

## RESEARCH ARTICLE

# Impact of Time Interval Between Chemoradiation and Surgery on Pathological Complete Response and Survival in Rectal Cancer

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## Abstract

**Background:** Limited data are available regarding the impact of time duration between chemoradiation (CRT) and surgery on pathological complete response (PCR). A PCR translates into better overall and disease free survival. The objective of this study was to determine effect of time duration on outcome after preoperative CRT in rectal cancer. **Materials and Methods:** A retrospective review of patients undergoing operations for rectal adenocarcinoma between January 2005 and December 2010 was performed. Patients were divided in two groups: Group 1 underwent surgery in  $\leq 8$  weeks post neoadjuvant CRT and Group 2 after 8 weeks. Patient characteristics, surgical procedure, histopathological details and number of loco-regional and distant failures were compared. Expected 5 year overall survival and disease free survival was calculated using Kaplan Meier curves and significance was determined using the log rank test. **Results:** There were 66 patients in group 1 and 93 in group 2. No significant difference in PCR was observed between the two. However, estimated 5 year DFS was significantly higher in Group 1 (66.7%) as compared to Group 2 (53.8%) ( $P=0.04$ ). Estimated overall 5 year overall survival was not significantly different at 68.2% versus 54.3% ( $P=0.09$ ). **Conclusions:** Delaying surgery more than 8 weeks after preoperative CRT does not impact for PCR in rectal cancer.

**Keywords:** Rectal cancer - PCR - chemotherapy - radiation - delay in surgery - survival

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## Introduction

Colorectal cancer (CRC) is the fourth most common malignancy in United States and the second most frequent cause of cancer-related death (Jemal et al., 2010). Locally advanced colorectal cancer is a major public health problem (Beart et al., 2007; Bray et al., 2013). Multimodal therapy has become popular and implemented more widely in the last 20 years (Cervantes et al., 2007; Rubbia et al., 2007). Surgery remains the mainstay of treatment but introduction of neoadjuvant chemoradiation (CRT) in locally advanced rectal cancer (LARC) has translated into increased long term survival. LARC accounts for approximately half of all diagnosed rectal cancer cases with lymph node metastasis (Rubbia et al., 2004). The standard approach for locally advanced rectal cancer (T3 and/or node-positive tumors of the mid/low rectum) is pre-operative CRT combined with total mesorectal excision (TME). This results in high rate of local disease control, sphincter-preservation and patient survival (Sauer et al., 2004; Du et al. 2011; Popek et al., 2011; Cellini et al., 2012; NCCN, 2013; Petersen et al., 2013).

Surgery after completion of preoperative CRT is

performed at 6-8 weeks to alleviate CRT related toxicity and to get sufficient time for tumor response. There is an emerging concept that tumor response to CRT is dependent on time period which may extend up to many months (Wang et al., 2005). But extending the interval between CRT and surgery is associated with radiation induced pelvic fibrosis resulting in surgical complications and increased risk of locoregional recurrence.

Since data is limited and results are conflicting, it remains unclear whether less or more than eight weeks is a better choice of time duration before surgical attempt (Stein et al., 2003; Moore et al., 2004; Tran et al., 2006; Supiot et al., 2006; Dolinsky et al., 2007; Kerr et al., 2008; Tulchinsky et al., 2008; Lim et al. 2008; Dhadda et al., 2009; Kalady et al., 2009). The objective of this study was to determine the impact of two different time durations between pre-operative CRT and surgery on outcome in patients with resectable rectal adenocarcinoma.

## Materials and Methods

A retrospective review of patients who underwent surgery for rectal adenocarcinoma between January

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2005 and December 2010 at Shaukat Khanum Memorial Cancer Hospital and Research Centre was performed. A total of 159 patients who underwent surgical resection with curative intent and received preoperative CRT were included. Patients who underwent palliative surgery and patients in whom PCR could not be determined were excluded.

Associated work up and planning has been discussed elsewhere (Akbar et al., 2014). The standard protocol was to administer preoperative CRT in T3/T4 and/or clinically node positive tumors. The standard chemotherapy regimen was to give 4 cycles of Capecitabine and Oxaliplatin 3 weeks apart. Each cycle consisted of Capecitabine 1000mg/m<sup>2</sup> oral twice daily on Day 1 and 14 and Oxaliplatin 130 mg/m<sup>2</sup> intravenous on Day 1. In the concurrent setting, 825 mg/m<sup>2</sup> of Capecitabine was given orally twice daily with radiation. A total of 50.4 Gy of radiation was administered in 28 fractions with 1.8 Gy per fraction. Details of follow up have been reported before (Bhatti et al., 2015)

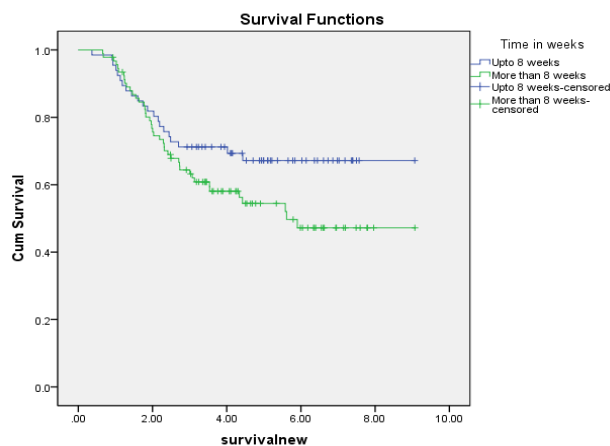
Patient demographics and clinicopathological variables were compared. Patients were divided into two groups. Group 1 underwent surgery up to or less than 8 weeks after CRT and Group 2 later than 8 weeks. The primary outcome of interest was pathological complete response (pCR). Adverse events and 5 year disease free survival (DFS) and overall survival (OS) was also determined. Disease free survival was defined as time between date of surgery and date of relapse. Relapse included local, regional and distant failures. Overall survival was defined

as time between date of surgery and date of death or last follow-up. Overall 5 year survival was calculated using Kaplan Meier survival curves and Log rank test was used to determine significance. A P value <0.05 was considered significant for all calculations.

## Results

### Patient characteristics

A total of 159 patients with rectal cancer underwent surgical resection. Out of these 66(42%) underwent



**Figure 1. Estimated 5 year overall survival between patients with CRT to surgery duration ≤8 weeks or >8 weeks**

**Table 1. Patient characteristics**

		Group 1 Number	Percent Number	Group 2	Percent	Total	P value
Gender	Male	43	65	63	67	106	0.73
	Female	23	35	30	33	53	
Family history	Yes	0	0	7	7.5	7	0.05*
	No	66	100	86	92.5	152	
Age group	Age > 30 years	49	75	76	82	125	0.2
	Age ≤ 30years	17	25	17	18	34	
Distance from anal verge (cm)	0-5	52	78	63	67	115	0.2
	10-Jun	13	20	26	27	39	
	>10	1	2	4	6	5	
Tumor stage	2	3	5	12	12	15	0.19
	3	45	68	60	64	105	
	4	18	27	21	24	39	
Preoperative nodal stage	0	9	13	15	16	24	0.66
	1	15	22	16	17	31	
	2	42	65	62	67	104	
Clinical stage	2	10	15	15	16	25	0.86
	3	56	85	78	84	134	
Radiological T stage	T0	6	9	5	5	11	0.06
	T1	3	4	5	5	8	
	T2	6	9	22	25	28	
	T3	39	60	38	40	77	
	T4	12	18	23	25	35	
Radiological N stage	N0	37	56	51	54	88	0.9
	N1	12	18	18	20	30	
	N2	17	26	24	26	41	
Radiological stage	Early	36	55	53	55	89	0.8
	Late	30	45	40	45	70	

**Table 2. Treatment Given**

		Group 1	Percentage	Group 2	Percentage		
		Number		Number			
Treatment Given	Induction chemo given	39	59	54	59	93	0.89
	IC not given	27	41	39	41	66	
Surgical procedure	APR	37	56	51	54	88	0.67
	Low AR	20	30	32	34	52	
	ULAR	8	12	7	7	15	
	Others	1	2	3	5	4	
Surgical method	Lap	18	27	37	40	55	0.1
	Open	48	73	56	60	104	

**Table 3. Chemoradiation Induced Toxicity**

	Gastrointestinal n=18	Percentage	Neurological n=18	Percentage	Myelosuppression n=2	Percentage	Others n=1	Percent age	Total n=39
Toxicity									
Grade I	1	6	8	44	0	0	0	0	9
Grade II	4	22	10	56	0	0	1	100	15
Grade III	13	72	0	0	2	100	0	0	15

**Table 4. Distribution of histopathological variables between the two groups**

		Group1 Number	Percentage	Group 2 Number	Percentage	Total	P value
TME	Complete	66	100	89	96	155	0.08
	Incomplete	0	0	4	4	4	
PCR	Yes	20	30	21	33	41	0.2
	No	46	70	72	77	118	
Grade	Well	14	21	18	19	32	0.79
	Moderate	40	60	55	59	95	
	Poor	11	16	16	17	27	
	Undifferentiated	1	3	4	5	5	
Mucinous	Yes	26	39	35	28	61	0.22
	No	38	61	58	62	96	
LV invasion	Yes	5	16	11	11	16	0.5
	No	56	84	77	89	133	
Path Nodal	0	37	56	58	63	95	0.72
	1	12	18	14	15	26	
	2	17	26	21	22	38	
	0	20	31	23	24	43	
Pthological T Stage	1	2	3	6	6	8	0.65
	2	8	12	17	18	25	
	3	32	48	41	44	73	
	4	4	6	6	8	10	
	0	20	30	21	24	41	
Pathological Stage	1	5	7	18	19	23	0.16
	2	12	18	19	20	31	
	3	29	45	35	37	64	

surgery within 8 weeks and 93 after 8 weeks of CRT. Median follow up was 3.6 years. No significant difference in demographics, clinical stage and treatments offered was observed between the two groups as shown in Tables 1 and 2. Significant difference was present between the two groups with respect to family history and clinical stage of tumor. As shown in Table 3, gastrointestinal and neurological toxicity was most common and seen in 18(11.3%) patients. Overall 13(38.5%) patients had grade III toxicity.

#### Histopathological variables

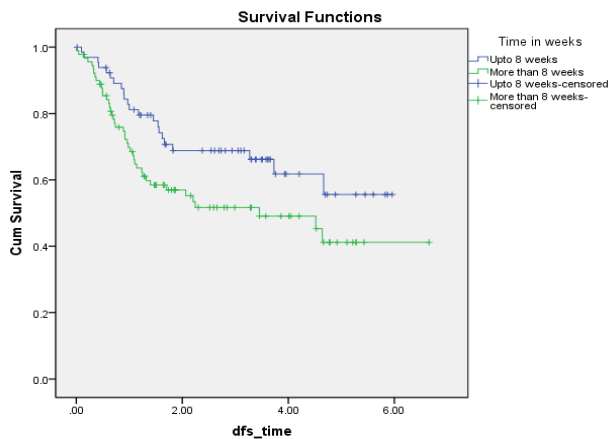
There was no significant difference between grade, presence of mucin, LV invasion, nodal stage, pathological T stage and histopathological stage between the two groups as shown in Table 4. A PCR was observed in 20(12.55%) patient in  $\leq$  8weeks group and 21(13.25%) in more than 8 weeks group with no significance. Only 4(2.5%) patients had incomplete TME all were in more than 8 weeks groups as shown in (Table 4)

#### Outcome

Out of 66 patients, 22(31.8%) experienced a relapse

**Table 5. Pattern of Relapse between The Two Groups**

		Group 1 Number	Percentage	Group 2 Number	Percentage	Total	P value
Overall recurrence	Yes	22	33	43	46	65	0.1
	No	44	67	50	54	94	
Recurrence	None	44	67	50	53	94	0.096
	Locoregional	8	12	24	25	32	
	Distant	14	21	19	22	33	
Status	Alive	45	69	50	53	95	0.06
	Dead	21	31	43	47	64	



**Figure 2. Estimated 5 year disease free survival between patients with CRT to surgery duration  $\leq 8$  weeks or  $>8$  weeks**

in Group1 while 43(46.2%) in Group 2 (Table 5). Median DFS was 1.8 (0.01-6.6) years and 1.2 (0.1-5.6) years for Group I and II respectively. Median overall survival was 3.8 (.37-8.53) years and 2.46 (0.93-9.07) years for Group I and Group II respectively. Estimated overall 5 year survival was 68.2% versus 54.3% in Group1 and 2 respectively and was not significantly different (P=0.09) as shown in Figure 1. Disease free survival was 66.7% versus 53.8% and was significantly different (P=0.04) shown in Figure 2.

**Discussion**

Precise time duration between preoperative CRT and surgery in LARC has been controversial in the past. It was first studied in R90-91 trial (Francois et al., 1999). It was a randomized controlled trial in which 201 patients were randomized to undergo surgery at 2 weeks or 6-8weeks after completion of radiotherapy. The results showed that patients with longer time duration between CRT and surgery had a better tumor response and pathological down staging. This 6-8-week interval has become a routine practice after CRT for rectal cancer. We did not find any significant difference in PCR rates between the two groups. This is consistent with the larger retrospective cohort study on 397 patients with PCR rate of 14 and 15% respectively in the two groups (Lim et al., 2008). Similar results have been demonstrated elsewhere (Moore et al., 2004; Dolinsky et al., 2007; Kerr et al., 2008). Kalady and colleagues, however, demonstrated a significant

difference in PCR rates i.e. 30% versus 16% between patient groups with 8 weeks time duration as the cutoff. (Kalady et al., 2009).

An important modality not discussed in previously published studies is induction chemotherapy before chemoradiotherapy. In the current study induction chemotherapy was routinely employed in locally advanced rectal cancer and increased PCR rate up to 30%.

We observed it better DFS and OS in patients operated within the 8 week cut-off despite a comparable PCR rate. We believe that patients operated after 8 weeks were more likely to have intense fibrosis with loss of surgical planes making it difficult to identify oncological planes clearly. There was a gender predilection for male patients in the current study. Male pelvis is narrower and in the background of intense fibrosis further increases the risk of non-oncological surgery. Probably, these factors translated into reduced local and distant failures with favorable survival outcome in patients operated within 8 weeks. The results of our study are supported by a retrospective multivariate analysis of 102 patients with locally advanced rectal cancer demonstrating a negative impact on DFS and OS with longer CRT-Surgery duration (Supiot et al., 2006).

The impact of CRT-surgery duration on survival has also been a matter of debate. Studies have demonstrated improved prognosis after longer CRT-surgery duration (Campos et al., 2001; Coucke et al., 2004; Tulchinsky et al., 2008; Wolthius et al., 2012).

Limitations of the current study include its retrospective design and relatively small sample size makes it difficult to generalize the results. Finally the results are based on only those patients who underwent surgery. Patients who did not proceed to surgery after CRT because of treatment-related toxicity, an inadequate response or disease progression were not recorded in the study. We are also unable to comment upon post operative complication rates between the two groups of patients and it is likely that they were significantly different. However, surgical morbidity assessment was not objective of this study.

The present study demonstrates no significant difference in PCR rates between patients operated within or after 8 weeks of preoperative chemoradiotherapy. Since PCR is a marker of better prognosis, this should translate into comparable DFS and OS in these two groups of patients. The different outcomes observed in the current study might be representative of other significant factors that ultimately impact outcome and should be considered when deciding upon appropriate time duration between

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