OUTCOMES OF SURGERY FOR RECTAL CANCER AFTER NEOADJUVANT CHEMORADIATION- COMPARISON BETWEEN OPEN & LAPAROSCOPIC SURGERY

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CERTIFICATE

This is to certify that dissertation on **"OUTCOMES OF SURGERY FOR RECTAL CANCER AFTER NEOADJUVANT CHEMORADIATION- COMPARISON BETWEEN OPEN & LAPAROSCOPIC SURGERY**" is a bonafide work done by **Dr. RITESH TAPKIRE,** in the department of Surgical Oncology, College of Oncological sciences, Cancer Institute(WIA), Chennai, under my supervision and guidance, to my satisfaction.

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CONTENTS

AIMS

1. To compare laparoscopic & open surgery for rectal cancer after neoadjuvant chemoradiation in terms of acute morbidity.

2. To assess oncological efficacy in terms of nodal yield and circumferential resection margin.

BACKGROUND

Preoperative chemoradiotherapy, as compared with postoperative chemoradiotherapy, improved local control & was associated with reduced toxicity although it didn't improve survival[1]. Thus preoperative chemoradiotherapy can be considered standard of care for locally advanced rectal cancer. Laparoscopic assisted surgery for colon cancer is as effective as open surgery in the short term & is likely to produce similar long-term outcomes[2]. However, impaired short-terms outcomes after laparoscopic assisted anterior resection for cancer of rectum do not yet justify its routine use. Furthermore, there is very limited data available on role of laparoscopy surgery for rectal cancer following neoadjuvant chemoradiation.

REVIEW OF LITERATURE

Globally, nearly 800,000 new colorectal cancer cases are believed to occur, which accounted for approximately 10% of all incident cancers, and mortality from colorectal cancer was estimated at nearly 450,000 [3]. In India, most of the patients presents with locally advanced rectal cancer (T3/T4, N+, As per UICC staging manual) & treatment involves multimodality treatment.

The last two decades have seen major advances in the understanding of the natural history of rectal cancer and its patterns of recurrence. This progress has led to significant improvements in treatment, especially for patients with clinically resectable rectal cancers, where surgery remains the cornerstone of treatment, and has driven technical advances in surgical technique with the increasing use of meticulous sharp dissection and total mesorectal excision (TME). Few recent surgical series suggest that TME is associated with much lower rates of local recurrence, even when employed in stage III patients[46].

Consequently the role of adjuvant treatment with radiotherapy or chemoradiotherapy has also evolved with changing surgical practice and outcomes.

Since it was first reported 20 years ago, laparoscopic rectal resection has been performed increasingly for benign and malignant rectal diseases [7]. Minimally invasive , laparoscopically assisted surgery was first considered in 1990 for patients undergoing colectomy for cancer[8].Concern that this approach would compromise survival by failing to achieve a proper oncologic resection or adequate staging or by altering patterns of recurrence (based on frequent reports of tumor recurrences within surgical wounds) promped a controlled trial evaluation. Current practice of laparoscopic surgery for rectal cancer depends on extrapolation of data from colon cancer trials. So far, five randomized trials reported survival data, all supporting non-inferiority of laparoscopy.[2,9,10,11,12]

COST (Clinical outcomes of surgical therapy) study group [9] conducted a noninferiority trial at 48 institutions and randomly assigned 872 patients with adenocarcinoma of the colon to undergo open or laparoscopically assessed colectomy performed by credentialed surgeons

. The median follow-up was 4.4 years. The primary end point was the time to tumor recurrence.

At three years , the rates of recurrence were similar in the two groups- 16 percent among patients in the group that underwent laparoscopically assisted surgery and 18 percent among patients in the open-colectomy group (two-sided p=0.32; hazard ratio for recurrence,0.86; 95 percent confidence interval,0.63 to 1.17). Recurrence rates in surgical wounds were less than 1 percent in both groups (p=0.50). The overall survival rate at three years was also very similar in the two groups (86 percent in the laparoscopic surgery group and 85 percent in the open-colectomy group; p=0.51; hazard ratio for death in the laparoscopic –surgery group, 0.91; 95 percent confidence interval , 0.68 to 1.21), with no significant difference between groups in the time to recurrence or overall survival for patients with any stage of cancer .Perioperative recovery was faster in the laparoscopic – surgery group than in the open- colectomy group, as reflected by a shorter median hospital stay (five days Vs six days , p<0.001) and briefer use of parenteral narcotics (three days Vs four days , p<0.001) and oral analgesics (one day Vs two days, p= 0.02). The rate of intraoperative

complications, 30-day postoperative mortality complications at discharge and 60 days, hospital readmission, and reoperation were very similar between groups.

In this multi-institutional study, the rates of recurrent cancer were similar after laparoscopically assisted colectomy and open colectomy, suggesting that the laparoscopic approach is an acceptable alternative to open surgery for colon cancer.

Although early reports on laparoscopic assisted colectomy (LAC) in patients with colon cancer suggested that it reduces perioperative morbidity, its influence on long-term results is unknown. Spanish single centre trial [10] done at IDIBAPS, University of Barcelona recruited patients with adenocarcinoma of colon from Nov 1993 to July, 1998. 219 patients took part in study (111 LAC group, 108 Open Colectomy group). Patients in LAC group recovered faster than those in the OC group, with shorter peristalsis-detection (p=0.001) and oral intake time (p=0.001), and shorter hospital stays (p=0.005). Morbidity was lower in the LAC group (p=0.001), although LAC did not influence perioperative mortality. Probability of cancer –related survival was higher in the LAC

group (p=0.02). The Cox model showed that LAC was independently associated with reduced risk of tumour relapse (hazard ratio 0.39, 95 percent confidence interval 0.19-0.82), death from any cause (0.48, 0.23-1.01) and death from a cancer related cause compared with open colectomy. This superiority of LAC was due to differences in patients with stage III tumors (freedom from recurrence, p=0.04, overall survival, p=0.02, and cancer-related survival, p=0.006). By contrast, in patients with stage I and II tumors, these variables were almost identical in both therapeutic groups. The improvement in tumor recurrence and survival in patients with stage III tumors operated on be LAC was of such magnitude that they were similar to those observed in patients with stage II tumors. Probable reason for this difference in survival might be due to evidence that surgical stress impairs immunity and that this feature is more intense in open surgery than in laparoscopic surgery. Immunity has a critical role in tumor progression and metastatic spread. This association could explain above findings from Spanish trial that LAC is associated with better outcomes only in stage III tumors. In stage I and II tumors, the probability of dissemination is very low and probably not affected by changes in immunological status. However, this situation

could not be the case in patients with stage III tumors, in whom a normal immunity may be essential to prevent tumor dissemination.

Of the few multicenter randomized, controlled trials initiated in the 1990s, the United Kingdom Medical Research Council trial of conventional Vs laparoscopic-assisted surgery in colorectal cancer (UK MRC CLASICC) [2] was the only one that did not exclude rectal cancer. Primary short-term endpoints were the rate of positive circumferential margins (CRMs) and longitudinal resection margins, proportion of Dukes' C2 tumors (ie, T3 and apical node metastasis), and in-hospital mortality. Patients were randomized to the laparoscopic arm in a 2:1 ratio. Of the 794 patients recruited to the trial, 381 had rectal cancer. Of these, 132 (48%) underwent open resection and 160 (46%) received laparoscopic-assisted resection. The overall conversion rate from laparoscopic to open surgery within the rectal cohort was 34% (82 of 242 patients). Within the actual treatment group, 87 patients (51 anterior resections and 36 APRs) underwent open TME; 189 patients (129 anterior resections and 60 APRs) underwent laparoscopic TME. The greater proportion of patients undergoing TME in the laparoscopic anterior resection group, despite the fact that the median distance of

rectal tumors from the anal verge was similar in both study groups, may be related to the inability of the surgeon to palpate the tumor during laparoscopic surgery. It has been hypothesized that TME was more commonly performed to ensure adequacy of the distal resection margin.

Positive CRMs were identified in 14% of patients who underwent open resection and 16% of those who had laparoscopic resection (*P*=.80). Among patients undergoing anterior resection, CRM positivity was 12% in the laparoscopic group Vs 6% in the open group (*P*=.19). Among patients undergoing APR, no difference in CRM positivity was noted between the laparoscopic and open groups (20% Vs 26%, respectively). Longitudinal resection margins were not significantly different between the two treatment arms. Although the proportion of Dukes C2 tumors was similar in both groups, a higher proportion was seen in patients whose procedures were converted from laparoscopic to open compared with those who were initially randomized to the open arm. However, after adjustment for stratification factors, this difference was not statistically significant (*P*=.12). In-hospital mortality rates were 5% after open surgery Vs 4% after laparoscopic surgery (*P*=.57). Patients whose procedures were converted from laparoscopic to open

had a higher mortality rate compared with patients in the open and laparoscopic arms, but this difference was not significant (*P*=.34). The main cause of death was cardiorespiratory failure. In view of the nonsignificant but concerning higher CRM positivity rate found in patients who underwent laparoscopic anterior resection, the authors concluded that routine use of laparoscopic resection for rectal cancer was not yet justified.

In 2007, the UK MRC CLASICC trial[19] reported its long-term outcomes based primarily on evaluation of 3-year overall survival rates, 3-year disease-free survival rates, and 3-year local recurrence rates. Secondary endpoints included 3-year distant recurrence rates, 3-year wound/port site recurrence rates, and quality of life. The 3-year overall survival rate was 67.8% for all patients. There was no difference in the 3-year overall survival rates between the laparoscopic and open groups (68.4% Vs 6.7%, respectively, *P*=.55). This finding was also true within the rectal cancer cohort (*P*=.12). On subset analysis, there was no difference between the two modalities in 3-year overall survival rates among patients undergoing anterior resection (74.6% for the laparoscopic group Vs 66.7% for the open group, *P*=.17). This was also

true for patients undergoing APR (65.2% Vs 57.7%, respectively, *P*=.41). The 3-year disease-free survival rate for all patients within the study was 66.8%, with no difference observed between the two modalities (*P*=.70). This was again found to be true on separate analyses of patients with rectal cancer (*P*=.87). Three-year disease-free survival rates for patients undergoing anterior resection (70.9% for the laparoscopic group Vs 70.4% for the open group, *P*=.72) or APR (49.8% Vs 46.9%, respectively, *P*=.64) were not statistically different. The 3-year local recurrence rate for all patients was 8.4%. Of particular note, among patients who underwent anterior resection, differences in CRM positivity did not translate into differences in 3-year local recurrence rates (7.8% for the laparoscopic group Vs 7.0% for the open group, *P*=.70). Additionally, the 3-year local recurrence rates for patients undergoing APR were not different between the treatment arms (15.1% Vs 21.1%, respectively, *P*=.47). However, the authors cautioned that further follow-up beyond the relatively short period of 3 years is required to ensure that a true difference does not become apparent in the long term. When looking at the secondary endpoints to the trial, the overall 3-year distant recurrence rate was 14.9%. Once again, there was no statistical difference in distant recurrence rates for patients undergoing

anterior resection (13.3% for the laparoscopic group Vs 13.9% for the open group, *P*=.98) or APR (32.9% Vs 25.4%, respectively, *P*=.64). Within the trial, there were 10 wound/port site recurrences (2.5% Vs 0.6%, respectively, *P*=.12). In the actual treatment group undergoing rectal resection (Vs the intention-to-treat population), the median hospital stay was 3 days shorter in the laparoscopic arm (10 days) compared with the open arm (13 days). However, this difference disappeared when comparing the open resection group with patients whose procedures were converted from laparoscopic to open. Of note, the overall (colon and rectal) conversion rate was 29%. However, this rate decreased with each year of the study (38% in year 1 to 16% in year 6). Tumor fixation, uncertainty regarding tumor clearance, patient obesity, anatomic uncertainty, and technical inability to access some tumors laparoscopically contributed to the high conversion rate (34%) initially observed in rectal cancer patients undergoing laparoscopic surgery. Quality-of-life data involving 696 patients within the study showed no differences between the laparoscopic and open treatment arms in any of the function scales (body image, sexual function, sexual enjoyment, and future perspective) or symptom scales (micturition problems, adverse effects of chemotherapy, gastrointestinal symptoms,

male sexual problems, female sexual problems, defecation problems, stoma-related problems, and weight loss). These findings are similar to the short-term quality-of-life outcomes data reported by the COST trial, in which the only statistically significant difference observed between the laparoscopic-assisted colectomy and the open colectomy groups was the global rating score at 2 weeks following surgery.[9] Mean global rating scale scores were 76.9 for the laparoscopic group vs 74.4 for the open colectomy group at 2 weeks (*P*=.009). The reasons for an apparent lack of significant difference in quality of life between the two groups have yet to be elucidated. The authors concluded that, in addition to adding to the growing body of evidence justifying the use of laparoscopic resection for colon cancer, the findings of their study (namely, that the higher CRM positivity seen after laparoscopic anterior resection has not translated into an increased incidence of local recurrence) extended to laparoscopic resection for rectal cancer.

Based on above trials, laparoscopic – assisted surgery is an acceptable alternative for resection of colon cancer with similar oncological outcomes & surgical morbidity while improving quality of life by reducing postoperative pain, hospital stay . Such evidence, however, are not yet available to support laparoscopic resection of rectal

cancer. Retrospective studies cautiously suggest the oncological adequacy of laparoscopic rectal resections.[13,14] Although laparoscopic rectal resection appear safe, additional concerns regarding increased conversion rates and associated complications in laparoscopic rectal resection remain [2].

Several other aspects of laparoscopic rectal surgery are attractive for oncologic application. Total mesorectal resection is more commonly achieved in laparoscopic cohort, and appears to be technically easier, possible due to better visualization and magnification[2]. Additionaly, an interesting phenomenon of decreased tumor growth after laparoscopic surgery was observed in both animal studies[15] and invitro studies [11]

However, data regarding laparoscopic rectal cancer surgery is limited. The results of a prospective randomized trial of laparoscopic – assisted (n=51) versus open APR (n=48) for low rectal cancer reported by Ng et al [16] with the aim of comparing post-operative recovery course (primary endpoint) and survival data (secondary endpoint) between to groups. Postoperative recovery was found to be improved after laparoscopic – assisted APR with regard to earlier return of bowel

function (p=<.001), improved time to patient mobilization (p=0.05), and reduced analgesic requirement (p=.007), at the expense of prolonged operative time and higher direct cost. Survival probability at 5 years after curative resection was 75.2% for laparoscopic arm Vs 76.5% for open group (p=0.20). Disease free probabilities were not significantly different between two groups (p=.55). Findings of this study supported the view that there are clear short-term benefits to laparoscopic rectal resection with regard to functional recovery, as well as equivalent oncologic adequacy and survival.

Most recently, a large, single-institute retrospective review of 579 patients who underwent laparoscopic resection for rectosigmoid and rectal cancer was reported by Ng et al,[17] evaluating short-term outcomes and long-term survival. Over a period of 15 years, 316 patients underwent laparoscopic anterior resection, 152 patients had sphincter – preserving TME, and 92 patients underwent laparoscopic APR. After a median followup of 56 months, the study concluded that laparoscopic resection of rectal cancer is safe and offers long-term oncologic outcomes equivalent to those of open resections.

In a subsequent retrospective study of 421 patients (310 in the open group and 111 in the laparoscopic group) comparing outcome between open and laparoscopic resection for stage II and stage III rectal cancer, Law et al [18] reported 5-year actuarial survival rates of 71.1% Vs 59.3% in the laparoscopic Vs open arms, respectively (*P*=.029). Median follow-up was 34 months, and there was no difference in local recurrence. In addition, laparoscopic resection was associated with decreased blood loss (200 mL Vs 350 mL, *P*< .001) and shorter hospital stay (7 Vs 9 days, *P*< .001). The conversion rate to open surgery was 12.5%. On multivariate analysis, laparoscopic resection was an independent factor associated with improved survival (*P*=.03, hazards ratio 0.558 [95% confidence interval, 0.339–0.969]). It should be noted that there is no delineation of the number of stage II Vs stage III rectal cancer patients. In addition, of the 310 patients in the open group, 273 (88.1%) underwent anterior resection, 31 (10%) APR, and 6 (1.9%) Hartmann's procedure. Within the laparoscopic group (n = 111), 102 (91.9%) underwent anterior resection, 8 (7.2%) APR, and 1 (0.9%) Hartmann's procedure. The reason for the disproportionate number of anterior resections in both groups is unclear. Furthermore, although implied, it is not specifically stated that both mid and upper rectal

cancers were treated with anterior resection. Nonetheless, the study concluded that compared to open resection, laparoscopic resection for locally advanced rectal cancer is associated with more favorable overall survival.

Sufficient evidence now exists to support the implementation of laparoscopy as an acceptable modality in colectomy for cancer. Overall survival and recurrence data have proven that, from an oncologic standpoint, laparoscopic colectomy is equivalent to open colectomy. The data on laparoscopic resection for mid to low rectal cancer are limited to predominantly retrospective series and two prospective randomized trials. The initial nonsignificant but concerning finding of increased CRM positivity within the laparoscopic anterior resection cohort reported in the MRC CLASICC trial4 raised questions about oncologic adequacy. However, these concerns did not translate into a difference in local recurrence at 3 years between the laparoscopic and open approaches.[19]

Based on results of German rectal cancer study group [1] , preoperative chemoradiotherapy, as compared to postoperative

chemoradiotherapy was found to improve local control and was associated with reduced toxicity but there was no improvement in overall survival. However , there is limited data available on role of laparoscopic surgery for rectal cancer following neoadjuvant chemoradiation.

One of the largest study reported by Skrovina et al,[20] compared laparoscopic rectal cancer surgery with or without neoadjuvant chemoradiation therapy. 81 patients received neoadjuvant treatment while 74 patients underwent primary laparoscopic surgery. Both groups were comparable in intraoperative ($p=0.632$) and postoperative surgical complications ($p=0.179$) and nonsurgical complications($p=0.654$) too. Operative time and postoperative stay were similar in both groups. Yield of resected lymph node was significantly higher for primary surgery group ($p<0.001$). Overall short term results didn't reveal worsening of perioperative period with neoadjuvant chemoradiotherapy.

Cheung Hy et al [21] evaluated perioperative short-term outcomes of laparoscopic rectal surgery after neoadjuvant chemoradiation therapy. 52 patients in neoadjuvant group were compared with 138 patients in control group(primary surgery). Median operating time was

significantly higher in the neoadjuvant group as compared to control group (155 minutes versus 135 minutes respectively, p=0.09). There was no significant difference in terms of blood loss, conversion rates, postoperative morbidity, length of hospital stay or sphincter preservation rates. Overall five year survival rates in two group remained similar. Author concluded that patients after neoadjuvant chemoradiation for rectal cancer should not be deterred from minimally invasive approach as their data showed that, other than slightly longer operating time, laparoscopic rectal cancer surgery in patients with neoadjuvant chemoradiation is safe with no increased morbidity.

However another retrospective analysis by Rezvani et al [22] revealed insignificantly higher conversion rate and significantly longer duration of surgery in laparoscopic rectal surgery following neoadjuvant chemoradiation. Although there was no difference in morbidity and mortality. Only 8 patients received neoadjuvant treatment while 52 patients underwent primary surgery. Conversion rate was 37%(3/8) in neoadjuvant group as compared to 13%(7/52) in primary surgical group. Operating time was longer in neoadjuvant group as compared to primary surgery (228 minutes versus 170 minutes respectively). Complication

rate and median number of harvested lymph nodes were similar in both groups.

Similary another retrospective study by R. Pugliese et al [23] showed that patients who underwent laparoscopic resection of rectal cancer after neoadjuvant chemoradiation had a significantly longer duration of surgery as compared to patients who didn't receive neoadjuvant treatment (268 minutes versus 241 minutes respectively,p=0.004). conversion was needed in 9.5% (n=24) patients. However, none of the patient treated with neoadjuvant treatment required conversion. Morbidity and leak rates were not different significantly between two arms. 48 patients were treated with neoadjuvant chemoradiation. 38 patients underwent laparoscopic low anterior resection(LAR) while laparoscopic abdomino-perineal resection was performed in 10 patients. Leak rate among laparoscopic LAR patients was not different between two groups. Average number of lymph nodes resected, were not significantly different between two groups. Distal resection margins were free in all patients in both groups. Author concluded that laparoscopic resection for rectal cancer is feasible and safe with

morbidity and long term results quite acceptable in patients receiving neoadjuvant chemoradiation.

Dan Geisler et al [24] did nonrandomized single arm study involving 42 patients who received 5644 cGy of radiation therapy before laparoscopic surgery for rectal cancer and concluded that, with proper selection and laparoscopic experience, laparoscopic surgery can be performed in the irradiated pelvis without undue morbidity and mortality.

Ricardo Rosati et al[25] reported no significant difference in operative time, in conversions to open surgery, in intra- and postoperative complications, and in anastomotic leakage rate between laparoscopic rectal surgery with or without neoadjuvant chemoradiation. In addition, they reported similar cumulative 3 and 5 year survival rates between two groups indicating oncological adequacy with laparoscopic surgery following neoadjuvant chemoradiation.

There are very few studies comparing laparoscopic surgery versus open surgery after neoadjuvant chemoradiation.

Denoya P et [26] al performed retrospective analysis of all rectal cancer patients who received neoadjuvant chemoradiation. Between 2002 to 2008, 64 patients were identified. 32 patients underwent laparoscopic surgery and 32 had laparotomy. Operative time was longer in the laparoscopic group (267+/- 76 versus 205+/- 49 minutes, $p<0.001$. Blood loss, complication rate, and mortality rate were all similar between two groups. However, the laparoscopic group benefited from shorter length of stay (6.1+/-2.4 versus 7.6+/-2.3 days, $p=0.012$), earlier first bowel movement (1.9+/-1 versus 3.3+/-2.4 days, $p=0.006$), and shorter time to regular diet(3.9+/-2.1 versus 5.8+/-2.5 days, $p=0.003$). There was no difference in lymph node harvest (both positive node harvest and total lymph node harvest), distal margin or radial margin. Overall it was found out that laparoscopic TME for rectal cancer was feasible and safe and patient benefitted from short-term advantages of laparoscopy.

The only prospective study to compare laparoscopic versus open abdomino-perineal resection following neoadjuvant chemoradiation was done by Araujo SE et al [27]. 28 patients with distal rectal adenocarcinoma were randomized to undergo surgical treatment by laparoscopic APR

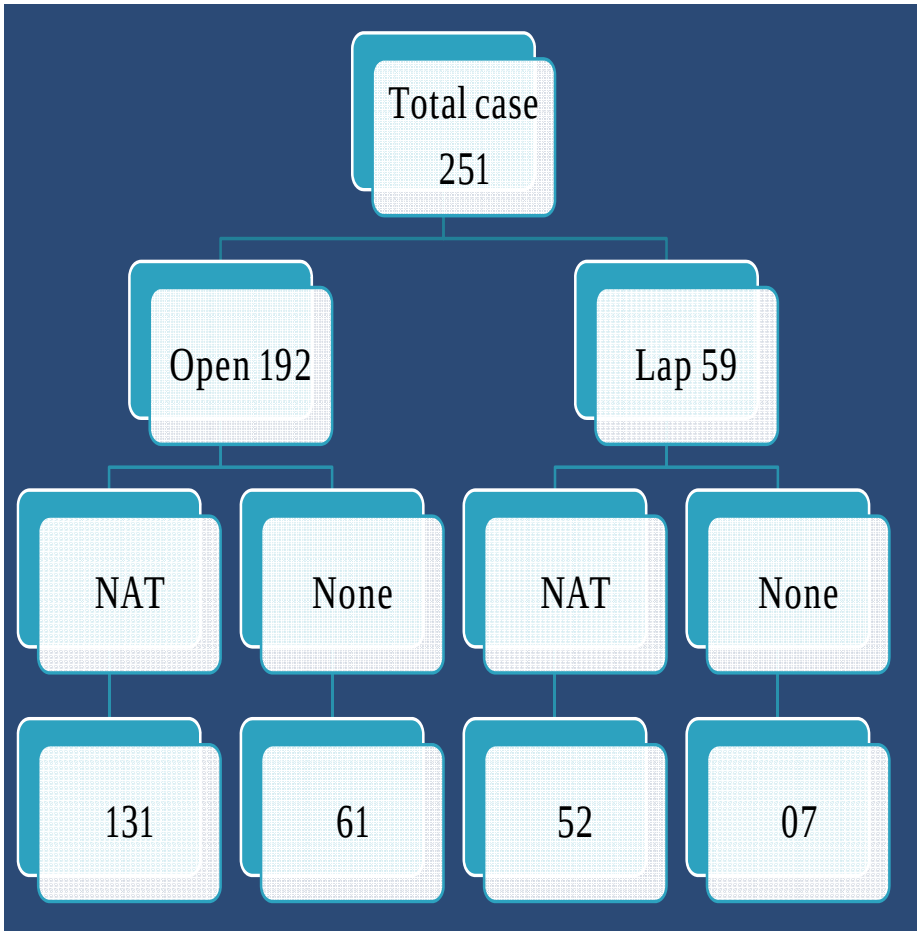
(n=13) or conventional open APR (n=15). There was no significant difference between two study groups regarding intra and post operative complications, need for blood transfusion, hospital stay after surgery, length of resected segment and pathological staging. Mean operation time was 228 minutes for laparoscopic APR versus 284 minutes for the conventional approach (p=0.04). Mean anaesthesia duration was shorter (p=0.03) for laparoscopic APR as compared to open APR. After a mean followup of 47 months and with exclusion of two patients in the open APR who presented with unsuspected synchronic metastasis during surgery, local recurrence was observed in two patients in the open APR and none in the laparoscopic group. However the sample size was very small to properly come for some recommendation.

Although laparoscopic rectal surgery following neoadjuvant chemoradiation has been found to be safe, with comparable oncological outcome with improvement in quality of life by reducing postoperative hospital stay, postoperative pain, less need for analgesics, reduced time to start diet , none of the studies have prospective with adequate sample size to come to any conclusion. Hence unless a properly randomized controlled trial is done, recommendation for superiority of laparoscopic or open surgery over one another can not be established.

MATERIAL AND METHODS

This study is a retrospective study, over a period of 6 years from January 2003 to april 2009 which included 251 patients. 192 patient underwent open surgery (Group I)as compared to 59 in laparoscopic surgery group(Group II). Neoadjuvant treatment was given to 131 patients in group I Vs 52 in group II which represents the study population. Neoadjuvant concurrent treatment was given in the form of 2 cycles of chemotherapy consisted of 5 Fu (325 mg/m^2) & Mitomycin (6 mg /m^2) & 50 Gy of radiation therapy (1.8 to 2 Gy /day x 5 days). Surgery was performed about 6-8 weeks after neoadjuvant treatment. Preclinical staging was performed by a combination of history, physical examination, imaging by contrast enhanced CT scan of abdomen/pelvis. TNM classification (UICC) was used to classify tumors. Data were collected retrospectively for age, gender, pretreatment staging, duration of surgery, intraoperative blood loss, conversion to open surgery & postoperative data including morbidity, mortality & histopathology report. Exclusion criteria for laparoscopic surgery were significant

comorbid illnesses (i.e. diabetes, hypertension & ischemic heart disease), history of previous pelvic surgery, & adherence to other structures on imaging.



SURGICAL PROCEDURE

Laparoscopy was performed using 4 port technique: 10 mm port infraumbilical and 5 mm ports in right and left lumber region and right iliac fossa region. Right lower port was positioned as low as possible, paying attention not to injure inferior epigastric vessels. In laparoscopic assisted low anterior resection, after laparoscopic mobilisation infraumbilical transverse laparotomy was done for retrieval of specimen & anastomosis. In laparoscopic abdominoperineal resection, specimen was removed through perineal wound. Laparoscopic harmonic scalpel was used to dissect & divide tissue. Inferior mesenteric vessels were dissected & ligated using ligaclips distal to origin of left colic vessels. Dorsal dissection was done in the avascular plane between parietal pelvic fascia and mesorectum , with preservation of the hypogastric nerve, sufficiently down to the floor of pelvis. Pelvic splanchnic nerves were preserved while doing lateral dissection. Thus, autonomic nerve preserving surgery were performed in principle except in those cases where extensive fibrosis subsequent to neoadjuvant chemoradiation

obscured tissue planes. Diversion transverse colostomy was done for all cases in low anterior resection. Postoperatively, APR patients and LAR patients with diversion colostomy were started liquids on 1st postoperative day which gradually increased to normal diet over a period of 3-4 days. Serial bladder catheter clamping usually started on 5th postoperative day to increase tonicity of bladder. Pelvic drains were removed at around 9th or 10th postoperative day. In all cases of APR and LAR in both groups, residual urine was checked with ultrasound of pelvis, after removal of bladder catheter and bladder was recatheterized if residual urine was reported to be more than 50 ml. These patients were then, discharged with catheter insitu and appropriate advice for maintenance of catheter and catheter clamping. Laparoscopic port site sutures removed on 9TH postoperative day. Perineal sutures were removed on 11th postoperative day in APR cases. Patients, who received neoadjuvant chemoradiation, were then referred for adjuvant chemotherapy.

Statistical analysis:

Analysis was performed with SPSS software version 14 and $p < 0.05$ was considered to be significant.

RESULTS

Gender ratio was equal in both groups (3:2). Mean age was more in group I (50.7 years Vs 48.6 years). Tumors in distal rectum (0-6cm) were more in group II (88.1% Vs 74.9 %) while middle rectal rectal tumors (6-12 cm) were more in group I (23.6% Vs 11.9%). There were no tumors in upper rectum in group II as compared to only 3 patients in group I (table 1).

Table 1.

Patient characteristics			
		Open ***(n=192)***	**Lap** ***(n=59)***
M:F		3:2	3:2
Mean age		50.7	48.6
Distance from anal verge (cm)	0-6	74.9% (*n=143*)	88.1%(*n=52*)
	6-12	23.6% (*n=45*)	11.9% (*n=7*)
	>12	1.6% (*n=3*)	nil

Most of the patients in both groups were in stage IIa as shown in table 2.

Table 2

Stage distribution(n=207) ***APR+LAR+AR***						
Stage	*NAT (n=160) %*			*None(n=47) %*		
	Open	Lap	Total	Open	Lap	Total
I a	-	-		-	14.2	2.1
I b	10.9	18	13.1	25	28.5	25.5
II a	70	68	69.3	55	57.1	55.3
II b	8.2	8	8.1	5	-	4.2
III a	2.7	6	3.7	-	-	-
III b	6.3	-	4.3	2	-	2.1
IV	1.8	-	1.2			

Most of the surgeries were APR, LAR or AR in both groups [table 3]. There was no significant difference in median duration of surgery in two arms (265 minutes for open surgery Vs 270 minutes for laparoscopic group). Similarly median hospital stay was same in both groups (15 days). However, mean blood loss was significantly less in group II (585 ml Vs 300 ml) [table 4]. Conversion rate to laparotomy was 3.8% (2/52) in laparoscopic rectal surgery following chemoradiation as intraoperatively lesion was found to be adherent posteriorly. Circumferrential resection margin was not significantly different in two groups with or without neoadjuvant chemoradiation [table 5,6,7]. There was no significant difference in mean nodal yield between two arms as shown in [table 8]. Although mean nodal yield appeared to be less in both arms (post neoadjuvant chemoradiation) but on a subset analysis mean nodal yield was found to be significantly less in open APR after neoadjuvant chemoradiation as compared to upfront open APR (8.51 versus 19) [table 9] . There was no significant difference in overall morbidity as well as minor (<30 days hospital stay) and major morbidity (>30 days hospital stay) when comparing major surgical procedures performed in both arms [table 10a]. Similarly there were no significant differences in perineal morbidity after APR in both arms [table 11].

Urinary morbidity in the form of urinary tract infection and prolonged catheterization was almost same following APR & LAR irrespective of neoadjuvant chemoradiation as shown in [table 12]. There was no significant difference between patients undergoing open or laparoscopic LAR [table 13].

Table 3

Surgery	***Open***	***Laparoscopic***	***Total***
APR	82	45	127
LAR	57	09	66
AR	11	03	14
Exenteration procedures	15	01	16
Hartmann's procedure	07	00	07
Total colectomy, ileorectal anastomosis	04	00	04
Total proctocolectomy	06	01	06

Table 4

	Open	***Lap***	***p value***
Median duration of sx	265 minutes	270 minutes	Ns
Mean blood loss	585 ml	300 ml	<0.001
Median hospital stay	15 days	15 days	Ns

Table 5

CRM (APR+LAR: n=193)

CRM distance	***Open*** *(n=97)*	***Lap*** *(n=45)*	***p value***
≥2 mm	83.5% *(n=81)*	80% *(n=36)*	Ns
<2 mm	16.4% *(n=16)*	20% *(n=09)*	Ns
Total	97	45	142

Note: CRM distance not available in 51 cases.

Table:6 CRM (Post NAT: n=113)

CRM distance	***Open***	***Lap***	***p value***
≥2mm	84.7%(n=61)	80.4%(n=33)	Ns
<2mm	15.2%(n=11)	19.5%(n=08)	Ns
Total	63.7%(n=72)	36.2%(n=41)	113

Table:7 Positive CRM

	Open	***Lap***	***p value***
PostNAT(n=160)	4.5%(5/110)	4%(2/50)	Ns
None (n=193)	5%(7/139)	3.7%(2/54)	Ns

Table 8: Mean nodal yield

	Year	***Open***	***Lap***	***p value***
APR+LAR Post NAT (n=161)	2003-2009	8.32 *(n=110)*	6.96 *(n=51)*	Ns
	2003-2005	7.32 *(n=37)*	6.88 *(n=26)*	Ns
	2006-2009	8.82 *(n=74)*	7.04 *(n=24)*	Ns

Table 9: Nodal yield after APR

	NAT	***None***	***p value***
Open APR	8.51	19	0.005

Table 10: Morbidity

		Open *(n=150)*	***Lap*** *(n=57)*	***p value***
Overall morbidity ***APR+LAR+AR*** *(n=207)*	**Minor**	39.3% *(n=59)*	36.8% *(n=21)*	Ns
	Major	10.6% *(n=16)*	21% *(n=12)*	
	Total	50% *(n=75)*	57.8% *(n=33)*	
Mortality				
		Nil	Nil	

Table 10 b Breakup of overall morbidity

Morbidity	***APR***	***LAR***	***AR***	***Total***
Nil	58	34	9	101
Perineal wound	42	NA	NA	42
Abdominal wound	4	14	3	21
Urinary	19	13	O	32
Others	4	5	1	10
Anastomotic leak	NA	0	1	01
	127	66	14	207

Table 11:

Perineal morbidity		***Open***	***Lap***	***p value***
APR *(n=127)*	**Minor**	14.6% *(n=12)*	15.5% *(n=07)*	Ns
	Major	13.4% *(n=11)*	26.6% *(n=12)*	
	Total	28% *(n=23/82)*	42.2% *(n=19/45)*	
Post NAT APR *(n=113)*	**Minor**	16% *(n=11)*	16% *(n=07)*	Ns
	Major	16% *(n=11)*	27.2% *(n=12)*	
	Total	31.8% *(n=22/69)*	43% *(n=19/44)*	

Table 12:

		Open	***Lap***	***p value***
Urinary morbidity *(n=193)* ***APR+LAR***)	*With NAT*	14.54% *(n=16/110)*	14% *(n=07/50)*	Ns
	Without NAT	24.13% *(n=07/29)*	25% *(n=01/04)*	
	Total	23	08	

Table 13: Morbidity after Low anterior resection

Morbidity	***Open*** *(n=57)*	***Lap*** *(n=9)*	***p value***
Nil	50.8% *(n=29)*	55.5% *(n=5)*	Ns
Abdominal wound	22.8% *(n=13)*	11.1% *(n=1)*	
Urinary	19.2% *(n=11)*	22.2% *(n=2)*	
Others	7% *(n=4)*	11.1% *(n=1)*	

DISCUSSION

Laparoscopic assisted surgery for colon cancer is an accepted alternative as it has shown comparable results in terms of morbidity, intraoperative complications, postoperative complications and equal oncological outcomes. But similar data is not available for laparocopic rectal cancer surgery. Further more there is paucity of data for doing laparoscopic surgery for rectal cancer following neoadjuvant chemoradiation.

This study was done to compare short-term outcomes between laparoscopic and open surgery for rectal cancer following neoadjuvant chemoradiation . Laparosopic surgery for rectal cancer was started in cancer institute in mid 2003. Locally advanced rectal cancer form almost 2/3rd of all cases. Neoadjuvant chemoradiation is practiced in our institute for locally advanced rectal cancer. Hence most of the patients usually undergo surgery after chemoradiation.

Operative time was longer in most of the series, [21,22,23] similar to our series which may be due to post chemoradiation fibrosis & difficulty in dissecting tissue planes . Most of the series didn't show any difference in intraoperative blood loss. However, in our series, mean blood loss was significantly less in laparoscopic arm as compared to open surgery. Nodal yield was significantly less in chemoradiation arm in series by skrovina et al [20] but this was a comparison between laparoscopic rectal surgery with or without chemoradiation. Although other series comparing laparoscopic surgery with or without chemoradiation[21,22,23] reported similar nodal yield between both groups. In open rectal surgery, different series [28,29,30] have reported significantly higher nodal yield with upfront surgery as compared to surgery after neoadjuvant chemoradiation. There was no significant difference in nodal yield in our series. Infact when entire study period was divided in two equal halves, there was a trend towards better nodal yield in later half of study period in laparoscopic group. Overall nodal yield is relatively less in our series(mean 6.96) as compared to other series with laparoscopic surgery after neoadjuvant chemoradiation [23,25] (mean 12-13 nodes). But as already shown in [table 7] that even in open APR, nodal yield was significantly less after chemoradiation as compared to upfront APR. Reason for less

nodal yield could be higher dose of radiation in our study (50 Gy in our study as compared to 45 Gy in other series [23,25]). Other factor could be use of two drugs (5 Fu and Mitomycin) in our study as compared to 5-Fu alone in other series [23,25]. Series which compared laparoscopic rectal surgery with or without neoadjuvant chemoradiation did not show any significant difference in intraoperative, postoperative complications, postoperative hospital stay. Oncological safety in terms of circumferential resection margin and distal margin status was not significantly different in our study. Postoperative morbidity and mortality were similar in both arms. Studies comparing laparoscopic rectal surgery with open rectal surgery following neoadjuvant chemoradiation are very few. Operative time was longer in one retrospective series [26] like our series but other prospective series [27] reported decresed operative time .Hospital stay was shorter in laparoscopic arm in Denoya P et al [26]series but in our series length of postoperative hospital stay is same for both arms (median hospital stay-15 days) as most of the patients are from rural areas & they wanted to have sutures removed before getting discharge. Other factor may be removal of bladder catheter which usually taken out at around 10 days after surgery (for APR or LAR). Perineal morbidity per se has not been

addressed separately in any of the series. In our study, major perineal wound morbidity (more than 30 days postoperative hospital stay) was high in laparoscopic rectal surgery group as compared to open surgery group, although it was not significant. Reason for this may be that after removal of specimen we routinely fill pelvic cavity with omentum in open surgery while it was not done in laparoscopic surgery. So once there was perineal wound breakdown, it took longer time to heal in laparoscopic rectal surgery due to large pelvic cavity. While in open surgery perineal wound healed faster because of small pelvic cavity due to presence of omentum. Major perineal morbidity was higher even in patients who underwent laparoscopic APR without neoadjuvant chemoradiation suggesting that a higher rate of perineal wound morbidity may not be due to chemoradiation alone but also due to differencs in operative procedures in the present study. The omentum possesses many physiologic properties that make it favourable for use as a flap in the pelvis after APR. It plays a major role in local immune response. Angiogenic properties of the omentum create vascular adhesions that may provide an alternate blood supply to surrounding ischemic tissues [31,32]. Furthermore, the omentum contains high concentration of tissue factor giving it significant hemostatic

properties[33]. These physiologic properties and its capacity to fill the pelvic dead space make the omentum an excellent candidate for tissue transfer to the pelvis. Several studies have reported good results with the use of omental pedicle flaps in the pelvis and perineum, with a 50 to 100% primary perineal wound healing rate [34,35,36]. However, a prospective non-randomized multicenter trial reported that omentoplasty after APR for cancer conferred no significant advantage in perineal wound healing compared with patients without omentoplasty [37]. A recent modification of the omentoplasty to include suturing of the omentum to the perineal subcutaneous tissue before perineal skin closure has resulted in an 80% primary perineal wound healing rate [36]. Collectively, these studies suggest that the omental pedicle flap is effective when sufficient in size to reach the pelvis and perineum. Distal margin was negative in all cases of low anterior resection and anterior resection in both groups. Conversion rate was 3.8% (2/52) in our series as compared to 5% in other series [25] . There were no conversions in neoadjuvant chemoradiation group in series by Pugliese et al [23]. Absence of anastomotic leak in our series may be explained by construction of covering stoma in all cases.

	Duration of surgery	Overall morbidity	Leaks	Conversion rate	Mean blood loss	Nodal yield
R.Pugliese et al (lap=48) *EJSO,35;2009:497-503*	More in NAT	No difference	7.9%	Nil	No difference	Equal
Rezvani et al (lap =8) *JSLS 2007(11):204-207*	More in NAT	No difference	Nil	37%	No difference	Equal
Cheung et al (lap = 52) *Surgical endoscopy 2008 sep 19*	More in NAT	No difference	Nil	Nil	No difference	Equal
Araujo et al (lap=13) *Rev hosp med clin fac med sao paulo 2003 may-june;58(3):133-40*	Less in lap	No difference	Nil	Nil	No difference	Equal
Skrovina et al (lap =81) *Rozhl chir2008 aug;87(8):417-25*	No difference	No difference	Nil	Nil	No difference	Less in lap
Cancer institute (WIA) (Lap=52)	**No difference**	**No difference**	**Nil**	**3.3%**	**Less in lap**	**No difference**

LIMITATIONS

Our study is one of the largest reported study to date regarding number of patients with laparoscopic rectal surgery following neoadjuvant chemoradiation (n=52). However, there are several important limitations of this study. First, this was a retrospective study hence assessment of need for postoperative analgesia, in terms of days and doses could not be assessed. Second, this was not a randomized study. Third, long term follow-up was lacking as cases were considered for inclusion in study till mid 2009. Hence long term oncological data in terms of local recurrence, disease free survival and overall survival are lacking.

CONCLUSION

Present study suggests that laparoscopic surgery for rectal cancer can be performed after neoadjuvant chemoradiation with equal morbidity and oncological safety with significantly less blood loss. This needs confirmation by prospective randomized trials.

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