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Surgical Outcomes in Carcinoma Rectum After Radical Radiation

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Abstract
There is a geographical variation in the incidence rates with more than half of the cases of CRC occurring in developed countries. However, mortality is higher in the less developed countries who have limited resources and inadequate health infrastructure. Mortality rates have been decreasing in many Western countries due to a combination of various factors like early detection due to screening and improved treatment of CRC. Rectal cancer patients who receive dose escalation in addition to standard neo-adjuvant chemoradaiation (prescribed whole pelvis radiotherapy dose of 50.4Gy with additional 9 Gy BOOST to GTV Primary with margin under standard fraction as 1.8Gy per fraction for 5 days a week for 7-8 weeks with concurrent capecitabine during the days of radiation) will be included in the study. In our study, perineal wound complications occurred in 4 cases out of 8 patients of APR which was managed conservatively but resulted in prolonged hospital stay and delay in adjuvant chemotherapy. In our study, out of 15 patients, 1 patient developed vesicocuteneous fistula which managed by prolonged foley's catheterisation. 1 patient developed urinary retention after removal of foleys on pod5 which was managed by reinsertion of foley's for 2 weeks.

INTRODUCTION

Colorectal cancer (CRC) is a common cancer worldwide. It is the third most commonly diagnosed cancer in males and the second in females, with more than 1.4 million new cancer cases every year[1]. There is a geographical variation in the incidence rates with more than half of the cases of CRC occurring in developed countries. However, mortality is higher in the less developed countries who have limited resources and inadequate health infrastructure. Mortality rates have been decreasing in many Western countries due to a combination of various factors like early detection due to screening and improved treatment of CRC[2].

The age standardized rate (ASR) for CRC in India is low at 7.2 per 100,000 population in males and 5.1 per 100,000 population in women[3]. Five-year survival of CRC in India is one of the lowest in the world at less than 40%.

Locally advanced carcinoma rectum patients are treated by radical radiation (neoadjuvant chemoradiation including dose escalation) and undergo surgery (TME excision)[4].

Thus by escalating preoperative radiation dose, the amount of patients with good clinical or radiological response might be eligible for organ-preserving approaches.

MATERIALS AND METHODS

Study Design: This was a cross-sectional observation study.

Source of Data: Rectal cancer patients who are treated at INSTITUTE OF ONCOLOGY AND REGIONAL CANCER CENTRE.

Inclusion Criteria:

- Histopathology proven adenocarcinoma rectum within 12cm from the anal verge
- Locally advanced rectal cancer patients who receive dose escalation in addition to standard neoadjuvant chemoradiation
- MRI staged tumor T3 orT4 and any lymph node positive disease

Exclusion Criteria:

- Patients not fit for anesthesia for surgery
- Metastatic disease
- Recurrent rectal cancer

Sample Size: Fifteen rectal cancer patients who receive radical radiation (dose escalation in addition to standard neoadjuvant chemoradaiation and undergo surgery).

Rectal cancer patients who receive dose escalation in addition to standard neoadjuvant chemoradaiation (prescribed whole pelvis radiotherapy dose of 50.4Gy with additional 9 Gy BOOST to GTV Primary with margin under standard fraction as 1.8Gy per fraction for 5 days a week for 7-8 weeks with concurrent capecitabine during the days of radiation) will be included in the study.

After receiving preop treatment, clinical and radiological response shall be assessed and planned for surgery as indicated. Patients were assessed five weeks after surgery regarding the response to treatment either regression or progression of the disease by clinical as well as by radiological methods.

Decision for abdominoperineal excision of rectum or low anterior resection was made preoperatively and modified according to the per operative findings. According to the standardized technique Total mesorectal excision was done. All patients who underwent low anterior resection had a protective ileostomy.

Postoperative Management: The patient leave the operating room with a nasogastric tube and can have liquids on postoperative day (POD) one. Isotonic intravenous fluids are run at a maintenance rate on POD #0 then decreased to three-quarters maintenance and changed to a dextrose-containing formula on POD #1. The foley catheter is removed on POD #5 to allow for any sympathetic and parasympathetic neuropraxia to resolve. An epidermal is used for pain control with the addition of parenteral narcotics when needed. The epidermal is typically left in place for 3 days as long as it is functional. Subcutaneous heparin venothrombotic prophylaxis is continued postoperatively. The diet is advanced on POD #3 unless the patient is distended or nauseated.

Histopathology was reviewed and pathological complete response of tumour, organ preservation and complications of surgery shall be evaluated. Data was collected and analyzed by ExelStat using appropriate statistical tests.

RESULTS AND DISCUSSIONS

In our study, Patient's age ranged from 25-70 years, mean age being 49.4 years. The most common location of tumor in our study is mid and lower rectum. Out of fifteen patients, seven patients had tumor involving mid and lower rectum, three patients had involvement of upper and mid rectum, two patients had involvement of upper, mid and lower rectum. Only one patient had tumor involving the lower rectum alone. In our study, out of 15 patients, Six patients (40%) had well differentiated tumor, seven (47%) had moderately differentiated tumor and in only two (13%) of them the tumor was poorly differentiated. In majority of them (12 patients) in our study, the clinical stage of tumor at the time of presentation to our hospital was Stage 3B followed by Stage 2A (3 patients).

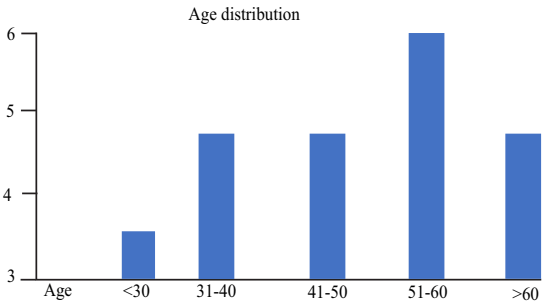

Fig. 1: Age distribution

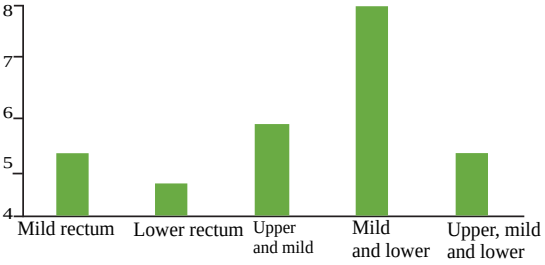

Fig. 2: Location of tumour

Table 1: Histology

Histology type	No (%)
Well differentiated	6 (40)
Moderately differentiated	7 (47)
Poorly differentiated	2 (13)

Table 2: Pre treatment clinical stage

Clinical stage of tumour	No (%)
Stage 1 (T1, T2, N0, M0)	0
Stage 2A (T3, N0, M0)	3 (20)
Stage 2B (T4a, N0, M0)	0
Stage 2C (T4b, N0, M0)	0
Stage 3A (T1, T2, N1, M0)	0
Stage 3B (T3, T4, N1, M0)	12 (80)
Stage 3C (Any T, N2, M0)	0
Stage 4 (Any T, Any N, M1)	0

Table 3: Time interval between CRT and surgery

Interval to CRT and surgery	No of cases
6 weeks	6
7 weeks	7
8 weeks	2

Table 4: Post-operative pathological staging

Pathological response	Number
Complete	6 (40%)
Incomplete	9(60%)

Table 5: Surgery

Surgery performed	Number
LAR	7 (47%)
APR	8 (53%)

Table 6: Complications

Intra operative complications	
Bleeding	1
Post-operative complications	1
Anastomosis leakage	
Anastomosis stenosis	1
Stoma complications	1
Pelvic abscess	2
Perineal wound complication	4
Urological complications	2
Sexual dysfunction	10

Table 7: Age comparison

Study	Mean age (yrs)
Couwenberg *et al*.[5]	64
Jing Zhao *et al*.[6]	59
Gunther *et al*.[7]	56
Present study	49.4

Table 8: Sex comparison

Study	Male %	Female %
Couwenberg *et al*.[5]	75	25
Jing Zhao *et al*.[6]	70	30
Gunther *et al*.[7]	66	34
Present study	73	27

Table 9: Comparison of histopathology

Study	Well differentiated (%)	Poorly differentiated (%)	Moderately differentiated (%)
Jing Zhao *et al*.[6]	22	60	18
Present study	40	47	13

Table 10: Comparison of location of tumour

Study	Lower rectum (%)	Rest of the rectum (%)
Jing Zhao *et al*.[6]	63	37
Present study	67	33

Table 11: Comparison of Pre NACTRT MRI Staging

Study	IIA (%)	IIIB (%)
Gunther *et al*.[7]	50	44
Present study	20	80

Table 12: Comparison of pathological complete response

Study	PCR(%)
Couwenberg *et al*.[5]	35.9
Alongi *et al*.[8]	17.5
Gunther *et al*.[7]	17.1
Jing Zhao *et al*.[6]	22
Vester mark *et al*.[9]	34
Jeremy Tey *et al*.[10]	35
Vinzeno picardi *et al*.[11]	27.7
Present study	40

Table 13: Comparison of organ preserving surgeries

Study	Sphincter saving procedure %
Couwenberg *et al*.[5]	56
Jeremy Tey *et al*.[10]	85
Gunther *et al*.[7]	72
Jing Zhao *et al*.[6]	80
Vinzeno picardi *et al*.[11]	43
Present study	47

Six patients underwent surgery at 6 weeks after chemoradiotherapy., seven patients after 7 weeks and two patients after 8 weeks of chemoradiotherapy.

Clinical (Postnactrt MRI) Down Staging of Tumour:

Stage 2A-3 PTS-all downgraded to stage 1 after NACTRT.

Stage 3B-12 PTS-11 patients downgraded to lower stage after NACTRT.

In our study, out of 15 patients, 5 patients (33%) had complete pathological response. Rest 10 patients (67%) had incomplete pathological response.

Of the fifteen patients, 10 patients were tentatively planned for APR before NACTRT with dose escalation. A sphincter conservation surgery was possible in two of them after neoadjuvant chemoradiotherapy and those patients underwent low anterior resection. Before neoadjuvant chemoradiotherapy only five low anterior resections

were planned. After it, seven anterior resections were done with covering ileostomy done to protect the anastomosis as well as to reduce leak related complications.

Finally APR was performed in 8 (53%) patients and LAR in 7 (47%) patients after Radical RT.

In our study, there was intra operative bleeding in 1 case due to difficulty in posterior plane which was controlled by packing.

Anastomosis leakage occurred in 1 of cases of LAR, in which patient developed fever and elevated WBC counts postoperatively. As patient already had diversion ileostomy and was managed conservatively.

Anastomosis stenosis occurred in 1case of LAR, because of which ileostomy couldn't be reversed early and patient was considered for dilatations.

Stoma retraction occurred in 1 of the cases of APR which was refashioned and sutured.

In our study, 2 cases developed pelvic abscess postoperatively and were managed by guided aspiration of abscess and IV antibiotics.

In our study, perineal wound complications occurred in 4 cases out of 8 patients of APR which was managed conservatively but resulted in prolonged hospital stay and delay in adjuvant chemotherapy.

In our study, out of 15 patients, 1 patient developed vesicocuteneous fistula which managed by prolonged foley's catheterisation.

1 patient developed urinary retention after removal of foleys on pod5 which was managed by reinsertion of foley's for 2 weeks.

In our study, out of 15 patients, 10 patients developed sexual dysfunction.

The role of radiation therapy in the treatment of rectal cancer has evolved over the past several decades. The efficacy and safety of neoadjuvant chemoradiotherapy (NACRT) have been demonstrated by a number of studies, most of which utilize low doses of radiation from 45-50.4 Gy. Of interest, the impact of radiation dose escalation beyond 50.4 Gy on pCR rates has been examined with a recent meta- analysis of patients treated with doses over 60 Gy which showed increased pCR rates (20%) and acceptable short-term toxicity. Surgical outcomes has been assessed in cases of radiation dose escalation. While the effect of a boost beyond historic doses of 45-50.4 Gy is under current investigation, there remains a gap in the literature delineating effective methods of planning and applying a radiotherapy boost.

The results of our study were analyzed and compared with other similar studies.

In our study, mean age is comparable to other similar studies.

In our study male female ratio is comparable to other studies.

Our study is comparable to Jing Zhao *et al.* in location of tumour site.

As the most studies conducted dose escalation on locally advanced rectal cancer, stages include were II and III in the studies.

Different studies have shown in variation in pathological complete response because these studies analysis have several limitations. First, most included data are from retrospective or small single-arm trials. Variation in his to pathological response assessment and PCR definition may have affected the overall pooled estimate. Although the reporting quality of treatment details and near-term outcomes within these trials was generally adequate, the short follow-up and significant heterogeneity between cohorts limit the conclusions that can be drawn.

But most studies have shown that increase in PCR due to dose escalation. PCR rates are also increased in some studies by prolonging the gap between the CTRT and surgery.

When compared to other studies we have lower rate of organ preserving surgeries because we performed only low anterior resection in our study, where as other studies performed ultra-low anterior resection by doing coloanal anastomosis. Thus sphincter saving surgeries are higher in number in other studies.

Surgical Complications: In study by Gunther *et al*. there was no increase in wound complications, urinary symptoms and sexual dysfunction on dose escalation in carcinoma rectum.

In study by Durim delishaj *et al*.[12], dose escalation >59 gy is associated with increase in surgical complications.

In study by Jermey Tey *et al.*[10], the surgical complications were about 5 % in the dose escalated sample studied.

In study by N. Hearn *et al.*[13], wound complication rates were 7% and overall surgical morbidity was 15%.The rate of anastomotic leak also did not seem to be increased with radiotherapy boost.

Engineer *et al.*[14], (n = 44 boosted patients) reported 100% incidence of postoperative wound complications with endorectal boost to 65 Gy., but this may be confounded due to high proportions of clinically fixed tumour and abdominoperineal resection procedures (73%) and dehiscence requiring restoring only occurred in three patients.

Wang *et al.*[15], (n = 60 boosted patients) described a higher incidence of wound complications with IMRT boost to 55 Gy and intensified XELOX treatment versus standard treatment to 50 Gy (23% versus 6%, p = 0.011).

Although preliminary results of the ongoing RECTAL BOOST trial have not shown increased surgical complications with boost to 65 Gy total (wound complication rate 46% in boost arm, 62% in control arm) 5 further data are needed.

In our study, 2 patients developed anastomosis related complications like leakage and stenosis respectively. 4

out of 15 patients developed wound related complications which resulted in prolonged hospital stay and delay in adjuvant chemotherapy.
Sexual dysfunction in 10 patients out of 15, of which 2 recovered within 3 months of follow up.
Limitations of our Study are findings could not be generalized as it is single institution study with small sample size and patients have to be evaluated for long term sequale.

CONCLUSION

In our study, the summary of neoadjuvant CTRT with dose escalation (Radical RT) in carcinoma rectum patients is

- Pathological complete response is increased.
- Downsizing and Down staging of tumour clinically (POST NACTRT MRI)
- Increased sphincter saving surgeries
- Toxicity of radiation dose escalation is acceptable and tolerable

As the latest literature is favouring towards wait and watch and organ preserving approach after complete clinical response. If the proportion of good responders can be increased by dose escalation, this strategy could provide an option to increase the number of patients that may benefit from organ preserving strategies in future.

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