



NEOADJUVANT CHEMORADIOTHERAPY FOR LOCALLY ADVANCED OPERABLE RECTAL CANCER - IS THERE A ROLE? STUDY FROM A TERTIARY CARE CENTRE

Dr. Manjunath .K. V	Assistant Surgeon, Dept Of Surgical Oncology, Kidwai Memorial Institute Of Oncology, Bangalore
Dr. Veerendra Kumar. K. V	Professor, Dept Of Surgical Oncology, Kidwai Memorial Institute Of Oncology.
Dr . Durgesh	Senior Resident, Dept Of Surgical Oncology, Kidwai Memorial Institute Of Oncology.
Dr. Ravi Arjunan*	Professor & Head Of The Department, Dept Of Surgical Oncology, Kidwai Memorial Institute Of Oncology. *Corresponding Author
Dr. Syed Althaf	Professor, Dept Of Surgical Oncology, Kidwai Memorial Institute Of Oncology.

ABSTRACT

AIM: This study evaluates the potential benefits and outcome following neoadjuvant chemoradiotherapy for locally advanced operable rectal cancer. Primary end points analyzed are the downsizing of tumor, downstaging of the tumor, sphincter saving rates, toxicity of chemoradiotherapy, patient compliance for the regimen. Secondary end points analyzed are the incidence of local recurrence, distant metastasis. The incidence of perioperative complications and postoperative complications are also analyzed

MATERIAL AND METHODS: Retrospective study was conducted in the Department of Surgical oncology, Kidwai memorial institute of oncology from March 2010 to November 2014

RESULTS: Patients age ranged from 22-51 yrs, mean age being 43.6 years. Thirty-one males and thirty were females in our study. Most of the tumours extended into anal canal (63 %). Thirty-nine patients had stage 3 B disease and nine had stage 3 a disease. Fifty one percent of patients had moderately differentiated carcinoma and thirty eight percent had well differentiated tumors. The interval from chemo radiotherapy to surgery ranged from six to nine weeks. The surgeries performed ranged from anterior resection, with concomitant hysterectomy in females to abdominoperineal excision of rectum. APR intended Sphincter saving planned for 54 patients but was only in 13/54 (24 %) Before neoadjuvant chemoradiotherapy only six anterior resections were planned. After it, fifteen anterior resections were done. Anterior resections intended Anterior resections done 6(12.5 %) but 15 (31.5 %) had anterior resection (P = 0.001). Neoadjuvant chemoradiotherapy increased sphincter conservation from 12.5% to 31.5%.

CONCLUSION: Neoadjuvant chemoradiotherapy given in operable locally advanced mid and low rectal cancers causes significant downsizing, downstaging of the tumour, increases the rate of sphincter conservation surgeries. The toxicity of chemoradiotherapy is minimal, patient compliance is good. The postoperative complications are not increased, and it helps decrease the incidence of local recurrence. The effect on survival has to be determined on long term follow up only. Hence it is beneficial to administer it to patients with locally advanced operable mid and low rectal cancers.

KEYWORDS : Chemoradiotherapy, Rectal Cancer, Abdomino Perineal Resection, Low Anterior Resection,

INTRODUCTION

The potential for curative resection is the most important component of the multimodality management of rectal cancer. In locally advanced rectal cancer lymph node involvement and positive resection margins are common, leading to local recurrence and metastatic disease. Postoperative chemoradiotherapy significantly improves both local control and overall survival. Several studies have shown that preoperative chemoradiotherapy has increased local control rates, sphincter saving procedures and resectability. This study evaluates the potential benefits and outcome following neoadjuvant chemoradiotherapy for locally advanced operable rectal cancer.

Primary end points analyzed are the downsizing of tumor, downstaging of the tumor, sphincter saving rates, toxicity of chemoradiotherapy, patient compliance for the regimen.

Secondary end points analyzed are the incidence of local recurrence, distant metastasis. The incidence of perioperative complications and postoperative complications are also analyzed.

MATERIAL AND METHOD

PATIENTS

Retrospective study was conducted in the Department of Surgical oncology, Kidwai memorial institute of oncology from March 2010 to November 2014. Patients with histologically confirmed

adenocarcinoma within 12 cm from anal verge with locally advanced operable rectal cancer (T 3, T 4, lymph node positive tumors) without distant metastasis. Patients were excluded who previously had histology, who had received chemotherapy or radiotherapy or contraindications to chemoradiotherapy or tumors involving pelvic side walls, upper sacral vertebra, involving upper rectum

PREOPERATIVE EVALUATION

After obtaining informed written consent, patients were enrolled into the study. A basic work up including complete hemogram, renal function tests, liver function tests, and cardiac tests like ECG was done to rule out any major illness and to confirm the patient's fitness for surgery.

Locoregional staging was done with contrast enhanced CT of abdomen and pelvis, and cystoscopy in cases suspected of bladder invasion. A lymph node metastasis of four or greater than four as detected by imaging was staged as N 2 disease. Distant metastasis was excluded by contrast enhanced CT of abdomen and pelvis, chest X-ray and if necessary, a CT chest. Colonoscopy was done to rule out synchronous lesions.

Preoperative external beam radiotherapy was given for a total dose of 45 Gy in 25 fractions of 180 cGy each, five times per week for total duration of five weeks. The radiotherapy was given to include the

tumor area and its drainage lymph nodes (pelvic-internal, external iliac, obturator). The upper margin of radiotherapy field was L 5-S 1. The lower margin was obturator foramen, 1.5 cm below lower border of pubic symphysis. The lateral margin was 1 cm lateral to true pelvis at level of mid inguinal point. If the tumor extended to anal canal, inguinal nodes were included in the field, laterally the radiotherapy field was extended to anterior superior iliac spine.

The chemotherapeutic agent used was 5 Flurouracil, used as a bolus of 350 mg/m² /d for 5 days, during the first and fifth weeks of radiotherapy along with 20 mg/m² of leucovorin.

Postoperatively 5 Flurouracil was given for four cycles (350mg/m²/five times weekly once in four weeks) started four weeks after surgery.

Patients were assessed six weeks after surgery regarding the progression of the disease.

Decision for abdominoperineal excision of rectum, an anterior resection or pelvic exenteration was made preoperatively and modified according to the peroperative findings. Total mesorectal excision was done in patients according to the standardized technique. All patients who underwent anterior resection had a protective ileostomy. Patients with locally advanced unresectable disease underwent only colostomy.

During therapy, patients were monitored weekly for signs of acute toxic effects requiring change in dosage or regimen. Acute and long-term toxic effects were graded according to the Radiation Therapy Oncology Group criteria with respect to acute and late adverse effects of radiotherapy.

Preoperative and postoperative complications assessed included bleeding, ileus, intestinal fistulas, intra-abdominal abscess, perineal wound complications, urinary retention and death.

Follow up

Patients were followed at three monthly intervals for two years and then at six monthlies intervals. Evaluations consisted of physical examination, a complete blood count and blood chemical analysis, proctoscopy, abdominal ultrasonography, CT of abdomen and chest radiography. Local recurrence was to be confirmed histopathologically or by sequential radiological studies to detect enlargement of mass. Distal recurrence was confirmed histopathologically.

All resected specimens were examined for histological grade, degree of fibrosis, resected margin status and nodal status. The primary end points analyzed were downsizing of tumor, downstaging of the tumor, sphincter saving rates, toxicity of chemoradiotherapy, and patient compliance for the regimen. Secondary end points analyzed were the incidence of local recurrence, distal metastasis.

Downsizing was defined as a reduction in the size of tumor after chemoradiotherapy as determined by physical examination. Downstaging was defined as decrease in TNM stage, as assessed after chemoradiotherapy in the surgically resected specimen.

Statistical Analysis

Statistical analysis was done using SPSS version 22.0 software. All data was entered in excel sheet and the categorical variables were tested using test of one proportion and chi square test. A p value of less than 0.05 was considered statistically significant.

RESULTS

From March 2010 to November 2014, Eighty patients were enrolled in the study. Nine patients lost for follow up, five data could not be retrieved, five patients after completion of chemoradiotherapy did not come for further treatment. so finally, sixty-one patients underwent surgery post chemoradiotherapy.

TABLE 1. DEMOGRAPHY OF THE PATIENTS

Age Mean	43.6
Range	22-51
Sex	
Female	30
Male	31
Distance from anal verge No (%)	
0-4 cm	38
4-8 cm	18
8-12 cm	5
STAGE	
1	0
2a	8
2b	3
3a	9
3b	39
3c	2
4	0
HISTOLOGY	
well	23
mod	31
poorly	7
Interval to Surgery in weeks	
6	29
7	23
8	7
9	2
Type of surgery	
Anterior Resection (AR)	20
AR with adjacent organ resection	3
Abdominoperineal resection (APR)	36
Colostomy alone	2
Peroperative complications	0
Bleeding 1 (2.08 %)	
Post-operative complications	16
Abdominal wound infection	12
Perineal wound infection	2
Intraabdominal abscess	2
Urinary retention	2
Chemoradiotherapy toxicity	15
Mild-Skin irritation & discoloration	11
Vomiting	2
Diarrhoea	1
Anaemia	1

TABLE 2. RESULTS

Downsizing of Tumour	54/61	p (<0.0001)
Down staging of Tumour	51/61	p (<0.0001)
Follow up Period (3 YRS)		
Local recurrence	2	NS
Distant metastasis	3	NS
APER Sphincter saving procedure		
Planned	54	NS
Done	13	NS
Anterior resections		
Planned	6(12.5 %)	P = 0.001
Done	15 (31.5 %)	

Patients age ranged from 22-51 yrs, mean age being 43.6 years. Thirty-one males and thirty were females in our study. Most of the tumours extended into anal canal (63 %). Thirty-nine patients had stage 3 B disease and nine had stage 3 a disease. Fifty one percent of patients had moderately differentiated carcinoma and thirty eight percent had well differentiated tumors. The interval from chemo radiotherapy to surgery ranged from six to nine weeks. The surgeries performed ranged from anterior resection, with concomitant hysterectomy in females to abdominoperineal excision of rectum.

Twenty-nine, twenty three and seven patients underwent surgery at six, seven and eight weeks after chemoradiotherapy, two patients underwent surgery at ninth week due to pulmonary infection and surgery was delayed.

Twenty patients underwent anterior resection, three patients had uterine involvement and underwent concomitant hysterectomy and posterior vaginectomy. Thirty-six patients underwent abdominoperineal resection. In two patient growth had extended up to pelvic side wall, was inoperable and a palliative sigmoid colostomy was done.

One patient developed intraoperative bleeding due to injury to pre-sacral fascia. It was controlled by placing pressure. Abdominal wound infection (75%) which was most common complication in later period. Fifty-four patient of sixty-one patients had responded well to neoadjuvant chemoradiotherapy with downsizing of tumor. (p value <0.0001). Downstaging occurred in fifty-one (p<0.0001).

Two patient developed local recurrence. Liver metastasis occurred in one patient who had disease progression up to two pelvic side walls and was hence inoperable.

APR intended Sphincter saving planned for 54 patients but was only in 13/54 (24 %) Before neoadjuvant chemoradiotherapy only six anterior resections were planned. After it, fifteen anterior resections were done. Anterior resections intended Anterior resections done 6(12.5 %) but 15 (31.5 %) had anterior resection (P = 0.001). Neoadjuvant chemoradiotherapy increased sphincter conservation from 12.5% to 31.5%.

DISCUSSION

Significant advances have been made in the study of colorectal cancer over the last few years. A more thorough understanding of the molecular basis for this disease, coupled with the development of new therapeutic approaches, has dramatically altered the way in which patients are managed. New strategies for screening and for the detection of recurrent disease have also impacted the way physicians approach the workup and disease staging of their patients. In resectable rectal cancers the rationale for giving preoperative chemoradiotherapy is not only to improve the survival but also on the potential advantage of delivering both the agents preoperatively. These advantages include improved compliance with the chemotherapy regimen if it is given before a major surgery as well as downstaging which may enhance the rate of curative surgery and permit sphincter preservation in low lying rectal tumours. In addition, because the tumor oxygenation is better if given preoperatively, irradiation is more effective when given preoperatively.

The rate of sphincter conservation surgery is also doubled after preoperative chemoradiotherapy. Postponing the surgery to six weeks later helps shrinkage of tumor and recovery of tissues after treatment. The addition of 5-FU to preoperative radiotherapy produces a higher pathological complete response (pCR) rate over radiotherapy alone¹, and there is evidence for better locoregional control, but no improvement in disease-free survival (DFS) or overall survival has been demonstrated. Distant metastases occur in at least 30% of cases.

Neoadjuvant chemoradiotherapy helps significant downsizing of tumor as it causes tumor shrinkage. In this study downsizing occurred in Fifty four of sixty-one patients (88.5%)

Downsizing is a indicator of good response to preoperative chemoradiotherapy. This is concurrence with the results of Polish trial¹ the tumor was 1.9 cm smaller in patients after chemoradiotherapy.

After preoperative chemoradiotherapy, postoperative histopathology shows downgrading of the tumor. In this study fifty one of sixty-one patients (83.6%) showed downstaging (p<0.0001).

A good pathological response is a good prognostic indicator, with patients having a good response having less incidence of local recurrence and improved overall survival. Chung Wah Lam et al² in 2005 has shown that 69 % of his patients had decreased tumor stages after chemoradiotherapy.

When the optimum time interval between radiotherapy and surgery was analyzed non randomized retrospective data led to the hypothesis that a long-time interval between radiotherapy and surgery led to sphincter preservation because of tumor downstaging. Francois et al²¹ in 1999, conducted a randomized trial to compare short interval (SI) outcome with long interval (LI) of 6-8 weeks. A long interval between preoperative radiotherapy and surgery was associated with a significantly better clinical tumor response (53.1% in the SI group 71.7% in the LI group, P.007) and pathologic downstaging (10.3% in the SI group v 26% in the LI group, P .005). At a median follow-up of 33 months, there were no differences in morbidity, local relapse, and short-term survival between the two groups. The ideal time interval is 6 weeks following surgery when there is an optimal tumor response and further delay does not enhance the effect of radiotherapy. When fibrosis sets in, dissection also becomes technically difficult with increased incidence of complications like intra-abdominal sepsis, increased bleeding etc. In this study, the interval ranged from 6 to nine weeks, median being six weeks.

This study Present 31.5 % underwent Sphincter Saving Procedures after neoadjuvant chemoradiotherapy. One of the advantages of preoperative chemoradiotherapy is that tumor downsizing helps sphincter saving procedures possible. The incidence of sphincter saving procedures range from 39 % up to 82 %. In this study, preoperatively only six patients were planned for an anterior resection. After neoadjuvant therapy, anterior resection was possible in fifteen patients, sphincter conservation rates were increased from 12.5 % to 31.5 % (p < 0.001). The lower number of sphincter saving procedures is due to the fact that most of the tumors (66.6 %) had already extended into the anal canal, hence necessitating abdominoperineal excision of rectum.

Despite the increasing use of sphincter preservation for rectal cancers, nearly 50% of patients still undergo abdominoperineal excision of rectum. In many circumstances, abdominoperineal excision of rectum is performed out of concern for adequate distal margins despite mounting evidence that more limited distal margins may be appropriate. For low lying rectal tumors doing an abdominoperineal excision does not increase the radicality of the procedure or improve survival Although distal margins as great as 5 cm were advocated in the past, Paty et al found no increase in pelvic recurrence when the distal margin was <2 cm compared with > 2 cm. More recent data suggest that 1 cm distal margins are adequate^{3,4}

A number of clinical pathological studies^{3,4} that examined distal intramural spread suggest that smaller distal margins, even 1 cm, may be adequate in the majority of cases. This is supported by pathological evidence that distal intramural spread rarely exceeds⁵. When significant distal spread does occur, longterm survival is affected adversely, despite treatment with abdominoperineal excision of rectum. The presence of distal spread is associated with decreased survival primarily due to distant disease recurrence. Although mounting evidence supports the use of 1cm distal margins in rectal cancer resections, the use of centimeter and subcentimeter margins is controversial. Jose G Guillem et al⁶ on prospective pathological analysis of whole mount sections of rectal cancer following combined modality therapy in 109 patients has shown that intramural extension occurred only in 1.8 % patients (<0.95 cm). Hence, he concluded 1 cm margins are sufficient after preoperative chemoradiotherapy and this increases the chances of sphincter preservation without increasing the chances of local recurrence.

Preoperative chemoradiotherapy also reduces circumferential resection margin positivity.

Circumferential resection margin positivity is as high as 25 % if no preoperative chemoradiotherapy is used. In this study a distal margin of one cm did not result in margin positivity in any of the postoperatively examined specimens.

Local recurrence depends on multitude of factors like stage of the tumor. Tumors that are locally extensive are far more likely to recur than those that are mobile, no matter which type of procedure is performed. The frequency of local recurrence is significantly higher in patients who have circumferential involvement than those without involvement. Recurrence is also influenced by site of lesion in rectum, lower one third tumors have higher incidence than upper third tumours.

Stage of the disease, preoperative therapy used, surgical technique whether TME is used or not influences local recurrence. Local recurrence ranges from 5.8 % as reported by Kapitjein et al 24 to 15 %. This study during a follow up ranging from 6 months to twenty-six months has had no evidence of local recurrence. This correlates well with the excellent response to chemoradiotherapy and an adequate TME as evidenced by downstaging and downsizing.

The use of TME also must be considered as a contributing factor in reducing pelvic recurrences to as low as 5% to 8% in highrisk patients³. Quirke et al. demonstrated that radial spread into the mesorectum is a common occurrence. Sharp dissection along the parietal pelvic fascia ensures resection of these small (5 mm) occult nodal metastases that otherwise might be left behind. Radial margins are a more important predictor of disease recurrence and survival than distal margins.

There is an increased risk of recurrence for patients who undergo have abdominoperineal excision of rectum as described previously and likely reflects the worse prognosis attributed to tumors of the low rectum compared with midrectal tumors. The location of the tumor may be a more important prognostic factor than the type of operation performed.

About 16.6 % of patients developed toxicity of chemoradiotherapy. Skin irritation and discoloration was the most common toxicity encountered. It was totally reversed after few weeks. This is comparable with other studies showing a range of 11 % to 15 %. The EORTC 2292117 trial showed a very high toxicity of 38.4 %. In this study no patient had a change in the chemoradiotherapy schedule due to toxicity.

There is always a fear that neoadjuvant chemoradiotherapy increases preoperative complications, delays wound healing, patients may need perineal flap cover to prevent post operative wound disruption. The postoperative complications in this study was 16.66 % only. Of 32 patients who underwent only on abdominoperineal excision of rectum only one developed perineal wound complication which was successfully treated conservatively. So preoperative chemoradiotherapy can be given safely with good patient compliance, minimal side effects and less postoperative complications.

Most of the randomized controlled studies have not shown any significant survival benefit compared to preoperative radiotherapy alone. Jose G. Guilem et al 25 analysed the long term outcome following preoperative combined modality therapy and total mesorectal excision of locally advanced rectal cancer. With a median follow-up of 44 months, the estimated 10-year overall survival was 58%- and 10-year recurrence-free survival (RFS) was 62%. On analysis, pathologic response of greater than 95%, lymph vascular invasion and/or perineural invasion (PNI), and positive lymph nodes were significantly associated with overall survival and disease-free survival. Patients with a 95% pathologic response had a significantly improved overall survival ($p < 0.003$) and disease-free survival ($p < 0.002$).

Rectal cancer recurrence may be delayed following preoperative

chemoradiotherapy and TME and that surveillance of more than 5 years may be warranted. The treatment of locally advanced rectal cancer with preoperative chemoradiotherapy and radical rectal resection with TME currently provides the optimal treatment standard for a durable long-term oncologic outcome in properly selected patients

CONCLUSION:

Neoadjuvant chemoradiotherapy given in operable locally advanced mid and low rectal cancers causes significant downsizing, downstaging of the tumour, increases the rate of sphincter conservation surgeries. The toxicity of chemoradiotherapy is minimal, patient compliance is good. The postoperative complications are not increased, and it helps decrease the incidence of local recurrence. The effect on survival has to be determined on long term follow up only. Hence it is beneficial to administer it to patients with locally advanced operable mid and low rectal cancers.

NO CONFLICTS OF INTEREST
NO FUNDING FOR THE STUDY

REFERENCES

1. Bujko K, Nowacki MP, Nasierowska-Guttmejer A et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: Report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. *Radiother Oncol* 2004;72: 15–24.
2. Chung-Wah Lam, William Tzu-Liang Chen, Effect of preoperative concurrent chemoradiotherapy in locally advanced low rectal cancer after radical resection surgery. *Int Surg* 2005;90:53-59
3. Heald RJ, Moran BJ, Ryall RD et al. Rectal cancer: The Basingstoke experience of total mesorectal excision, 1978-1997. *Arch Surg* 1998; 133:894-899.
4. Boris Kuvshinoff, Irfan Maghfoor, Brent Miedema, David Ota Distal Margins requirements after preoperative Chemoradiotherapy for distal rectal carcinomas: Are ≤ 1 cm margin sufficient?. *Annals of Surgical Oncology*:8(2): 163-169.
5. S. Boulis Wassif, Gerard MD, J Loygue. Final Results of a Randomized Trial on the Treatment of Rectal Cancer With Preoperative Radiotherapy Alone or in Combination With 5-Fluorouracil, Followed by Radical Surgery, Trial of the European Organization on Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group, *Cancer* 1984;53: 1811-1818
6. Jose G. Guillem, David B Chessin, Jinru Shia, A Prospective Pathologic Analysis Using Whole Mount Sections of Rectal Cancer Following Preoperative Combined Modality Therapy, Implications For Sphincter Preservation; *Ann Surg* 2007; 245:88-93.