Chemo-Radiation After Upfront Rectal Resections—a Clinical Dilemma

A. Saklani¹ · P. Sugoor¹ · M. Bhandare¹ · S. Jatal¹ · A. Desouza¹ · V. Ostwal¹

Received: 20 December 2017 / Accepted: 17 July 2018 / Published online: 18 August 2018
© Indian Association of Surgical Oncology 2018

Abstract

To compare the impact of adjuvant chemo-radiotherapy (ACRT) versus adjuvant chemotherapy (ACT) alone on recurrence and survival in patients with stage II and III rectal adenocarcinoma undergoing upfront curative resection. Prospective observational review of colorectal database at Tata Memorial Hospital from July 2010 to March 2015 identified 84 patients who underwent upfront curative resection for stage II or III rectal cancer. None of the patient received preoperative chemo-radiation. Of these, adjuvant chemo-radiotherapy was administered to 29 patients (ACRT group) and 55 patients received CAPEOX/FOLFOX-based adjuvant chemotherapy (ACT group) alone. At a median follow-up of 20 months, there were 10 recurrences (3 local recurrence) in the ACRT group and 15 (2 local recurrence) in ACT group. The estimated disease-free survival at 3 years in the ACRT group was 62.7% and in ACT group was 49.7% ($p = 0.417$) with an estimated 3-year overall survival of 74 and 78% in the ACRT and ACT group, respectively ($p = 0.241$). Subgroup analysis was performed after risk stratifying prognostic features (pT4, pN2, poor differentiation, involved resection margin). Our study does not show any benefit of ACRT over ACT on local control, disease-free and overall survival after upfront rectal cancer resection for low-risk stage II–III. In the subgroup analysis, local recurrence did not occur in patients who did not have poor prognostic features irrespective whether they received ACRT or ACT. Adjuvant chemo-radiation can be avoided in low-risk stage II–III rectal cancer after upfront resection.

Keywords Rectal cancer · Adjuvant chemotherapy · Adjuvant chemo-radiotherapy · Postoperative chemo-radiotherapy · Upfront rectal cancer resection

Introduction

The German Rectal Cancer Study Group trial [1] demonstrated improved local control and sphincter preservation rates following neo-adjuvant chemo-radiotherapy (NACTRT), since then

NACTRT has been established as a standard of care for AJCC stage II and III rectal cancer [2–5]. Gastrointestinal Study Group [6], North Central Cancer Treatment Group [7], National Surgical Adjuvant Breast and Bowel Project R01 [8] established the role of adjuvant chemo-radiotherapy for upfront resected stage II, III rectal cancer; however, it was mostly in the pre-total meso-rectal excision (TME) era and with inferior chemotherapy protocols. Although the outcome of rectal cancer treated with surgery and adjuvant chemo-radiotherapy (ACRT) is currently published worldwide, most of the reports are from the western countries, and there are relatively few studies from Asian countries [9–12]. Combined modality therapy in the adjuvant setting is associated with increased morbidity. In recent times, studies have questioned the need for combined therapy in the adjuvant setting especially in low-risk subgroups.

This study aimed to compare the impact of adjuvant chemo-radiotherapy (ACRT) versus adjuvant chemotherapy (ACT) alone on recurrence and survival in patients with stage II and III rectal adenocarcinoma undergoing upfront curative resection.

What does this paper add to the literature?

There is a difference in practice guidelines regarding the type of adjuvant therapy to be instituted whether adjuvant chemo-radiation or adjuvant chemotherapy, following upfront total mesorectal excision (TME) for stage II–III rectal cancer. Our study does not show any benefit of ACRT over ACT alone on local control, disease-free survival and overall survival following up front good quality TME in low-risk stage II–III rectal cancer. We conclude that ACRT can be avoided in low-risk stage II–III rectal cancer after upfront resection.

✉ A. Saklani
asaklani@hotmail.com

¹ Department of Gastrointestinal Surgery and Colorectal Surgical Oncology, Tata Memorial Hospital, Mumbai, Maharashtra 400012, India

Method

Preoperatively, all patients were optimally investigated with routine blood investigations, including blood counts, liver and renal functions, and a colonoscopy to map the location of the disease and to obtain tissue diagnosis. From July 2010 to Dec 2012, contrast-enhanced CT (CECT) scan of abdomen-pelvis and thorax was used to stage the rectal primary, subsequently from Jan 2013 to March 2015 magnetic resonance imaging (MRI) of the pelvis to delineate and local staging, and CECT of the thorax, abdomen and pelvis for distant metastatic evaluation.

Planning of Treatment Modality

All patients with rectal cancer were reviewed at the joint meeting of Multidisciplinary Colorectal Cancer Group (MDCRG), comprising a colorectal surgeon, a radiation oncologist, a gastroenterologist and a radiologist. The upper and lower margins of the tumour from the anal verge was assessed by preoperative digital rectal examination (DRE), CECT, MRI, colonoscopy and/or rigid proctoscopy. Cancer localization was divided into lower third (0–5 cm from the anal verge), middle third (6–10 cm from the anal verge) and the upper third rectal tumours (11–15 cm from the anal verge). Surgery performed was anterior resection (AR) or abdomino-perineal resection (APR) depending on the location of tumour and ability to achieve desired distal resection margin, either laparoscopically or via open approach.

The tumour stage was classified by using the 7th edition of the AJCC staging system. Pathological assessment of the specimen was done as per a standard protocol reporting pT, pN stage, number of nodes harvested, margin status and for presence of lympho-vascular invasion (LVI), peri-neural invasion (PNI). Involved resection margins were defined as tumour cell involvement within 1 mm of the circumferential resection margin or within 1 mm of the distal resection margin.

Histopathology report was reviewed in MDCRG and a decision was taken to plan the adjuvant treatment. The adjuvant modality (ACRT/ACT) was at the discretion of MDCRG. ACRT consisted of capecitabine with 45 Gy EBRT followed by four to six cycles of, Leucovorin, 5-fluorouracil and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (CAPOX)-based chemotherapy or ACT alone (FOLFOX/CAPOX).

Disease-free survival (DFS) was calculated from the time of surgery to the time of clinical evidence of recurrent or metastatic disease. Overall survival (OS) was calculated from the time of surgery to the last follow-up or patient death.

Ethics

Data of this study were collected in the course of common clinical practice and, accordingly, the signed informed consent was obtained from each patient for any surgical and clinical procedure. The study protocol conforms to the ethical guidelines of the ‘World Medical Association Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects’ adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, as revised in Tokyo 2004. No approval of the institutional review committee was needed.

Statistical Analysis

All statistical analyses were carried out with the statistical software package SPSS 20.0 (SPSS Inc., Chicago, Illinois). Survival curves were plotted using the Kaplan–Meier method and were analysed using the log-rank test. A *P* value of less than 0.05 was considered to be statistically significant.

Results

Since its inception, the Multidisciplinary Colorectal Cancer Group at Tata Memorial Hospital, Mumbai, Maharashtra, India, has maintained a database of all patients with rectal cancer who undergo surgery within the department. Medical records of 925 patients who were diagnosed and treated for rectal cancer between 1st July 2010 to March 2015 were evaluated from a prospectively maintained database. Of these 925 patients, 150 cases underwent upfront rectal cancer curative resection in the defined time period. Based on the final histopathology report (those with pT3, pT4 and node positive disease), 84 were considered eligible for adjuvant therapy. Of the 84, 29 received ACRT and the remaining 55 received ACT.

The two groups were similar in terms of age distribution, gender, pT3 stage, N stage, histologic grade, tumour size, preoperative CEA level, presence of lympho-vascular invasion (LVI) and peri-neural invasion (PNI). The characteristics of patients stratified by treatment type are illustrated in Table 1.

Forty-three were upper rectal tumours and 41 were mid-lower rectal tumours. Mid-low rectal cancer was predominant in ACRT group (69 vs. 38.2%). The ACRT group had high rates of poor prognostic features than ACT group, i.e. there were higher proportion of patients with pT4 stage (25 vs. 12%) and involved resection margin (13.8 vs. 3.6%) in the ACRT group than in the ACT group, although not statistically significant.

The median follow-up for survivors was 20 months. There were no statistically significant differences in

Table 1 Characteristics of patients, stratified by treatment type (ACRT vs. ACT)

Variable	ACRT (<i>n</i> = 29)	ACT (<i>n</i> = 55)	<i>P</i> value
Age			0.875
< 50 years	09 (31%)	18 (32.7%)	
> 50 years	20 (69%)	37 (67.3%)	
Gender			0.397
Male	16 (55.2%)	25 (45.5%)	
Female	13 (44.8%)	30 (54.5%)	
Site			0.007
Upper rectum	09 (31%)	34 (61.8%)	
Mid/lower rectum	20 (69%)	21 (38.2%)	
pT stage			0.093
pT1	02 (6.8%)	00 (0%)	
pT2	02 (6.8%)	04 (7.2%)	
pT3	19 (65.5%)	45 (81.8%)	
pT4	06 (20.6%)	06 (10.9%)	
pN stage			0.602
pN0	13 (44.8%)	26 (47.27%)	
pN1	09 (31%)	18 (32.72%)	
pN2	07 (24.2%)	11 (20%)	
Stage			0.057
II	13 (44.8%)	26 (47.2%)	
III	16 (55.2%)	29 (52.8%)	
Preoperative CEA (ng/mL)	4.180 (0.94–1004.8)	4.74 (0.58–688.4)	
Histological grade			0.339
Well differentiated	0 (0%)	03 (5.5%)	
Moderately differentiated	24 (82.8%)	46 (83.6%)	
Poorly differentiated	05 (17.2%)	06 (10.9%)	
Lympho-vascular invasion			0.739
Yes	10 (34.5%)	17 (30.9%)	
No	19 (65.5%)	38 (69.1%)	
Peri-neural invasion			0.991
Yes	09 (31%)	17 (30.9%)	
No	20 (69%)	38 (69.1%)	
Margin positivity			0.086
Yes	04 (13.8%)	02 (3.6%)	
No	25 (86.2%)	53 (96.4%)	
Local recurrence			0.335
Yes	03 (10.3%)	02 (3.6%)	
No	26 (89.7%)	53 (96.4%)	

ACRT adjuvant chemo-radiation, ACT adjuvant chemotherapy, CEA carcinoembryonic antigen

oncological outcomes between the two groups. The estimated 3-year local control rates were 85.3% in the ACRT group and 86.8% in the ACT group ($p = 0.799$, Fig. 1). There were no differences between the ACRT and ACT groups for estimated 3-year DFS (62.7 vs. 49.7%, $p = 0.417$, Fig. 2). The estimated 3-year OS rates were 74 and 78% in the ACRT and ACT groups, respectively ($p = 0.241$, Fig. 3).

Subgroup Analysis

To identify subpopulations of patients that benefit most from receiving ACRT, subgroup analysis was performed by stratifying patients according to these prognostic features (Table 2, 3 and 4). Of the 84 patients, 48 were considered low-risk (no poor prognostic features) and 36 as high-risk (having any of poor prognostic features including pT4,

Fig. 1 Local control rates in ACRT versus ACT group 85.3% vs 86.8% ($p=0.799$)

pN2, poor differentiation, presence of LVI and/or PNI and involved resection margin).

ACRT conferred no benefit in low-risk patients. Local recurrence did not occur in low-risk patients regardless of the receipt of ACRT. For high-risk patients, those who received ACRT had a marginally better estimated 3-year local control rate than those who did not (68.8 versus 61.1% ($p=0.971$, Fig 4). The estimated 3-year OS rates were 75.5 and 75% in the ACRT and ACT groups, respectively ($p=0.333$).

Fig. 2 Disease free survival in ACRT versus ACT group 62.7% vs 49.7% ($p=0.417$)

Fig. 3 Overall survival in ACRT versus ACT group 74% and 78% in the ($p=0.241$)

Discussion

The German rectal cancer study established superiority of pre-operative chemo-radiotherapy over postoperative chemo-radiotherapy in locally advanced rectal tumours (T3–T4, N0) by demonstrating improved local control and reduced treatment toxicity levels without an improved overall survival. While NCCN recommends preoperative chemo-radiotherapy for stage II–III rectal cancers [13], ESMO, however, recommends upfront surgery for upper and middle cT3aN0 tumours with uninvolved mesorectal fascia and absent extramural vascular invasion with postoperative chemoradiotherapy recommended in patients with positive circumferential resection margin, perforation in the tumour area, defects in the mesorectum or in other cases with high risk of local recurrence if preoperative radiotherapy has not been given. Gunderson et al. [14, 15] classified the rectal cancer patients into

Table 2 Subgroup analysis of local recurrence after risk stratification

		ACRT	ACT alone	Total
High-risk group	Local recurrence			
	Yes	03	02	05
	No	12	19	31
Low-risk group	Local recurrence			
	Yes	0	0	0
	No	14	34	48
Total		29	55	84

Table 3 Distribution of recurrence pattern

Recurrence pattern	ACRT	ACT alone	Total
Local recurrence	0	02	02
Distant recurrence	5	13	18
Local + distant recurrence	3	00	03

intermediate (T1-2/N1, T3/N0), moderately high (T1-2/N2, T3/N1, T4/N0) and high risk (T3/N2, T4/N1, T4/N2) groups based on differential relapse and survival rates. Reports indicate that for patients with intermediate risk stage of disease, use of ACRT in all patients may be excessive as it did not improve the clinical outcome in comparison with ACT alone.

Traditionally, postoperative chemo-radiotherapy was recommended for all stage II–III patients based on 1990 national institute of health consensus [16], but the routine use of this has been questioned for all pT3N0 tumours [17, 18] and needs to be revisited.

Postoperative radiotherapy is associated with various complications, characterised by small bowel toxicity, increased risk of faecal incontinence. Of note, some complications have an exceedingly late onset, not occurring until 10 years after therapy [19–21].

As per rectal cancer treatment guidelines, preoperative chemo-radiation was administered to all our patients who were staged locally advanced on MRI or CECT. In our analysis, imaging studies understaged 150 patients (16.21%), with final histology being T3/4 and/or N+. Frasson et al. [22] report similar results of under staging, i.e. 20% of CT2 TUMORS were upstaged T3 on HPR and 22% of cN0 tumours were considered pN+. MRI understages cT2NO tumours by 20–22% leading to upfront curative surgical resections. Local recurrence for such understaged cT3 tumours with surgery alone is 29%, 6.3% with surgery and postoperative radiation and 3.84% with surgery and postoperative chemoradiation [23]. Frasson et al. reported 5-year local recurrence rates of 9.5% in upfront resected stage II–III rectal cancer cases treated with ACRT. Local recurrence was significantly high when

Table 4 Distribution of distant recurrence site

Distant recurrence site	N = 21
Liver	6 (28.5%)
Lung	6 (28.5%)
Liver + lung	4 (19.0%)
Liver + para-aortic	1 (4.7%)
Ascitis	1 (4.7%)
Adnexa	1 (4.7%)
Non regional nodes	1 (4.7%)
Mesentric deposits	1 (4.7%)

Fig. 4 Local control rates with ACRT versus ACT in high risk group 68.8% versus 61.1% ($p=0.971$)

CRM was involved. Kim, M. S. et al. [24] reported 5-year local recurrence rates of 14.3% in T3N0 low rectal cancers after surgery alone and concluded most recurrences were at local site and suggest that it might seem reasonable to consider postoperative RT with a smaller radiation field to the primary tumour site rather than the conventional whole pelvic irradiation. However, whether ACT alone or ACRT needs to be administered in all upfront resected stage II–III tumors is uncertain and the data on it is sparse as not many good quality studies have compared ACT alone versus ACRT in this group of patients. Our study analysed the treatment outcomes in this cohort. This was possible since 2013, as our treatment policy was changed to offer ACRT to upfront operated patients with only involved circumferential margin.

In our study, 5/84 [6%] cases had local recurrence. Local recurrence in ACRT and ACT group was 10 and 3%, respectively. All patients with local recurrence had positive CRM. ACRT conferred no benefit in low-risk patients. Local recurrence did not occur in low-risk patients regardless of the receipt of ACRT. For high-risk patients, those who received ACRT had a marginally better estimated 3-year local control rate than those who did not.

There were several limitations to our study. First, due to the relatively small sample size of patients who received ACRT, the benefit in local control and survival of ACRT in high-risk patients ($n=36$) did not reach statistical significance. Being a retrospective analysis, unknown or unmeasured confounders may have been present, highlighting the need for large-scale prospective randomised trials to confirm the findings.

Conclusion

There seems to be a trans-Atlantic difference in practice guidelines regarding type of adjuvant therapy for upfront resected stage II–III rectal cancer. Our study does not show any benefit of ACRT over ACT alone on local control, disease-free survival and overall survival following upfront good quality TME in low-risk stage II–III rectal cancer. We conclude that ACRT can be avoided in low-risk stage II–III rectal cancer after upfront resection especially in light of more favourable and recently available chemotherapy regimens. However, in population-based studies where TME is not assured, ACRT may still be practised.

Compliance with Ethical Standard

Ethics Data of this study were collected in the course of common clinical practice and, accordingly, the signed informed consent was obtained from each patient for any surgical and clinical procedure. The study protocol conforms to the ethical guidelines of the ‘World Medical Association Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects’ adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, as revised in Tokyo 2004. No approval of the institutional review committee was needed.

References

- Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R et al (2004) Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 351:1731–1740
- Engstrom PF, Arnoletti JP, Benson AB 3rd, Chen YJ, Choti MA, Cooper HS et al (2009) NCCN Clinical Practice Guidelines in Oncology: rectal cancer. *J Natl Compr CancNetw* 7:838–881 PMID:19755047
- Schmiegel W PC, Reinacher-Schick A, Adler G, Arnold D, Fleig W et al (2010) S3 guidelines for colorectal carcinoma: results of an evidence-based consensus conference on February 6/7, 2004 and June 8/9, 2007 (for the topics IV, VI and VII). *Z Gastroenterol* 48: 65–136. <https://doi.org/10.1055/s-0028-1109936>
- Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti a. AJCC cancer staging manual (7th ed) New York: Springer; 2010
- NCCN (2014) Clinical practice guidelines in Oncology, Rectal Cancer, Version 3. Available: http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf
- Gastrointestinal Tumor Study Group (1985) Prolongation of the disease-free interval in surgically treated rectal carcinoma. *N Engl J Med* 312:1465–1472
- Krook JE, Moertel CG, Gunderson LL, Wieand HS, Collins RT, Beart RW et al (1991) Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med* 324:709–715
- Fisher B, Wolmark N, Rockette H, Redmond C, Deutsch M, Wickerham DL et al (1988) Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. *J Natl Cancer Inst* 80:21–29
- Yeh CH, Chen MF, Lai CH et al (2012) Comparison of treatment results between surgery alone, preoperative short-course radiotherapy, or long-course concurrent chemoradiotherapy in locally advanced rectal cancer. *Int J ClinOncol* 17:482–490
- Lee JH, Kim SH, Jang HS et al (2013) Preoperative elevation of carcinoembryonic antigen predicts poor tumor response and frequent distant recurrence for patients with rectal cancer who receive preoperative chemoradiotherapy and total mesorectal excision: a multi-institutional analysis in an Asian population. *Int J Color Dis* 28:511–517
- Akhavan A, Binesh F, Soltani A (2014) Survival of rectal cancer in Yazd, Iran. *Asian Pac J Cancer Prev* 15:4857–4860
- Park P (2014) Comparative survival effectiveness between pre-operative and postoperative chemoradiotherapy for locally advanced rectal cancer: a retrospective study in Phramongkutklao hospital. *J Med Assoc Thai* 97:1–8
- Benson AB 3rd, Bekaii-Saab T, Chan E et al (2012) Rectal cancer. *J Natl Compr Canc Netw* 10(12):1528–1564
- Leonard L (2008) Gunderson, Matthew Callister, Robert Marschke at al, stratification of rectal Cancer stage for selection of postoperative Chemoradiotherapy: current status. *Gastrointest Cancer Res* 2(1):25–33
- Leonard LG, DJ Sargent, Joel E et al (2004) Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer A pooled analysis. *J Clin Oncol* 22(10):1785–1796
- Steele GD, Augenlicht LH, Begg CB et al (1990) Adjuvant therapy for patients with colon and rectal cancer. *JAMA* 264(11):1444–1450. <https://doi.org/10.1001/jama.1990.03450110090034>
- Valentini V, Aristei C, Glimelius B et al (2009) Multidisciplinary rectal cancer management: 2nd European rectal Cancer consensus conference (EURECACC2). *RadiotherOncol* 92:148–163
- Glimelius B, Tiret E, Cervantes A, Arnold D, on behalf of the ESMO Guidelines Working Group (2013) Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 24(suppl_6):vi81–vi88. <https://doi.org/10.1093/annonc/mdt240>
- Henson CC, Andreyev HJ, Symonds RP, Peel D, Swindell R, Davidson SE (2011) Late-onset bowel dysfunction after pelvic radiotherapy: a national survey of current practice and opinions of clinical oncologists. *ClinOncol (R CollRadiol)* 23(8):552–557
- Zucali R, Gardani G, Volterrani F (1980) Adjuvant postoperative radiotherapy in locally advanced rectal and rectosigmoidal cancer. *Tumori* 66(5):595–600
- Komori K, Kimura K, Kinoshita T et al (2014) Complications associated with postoperative adjuvant radiation therapy for advanced rectal Cancer. *Int Surg* 99:100–105
- Frasson M, Garcia-Granero E, Roda D et al (2011) Preoperative chemoradiation may not always be needed for patients with T3 and T2N+ rectal cancer. *Cancer* 117(14):3118–3125
- Kennecke H, Lim H, Woods R et al (2012) Outcomes of unselected patients with pathological T3N0 rectal cancer. *RadiotherOncol* 105(2):214–219
- Kim MS, Keum KC, Rhee WJ et al (2013) The location of locoregional recurrence in pathologic T3N0, non-irradiated lower rectal cancer. *Radiation Oncology J* 31(2):97–103