were expressed as mean±standard deviation (SD) or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, comparison between two groups was done using Student t-test.

For tumor size, stage and CEA level, two way analysis of variance for repeated measures was carried out to assess the "group", "time " and group x time effects. The F ratios of the mean squares were calculated with respect to the residual mean of the square, and each ratio was tested against the critical F value (as a function of different degrees of freedom).

Survival analysis was done using Kaplan-Meier method and comparison between two survival curves was done using log-rank test. $P<0.05$ was considered significant.

Results

Patients characteristics

Patients in both groups were comparable as regards age (P=0.905), sex (P=0.618), clinical and histopathological findings. The clinical presenting symptoms among studied patients were illustrated in Figure 1.

A two ways ANOVA was conducted to assess whether there were procedure and CEA difference in the studied groups. Results indicated a significant main effect of time regarding CEA reduction ($P<0.001$), however the results were of no significance regarding procedure between both groups (P=0.771).

Pre-treatment radiological evaluation

The current study reported no statistically significant difference between both groups regarding pre-treatment TRUS, CT and MRI (T and N stage of the patients, P=0.146 and 0.235 respectively).

As regards wall infiltration and organ invasion, no statistical significant difference could be obtained between both groups for TRUS and CT (P=0.984), TRUS and MRI (P=0.906) or CT and MRI (P=0.842). Similar findings observed in determination of perirectal lymph nodes status with P value equals to 0.873, 0.953 and 0.825 for TRUS vs. CT, TRUS vs. MRI and CT vs. MRI, respectively.

Also there was no reported superiority of MRI over CT in determination of pelvic nodes status other than perirectal group (P=0.652).

Endoscopic biopsies showed invasive adenocarcinoma by histopathological examination in all patients.

Treatment results

I-Treatment related toxicity: All patients completed their neoadjuvant CRT with no delay. Treatment related complications occurred in 9/52 patients (17.3%), in the form of; GIT toxicity, skin reaction, hematological toxicity, urinary toxicity, renal toxicity, and hepatic toxicity. The difference in treatment related toxicity in between both groups was not statistically significant (P=0.233) (Table 1).

II-Post chemo-radiation clinical and radiological evaluation: A-Post treatment digital rectal examination (DRE) & examination under anaesthesia (EUA):

At the 5th week after the end of treatment, DRE was performed for all patients. EUA was performed at time of surgery to allow maximum tumor regression and recovery of acute reactions.

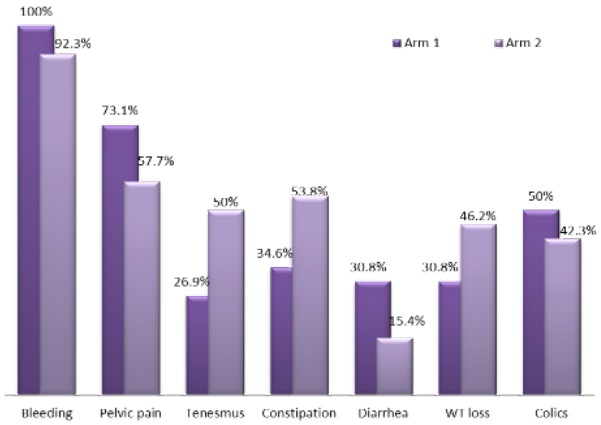

Figure 1. Percentage Distribution of Studied Cases in Both Groups According to the Main Complaint

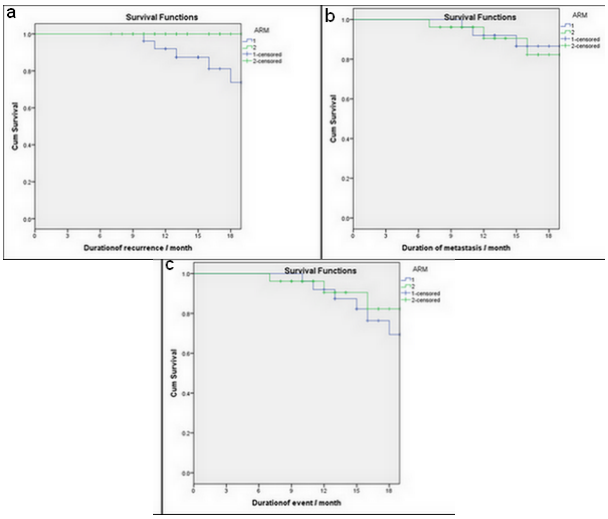

Figure 2. a) Local Control Rate for Each Group of the Current Study, b) Metastases free survival for Each Group of the Current Study, c) Disease Free Survival for Each Group of the Current Study

1-Tumor regression and lumen patency

Twenty five patients (48%) had stationary course as regards tumor size and lumen obstruction. In group I, 21 patients (81%) had stationary course, while 5 patients (19%) had more than 50% reduction of tumor size. No changes in lumen obstruction were observed in this group. In group II, tumor size reduced to half in 22 patients (85%), meanwhile 4 patients had stationary course (15%). Regarding lumen obstruction, 16 patients (62%) had decreased degree of obstruction, while the remaining 10 patients (38%) had no change in lumen patency. The difference between both groups in both tumor regression and changes in lumen obstruction was statistically significant (P<0.001).

2-Degree of mobility

Out of 52 patients 30 showed increased mobility (Table 1). The difference between the 2 arms was statistically significant (P<0.001).

3-Distance from the anal verge and length of the lesion

Twenty eight out of 52 patients (54%), showed increased distance from the anal verge and decreased length of the lesion, while 24/52 patients (46%) had stationary disease. 19 patients (73%) in group I showed no changes in the distance from the anal verge and the length of the lesion, while only 7 patients (27%) showed increase in the distance >5 cm from the anal verge and ≥3 cm decreased length of the lesion, i.e significant gross reduction. In group II, 21/26 patients (81%) showed increase distance from the anal verge to >5cm, with ≥3cm decreased length of the lesion, while 5 patients (19%) had stationary course. The difference between both groups was statistically significant (P<0.001).

B-Post chemo-radiation radiological evaluation:

Radiological tumor down staging: Post treatment MRI was performed at the end of the 5th week for the patients in group I, while in group II; it was performed at the end of 6th-7th week to allow measurement of maximum tumor regression. MRI radiological response was statistically significant better in group II (P=0.048) (Table 1).

III-The interval between the end of neoadjuvant chemo-radiation and surgery: In group I, surgery performed 6-8 weeks (median±SD 7±1.033) after completion of CRT and in group II, surgery performed 9-14 weeks (median±SD 11±2.125) after completion of chemo-radiation.

IV-Surgery: Radical surgery was performed in all patients. 16 patients (30.8%) were candidate for APR, with a distance from the anal verge <5cm, while 36/52 patients (69.2%) were candidate for LAR with sphincter preservation, with tumor distance of 5 cm or more from the anal verge with no significant difference between both groups (Table 1).

In group I, one patient (3.85%) who was candidate for APR became candidate for LAR. This patient showed post chemo-radiation significant gross regression with recession of the distal end of the tumor >5cm from the anal verge and pathological more than 70% necrosis. SSP instead of APR resection was performed. In group II, 4 patients (15.38%) who were candidate for APR became

candidate for LAR. Significant tumor gross regression occurred in these patients post chemo-radiation with delay of surgery to more than 8 weeks, with recession of the distal end of the tumor to >5 cm from the anal verge, and more than 70% pathological tumor necrosis. SSP instead of APR resection was performed. The total significant response rate that could result in functional preservation was estimated to be 1/26 (3.85%) in group I and 4/26 (15.38%) in group II.

In the current study, open surgery was done in 41/52 patients (78.85%), while laparoscopic surgery was done in 11/52 patients (21.15%). In group I, 24/26 patients (92.31%) underwent open surgery, 2 patients of them had failed trial of laparoscopic surgery due to extensive adhesions and fibrosis and turned open, while 2/26 patients (7.69%) underwent successful laparoscopic surgery.

Table 1. Treatment results in both studied groups

	Group I	Group II	P value
Radiotherapy complications			
Present	3 (11.5%)	6 (23.1%)	0.233
Absent	23 (88.5%)	20 (76.9%)	
Mobility changes after chemo-radiation	8/26 (31%)	22/26 (85%)	<0.001*
Restricted to mobile	4	9	
Fixed to mobile	3	13	
Fixed to restricted	1	-	
Post treatment MRI response			
Complete response	0 (0.0%)	4 (15.4%)	
Partial response	24 (92.3%)	22 (84.6%)	0.048
Progressive disease	2 (7.7%)	0 (0.0%)	
Types of surgery			
APR	9 (34.6%)	7 (26.9%)	0.382
LAR	17 (65.4%)	19 (73.1%)	
Operative time length/hours (mean±SD)	4.38±1.29	4.38±1.07	0.845
Post-operative morbidity:			
wound infection	13 (50%)	4 (15.4%)	0.017*
pelvic abscess	8 (30.8%)	2 (7.7%)	0.038*
anastomotic leakage	3 (11.5%)	1 (3.85%)	0.609
anastomotic stenosis	2 (7.7%)	1 (3.85%)	1
stool incontinence	5 (19.2%)	2 (7.7%)	0.419
stoma retraction or necrosis	1 (3.85%)	1 (3.85%)	1
urinary complications	1 (3.85%)	3 (11.5%)	0.609
intestinal obstruction	1 (3.85%)	1 (3.85%)	1
Tumor size before	5.62±2.13	5.73±0.91	0.054
Tumor size after	3.77±1.98	2.36±1.43	
Pathological (T) stage			
T0	1 (3.85%)	7 (26.9%)	
T1	0 (0%)	3 (11.5%)	
T2	13 (50%)	8 (30.8%)	
T3	11 (42.3%)	8 (30.8%)	
T4	1(3.85%)	0 (0%)	
Pathological (N) stage			
N0	12 (46.1%)	17 (65.4%)	
N1	10 (38.5%)	7 (26.9%)	
N2	4 (15.4%)	2 (7.7%)	
N3	0 (0%)	0 (0%)	
Tumor pathological grade			0.07
G0 (complete pathological response)	1 (3.8%)	7 (27%)	
G1	4 (15.4%)	3 (11.5%)	
G2	21 (80.8%)	16 (61.5%)	

In group II, 17/26 patients (65.38%) underwent open surgery, 2 patients of them had failed trial of laparoscopic surgery due to extensive adhesions and fibrosis and turned open, while 9/26 patients (34.62%) underwent successful laparoscopic surgery.

The surgical operative time length ranged from 3-9 hours, with no significant difference between both groups (Table 1).

In the present study, significant operative blood loss during surgery followed by intra-operative blood transfusion occurred in 21/52 patients (40.4%), 14 patients (53.8%) in group I and 7 patients (27%) in group II (P=0.044).

Intra-operative complications, in the form of tumor perforation, injury to pre-sacral venous plexus, urinary bladder injury or injury of hypogastric nerve plexus, occurred in 4/52 patients (7.69%), 3/26 patients (11.54%) in group I and only one patient (3.85%) in group II (P=0.609).

Diverting ileostomy was done temporary in patients with very low anastomosis to protect the anastomosis and to decrease the hazards of anastomotic leakage, if occurred. Reversal of ileostomy and restoration of gut continuity was done 12 weeks after surgery after exclusion of anastomotic stenosis or tumor recurrence with proctoscopy +/- biopsy. Diverting ileostomy was done in 23/52 patients (44.23%), 11/26 patients (42.31%) in group I and 12/26 patients (46.15%) in group II.

Patients in group I had a mean post-operative hospital stay period of 15.12±7.654 days, while in group II patients, the mean hospital stay period was 10.69±3.845 days (P=0.012).

Post operative morbidity:

The most common post-operative acute complication was wound infection and delayed wound healing, occurred in 17/52 patients (32.7%) (Table 1).

V-Histopathological results

1- Tumor regression and tumor necrosis: A mixed ANOVA was conducted to assess whether there were procedure and tumor size difference in the studied groups. Results indicated a significant main effect of time (F=61.7, P<0.001) and a non-significant effect of procedure (F=3.89, P=0.054) (Table 1).

The percentage of necrosis which was defined according to tumor regression grade (TRG) score also was detected in the post-treatment surgical specimens, the difference between both groups was also statistically significant (P=0.014). No malignancy (100% necrosis) was detected in one patient (3.85%) in group I, versus 7 patients (26.92%) in group II. Necrosis < 50% was found in 35% of group I and 13% of group II patients. The degree of necrosis ranged from 0 to 100% with a median of 50% in group I, while group II showed a range from 10% to 100% with a median of 70%.

2- Pathological T stage: Pathological staging of the tumors (pT) showed that most of the cases had T2 and T3 tumors, 40.39% and 36.54% respectively (Table 1). Pathological T stage between both groups indicates better response in group II.

Table 2. Comparison between the pre-treatment T/N and the pathological T/N stage in the studied groups

		Group I				Group II	
Pre treatment T	pT	Patients	Down staging	Pre treatment T	pT	Patients	Down staging
T3	T0	2/26 (8%)	Complete response	T3	T0	6/26 (23%)	Complete response
T3	T1-T2	13/26 (50%)	Partial response	T3	T1-T2	9/26 (35%)	Partial response
T3	T3	8/26 (31%)	Stationary	T3	T3	4/26 (15%)	Stationary
T4	T0	0/26	-----	T4	T0	1/26 (4%)	Complete response
T4	T1-T2	0/26	-----	T4	T1-T2	2/26 (8%)	Partial response
T4	T3	2/26 (8%)	Partial response	T4	T3	4/26 (15%)	Partial response
T4	T4	1/26 (4%)	Stationary	T4	T4	0/26	-----
Pre treatment N	pN	Patients	Down staging	Pre treatment N	pN	Patients	Down staging
Positive	Negative	11/26 (42%)	Complete response	Positive	Negative	17/26 (65%)	Complete response
Positive	Positive	12/26 (46%)	Stationary	Positive	Positive	9/26 (35%)	Stationary
Negative	Negative	1/26 (4%)	Stationary	Negative	Negative	0/26	-----
Negative	Positive	2/26 (8%)	Pre-treament False -ve	Negative	Positive	0/26	----

pT: pathological T, pN: pathological N

3-Pathological N stage: The pathological nodal status was studied (pN) and most of the cases were with nodes negative, 29/52 patients (55.77%) (Table 1). Pathological N stage between both groups indicates better response in group II.

4- Tumor pathological grade: The pathological tumor grade (G) was studied and most of the cases were with G2 tumors, 37/52 patients (71.15%). The difference in tumor pathological grade between both groups indicated better response in group II (P=0.07).

5- Surgical margins: Distal surgical margins: At the surgical margins, study of the lower tumor margin at one and two cm was performed. All patients had negative margin at 2 cm. 5/52 patients (9.62%) had residual malignant cells at one cm surgical margin. All those 5 patients with positive margins at one cm were in group I, 5/26 (19.23%).

Circumferential surgical margins

Positive circumferential margins was reported in 5/52 patients (9.62%), all were in group I, 5/26 patients (19.23%).

VI- Correlations:

A- Tumor down staging: Tumor down staging was assessed in both groups according to the pathological T and N stage compared to the pre chemo-radiation clinical and radiological staging (Table 2).

The first group had 17/26 cases (65%) that showed tumor down staging and 65% of them (n=11/17) who had radiological evidence of positive nodes at presentation, showed pathological negative nodes after surgery. While in group II, 22 patients (85%) showed tumor down staging according to T stage, 77% of them (n=17/22) showed nodal down staging.

B- Assessment of radiological investigations: Correlation between post chemo-radiation radiological T N stage and pathological T N stage was performed in order to assess the accuracy of the radiological investigations used in the current study.

The current study reported no statistically significant difference between the data obtained from post chemo-radiation MRI as regards T N stage in one side and the pathological T N stage in the other side (P=0.936).

VII- Survival data

Local control rate (LCR): The local disease free interval for the whole group ranged from 6-48 months (mean±SD 33.88±2.8). The LCR was 81% at 18 months follow up.

Local failure was detected as 7/52 patients (13.46%). The 7 patients were detected in group I (26.92%), 5 of them developed local recurrence (LR) at the first year, and 2 during the second year.

Four out of seven patients who developed LR (4/26 patients, 15.39%) presented with isolated LR (no distant metastases), while 3/26 patients (11.54%) developed LR and distant metastases. No patients in group II showed LR (Figure 2a). In group I, survival rate at the same duration was 73.8%, however none of group II cases had LR (censored). The difference was of statistical significance (P=0.031).

Prognostic factors affecting LC

a). Correlation between gross tumor size reduction and LC: 85.71% (6/7) of patients showed either disease progression, stationary or mild tumor size reduction. 3/7 (42.56%) showed tumor progression, 1/7 (14.29%) showed stationary tumor size, 2/7 (28.57%) showed mild tumor gross size reduction (≤1 cm), and only one patient (14.29%) showed complete response with tumor disappearance in the surgical specimen.

b). Correlation between the change in T stage and LR: 28.57% (2/7) of patients showed no response to treatment, 4/7 (57.14%) showed partial tumor response (T4 to T3 in 2 patients and T3 to T2 in the other 2 patients), and only 1 patient (14.29%) had complete response.

c). Correlation between the change in N stage and LR: 71.43% (5/7) of patients had pathologically N positive, one of them was false negative N stage by pre-treatment MRI and came as pathological N1. Two patients (28.57%) who developed LR had pathologically negative nodes.

d). Safety margin (SM): Effect of the microscopic residual disease at one cm from the distal margin on local recurrence: 28.57% (2/7) of patients LR had microscopic residual disease, while 5/7 (71.43%) had negative microscopic margins.

e). Effect of circumferential margins status on local recurrence: 71.43% (5/7) had positive circumferential resection margins, and 2/7 (28.57%) had pathological

negative circumferential margins.

Distant metastases

Median (95% CI) duration of metastasis free survival was 42 (16.6-67.4) months. Metastases FSR for all patients was 85% at 18 month.

Distant metastases occurred in 9/52 patients (17.31%). 5/26 (19.23%) in group I, and 4/26 (15.39%) in group II. 3/5 patients (11.54%) who developed distant metastases in group I had associated local recurrence. None of the 4 patients who developed distant metastases in group II had associated local recurrence. Metastases free survival was better in group II, but the difference was statistically insignificant (P=0.916).

Metastases occurred in the first year of follow up in 3/5 (60%) in group I and 2/4 (50%) in group II. 2/5 patients (40%) and 2/4 patients (50%) developed metastases during the second year in group I and II, respectively. As shown in figure 2b, Survival rate for group I was 86.6 month, while it was 82.3 for group II. The difference was proved to be of no statistical significance (P=0.916).

Prognostic factors affecting distant metastases

a). Correlation between gross tumor size reduction and distant metastases: 88.89% (8/9) of patients showed either disease progression or mild tumor size reduction. Only one patient with distant metastases (11.11%) showed complete response with tumor disappearance in the surgical specimen. In group I, 5/26 (19.23%) developed distant metastases, 60% of them (3/5) had tumor size progression, 20% (1/5) showed 1 cm tumor gross size reduction, and 20% (1/5) had pathological complete response (pCR) with tumor disappearance in the surgical specimen. In group II, 4/26 (15.38%) developed distant metastases, all of them had tumor size regression.

b). Correlation between the change in T stage and distant metastases: 77.78% (7/9) of patients showed either no response or partial response regarding tumor T stage. In group I, 1/5 (20%) who developed distant metastases had no response to treatment, 3/5 (60%) had partial tumor response (T3 to T2 in 2 patients and T4 to T3 in 1 patient), and 1/5 (20%) had complete response. In group II, 1/4 (25%) had no response to treatment, 2/4 (50%) had partial tumor response (T3 to T2), and 1/4 (25%) had complete response.

c). Correlation between the change in N stage and distant metastases: Five out of 9 patients (55.56%) who developed distant metastases had pathologically N positive disease. In group I, 40% (2/5) had pathological positive nodes, and 60% (3/5) had pathological negative nodes. In group II, 50% (2/4) had pathological positive nodes.

Disease free survival (DFS)

Median (95% CI) of event free survival (EFS) was 42.0 months (22.4 - 61.6) month. For all patients EFS or DFS was 74.3 after 18 months. DFS was better in group II than group I. Either local recurrence or distant metastases or both occurred in 13/52 patients (25%).

In group I, 9/26 patients (34.62%) had events, 4/26 patients (15.39%) had only local recurrence, 2/26 patients (7.69%) had only distant metastases, and 3/26 patients (11.54%) had both local recurrence and distant metastases. In group II, 4/26 patients (15.39%) had events, all of them had only distant metastases.

As shown in Figure 2c, during the same duration (18 months), EFS for group I was 69.4 %, while it was 82.3% for group II (P=0.429). Median (95% CI) EFS duration for group I was 36.0 (27.61 - 44.4) months, while in group II, Median (95% CI) EFS duration was 37.3 (31.64 - 41) months.

Prognostic factors affecting DFS

a). Correlation between DFS and gross tumor size reduction: 92.31% (12/13) of patients who developed either local recurrence or distant metastases or both, showed either disease progression or mild tumor size reduction.

In group I, events occurred in 9/26 (34.62%), 44.44% of them (4/9) had tumor size progression, 1/9 (11.11%) showed stationary disease, 3/9 (33.33%) had partial tumor size reduction, and 1/9 (11.11%) had pCR. In group II, 4/26 (15.38%) developed distant metastases, all of them had tumor size regression.

b). Correlation between the change in T stage and DFS: 84.62% (11/13) of patients with local recurrence or distant metastases or both showed either no response or partial response regarding tumor T stage. In group I; no response to treatment occurred in 22.22% (2/9), partial tumor response occurred in 66.67% (6/9), (T3 to T2 in 4 patients and T4 to T3 in 2 patients), and 11.11% (1/9) had complete pathological response. In group II; 25% (n=1/4) of patients had no response to treatment, 50% (n=2/4) had partial tumor response (T3 to T2), and 25% (n=1/4) had complete response.

c). Correlation between the change in N stage and distant metastases: 53.85% (7/13) of patients had pathologically N positive disease. In group I, 55.56% (5/9) had pathological positive nodes, and 44.44% (4/9) had pathological negative nodes. In group II, 50% (2/4) had pathological positive nodes.

Discussion

The impact of delaying surgery up to 9-14 weeks after CRT was tested in comparison to surgical resection as early as 6-8 weeks after completion of CRT. The current study showed higher tumor response with more possibility of SSP, more tumor down staging, percentage of tumor gross reduction and tumor necrosis for group II than group I. The total significant response rate that could result in functional preservation was estimated to be 3.85% in group I and 15.38% in group II. This was in favor of delaying surgery aiming at improving tumor response and increasing the possibility of SSP, however this difference in tumor response had no impact on survival, this might be due to the high percentage of patients with T4 (29.9%), N +ve (100%), the relatively short period of follow-up and the small sample size.

The optimal timing between the end of neoadjuvant chemo-radiation and surgical resection for locally advanced rectal cancer has been recommended to be ≥60 days, increasing the radiationsurgery interval was

associated with an increase in the rate of pathologic complete response (pCR) (Crimaldi et al., 2016).

Although there was no significant increase in tumor down staging with delaying surgery beyond 6-8 weeks after chemo-radiation, it was safe to do (Smith et al., 2011). This study supports the observation that maximal tumor response occurs significantly later than 6-8 weeks following treatment with radiotherapy. There was no disease progression noted with the delay of surgical resection up to 14 weeks after the neoadjuvant CRT.

This was in agreement with others (Holt et al., 2006) supported the observation that maximal tumor response occurs significantly later than 6-8 weeks following treatment with radiotherapy. Although a small number of patients did have "upstaging" of their tumors, this was likely due to the inaccuracy of the clinical staging rather than true progression (Holt et al., 2006). Additionally, no patient had progression to metastatic disease.

There was no reported higher morbidity or mortality associated with delaying surgery for >8 weeks after chemo-radiation (Smith et al., 2011).

In the current study, the total significant response rate that could result in functional preservation was not significant in between both groups. This was in favor of delaying surgery aiming at increasing the possibility of SSP.

This agreed with the original Lyon R90-01 trial (Francois et al., 1999), suggested that extending the interval from radiotherapy (RT) to surgery from 6-9 weeks led to a trend of reduced rates of APR in the longer-interval group. Yet in neither this study nor others that investigated sphincter preservation rates by CRT-surgery interval were the findings significant (Buskens et al., 2013; Cooper et al., 2013). Others reported that the preoperative administration of CRT led to a higher rate of sphincter preservation (Hess et al., 2004).

By contrast, a systematic review and meta-analysis of trials comparing preoperative radiation with preoperative chemo-radiation showed that although preoperative CRT significantly increased the rate of pCR, this did not translate into a higher rate of sphincter preservation (Fierens et al., 2009).

The current study reported that patients with residual malignant cells at one cm surgical margin or with positive circumferential were all in group I. This was in favor of delaying surgery to more than 8 weeks and up to 14 weeks after the conclusion of neoadjuvant CRT to achieve negative longitudinal and circumferential margins; this would also decrease the LRR, as the tumor resection margins are the most important prognostic factor that affects LRR (Wibe et al., 2002). Neoadjuvant CRT has been associated with reduced rates of local recurrence and tapering of the recommended margins (Gutman and Wasserberg, 2008). Among the studies that examined the effect of a prolonged CRT-surgery interval on resection margin clearance (Gittleman et al., 2004; Lim et al., 2008), one found microscopically involved margins in 2% of patients who underwent surgery before 44 days from CRT and in 1% of patients who underwent surgery later (Holt et al., 2006).

The current study showed less operations time length in group II, but the difference between the 2 groups was insignificant. This was against others who reported a longer operative time when the CRT to surgery interval was longer, which might reflect increased surgical difficulty (Figer et al., 2008).

There was no significant difference between the studied groups regarding other intra-operative complications. Smith et al., (2011) examined the surgical difficulty and complication rate in patients who underwent TME at 6 or 11 weeks after CRT and reported no significant between-group differences. Post-operative hospital stay period was significantly less in group II.

Many studies showed that delaying surgery did not affect the proportion of patients having an R0 resection or a sphincter-saving procedure. Surgeons reported more pelvic fibrosis in patients operated on 11 weeks compared to 6 weeks after CRT, but these results should be interpreted with caution because the surgeons were not blinded to the timing of surgery. Interestingly, the increase in fibrosis did not translate into a significant increase in technical difficulty of the operation and more importantly, addition of chemotherapy during the longer CRT-to-surgery interval, did not increase the risk of postoperative complications, confirming previous observations (Glynne-Jones et al., 2008).

In the current study, post-operative wound infection and pelvic abscess was significantly less in group II. There was no significant difference between both groups regarding other post-operative morbidity. This agreed with many studies reporting that neoadjuvant radiotherapy for rectal cancer increases postoperative complications, predominantly because of an increased risk of anastomotic leaks and delayed perineal wound healing after APR (Glimelius and Pahlman, 1990; Figueredo et al., 2007). Delaying surgery after CRT will allow more time for resolution of the acute inflammatory response to radiotherapy (Brown et al., 2011).

There were concerns about postoperative complications followed by neoadjuvant chemo-radiation, but reports have shown safety in extending the time interval for surgery (Serrano et al., 2003; Allegra et al., 2009).

The current study showed more tumor regression and necrosis in group II, results indicated a highly significant main effect of time and procedure. Pathological TN stage between the two groups indicated better pathological tumor response in group II. This was in favor of delaying surgery >8 weeks, aiming at increasing the achievement of maximum tumor response and down staging with subsequent improves in LC and DFS.

In many studies, lower pathological nodal stage was associated with improved recurrence and DFS rates, and was considered a consistent and strong predictor of survival rates (Cohen et al., 2005; Feig et al., 2006; Cho et al., 2006).

The difference in tumor pathological grade between both was significant, with better pathological tumor response in group II. This agreed with da Luz Moreira et al., (2011), who showed that a >8-week interval between completion of CRT and surgery was associated with significant improvement in the pCR rate and

decreased the 3-year LRR. Figer et al. (2008) also found that a neoadjuvant CRT-surgery interval >7 weeks was associated with higher rates of pCR, decreased recurrence, and improved DFS.

Some investigators (Allegra et al., 2009; Smith et al., 2011) attempted to show that an interval >10 weeks between completion of CRT and surgery is more effective.

The current study showed recurrence free survival for all cases at 18 months of 84.2%. In group I, survival rate at the same duration was 73.8%, however none of group II cases had local recurrence (censored). This was in favor of delaying surgery more than 8 weeks after chemo-radiation, aiming at improving local control and recurrence free survival.

There was no significant difference regarding metastasis free survival rate or DFS rate during the same duration in between both groups. This might be due to the relatively small number of patients in each group and the relatively short follow up period.

Many studies concluded that, both tumor down staging and pCR were correlated with a better oncological outcome after CRT for rectal cancer (Rödel et al., 2010; da Luz Moreira et al., 2011).

Some reported an improved prognosis after a longer CRT-surgery interval (Stamm et al., 2006; Figer et al., 2008; da Luz Moreira et al., 2011; Kulig et al., 2012; D'Hoore et al., 2012). On analysis of the oncological results of the Lyon R90-01 trial after a median follow-up of 6.3 years, it failed to find any significant between-group differences (Nemoz et al., 1999). These results were supported by a Korean study, in which 397 patients were randomized to undergo surgery 28-41 or 42-59 days after long-course CRT, rates of local and distal recurrence and of overall survival were similar in both groups (Kim et al., 2008).

By contrast, a retrospective multivariate analysis of patients with low rectal cancer demonstrated that delaying surgery beyond 16 weeks had a negative impact on overall and metastasis-free survival. A long interval between RT and surgery (6-8 weeks) was recommended only for patients who may benefit from tumor down staging by sphincter preservation (Buecher et al., 2006).

As a conclusion, surgical resection delay to >8 weeks and up to 14 weeks after the conclusion of neoadjuvant CRT in locally advanced rectal carcinoma is safe, allowing maximum tumor response with less morbidity, better oncological outcomes and better LCR and DFS.

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