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Original Article

3-year Disease Free Survival After Low Tie for Rectal Cancer Surgery

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ABSTRACT

Background: In rectal cancer surgery, the approach towards the Inferior Mesenteric artery (IMA) has always been debated among the performers of "high tie" and "low tie" technique. The debate is centred on three factors; a) Oncologic outcomes, b) Vascular factor (evidenced by leak rate) and c) Injury to hypogastric nerves.

Objectives: This study aims to assess the oncologic adequacy with regard to 3-year Disease Free Survival (DFS) following low tie in rectal cancer surgery with Lymph Node (LN) yield and anastomotic leak rates as secondary outcomes.

Materials and Methods: This is a retro-prospective study of all consecutive patients with histologically proven rectum and recto-sigmoid adenocarcinoma who underwent low tie resections with curative intent with curative intent over a period from 01/01/2009 to 31/12/2016. Those patients with familial syndromes or history of other malignancies in the past were excluded from the study.

Results: There were 254 patients during the study period, of which 53 patients lost to follow up and 29 patients expired while on follow up due to others causes. The remaining 172 patients were included for analysis. Median follow-up was 61 months (8-117 months). The mean DFS was 81.6 months [standard error (SE): 3.2; 95% Confidence Interval (CI): 75.35-87.91]. The mean Overall Survival (OS) was 90.7months (SE:2.78, 95% CI 85.2 – 96.1). The 3-year DFS and the 3-year OS was 76.9% and 83.5% respectively. The stage of the tumor and LN positivity was found to have significant impact on DFS (p=0.006) and OS (p<0.001). There was no statistically significant impact of the number of positive LNs on DFS (0.931) and OS (p=0.783). Loco-Regional Recurrence (LRR) was seen in 11(6.3%) patients. Liver was the most common site of distant metastasis. Median LN yield in patients who underwent upfront surgery and those with NACRT was 14 (8-24) and 5(0-20) respectively. Anastomotic leak was seen in 6/121 (4.9%) patients.

Conclusion: Low tie in rectal cancer surgery provides comparable 3-year and 5-year DFS and OS with that of high tie reported in literature. Adequate LN yield can be achieved in low tie rectal cancer surgery with a low clinical anastomotic leak rate compared to that of other studies reported.

KEYWORDS: Rectal cancer surgery, Low tie, High tie, 3-year DFS, Overall survival, LN yield, Loco-regional recurrence, Anastomotic leak rates.

Introduction

The optimal approach towards IMA in rectal cancer surgery has been debated among the low tie and high tie performers. The debate among them is primarily based on three factors viz) Oncologic outcome b) Vascular factor (evidenced by leak rate) and c) Injury to hypogastric nerves. The most important advantage of high tie is its clearance of Inferior Mesenteric Artery (IMA) root or apical lymph node (LN) i.e. D3 or central Lymphadenectomy. But the reported incidence of IMA root LN metastasis is 0.3 to 8.6%[1,2]. The concept of avoiding routine dissection of IMA root LN unless clinically indicated and avoiding routine splenic flexure mobilisation in low tie approach has gained wide spread interest. Thus, in low tie there is less dissection, better blood supply to the proximal anastomotic limb with less chance of injury to hypogastric nerves and adequate LN clearance following rectal cancer surgery.

In our centre we do Low tie resections in rectal and rectosigmoid cancer surgery without routine mobilisation of splenic flexure (unless there is tension on mesocolic vasculature or proximal limb) and IMA root LN clearance unless clinically indicated. This study intends to explore the effectiveness and safety of low-tie of IMA for rectal cancer surgery by evaluating the oncologic outcome in the form of 3-year Disease Free Survival (DFS) rates; with LN yield and clinical leak rates as the secondary endpoints.

Materials and Methods

This study included all consecutive patients in this Department who underwent Rectal/rectosigmoid cancer surgery with curative intent (R0) by low tie of IMA from 01/01/2009 to 31/12/2016. Patients associated with familial syndromes or history of other malignancies in the past were excluded. Data was obtained from the prospectively held computerized operation register which holds the demographic details as well as the intraoperative details and 30-day postoperative outcomes. Follow up data was collected from patients directly as per the departmental protocol for follow up as well as from the tumour board register maintained prospectively in the Department. Follow up was done by clinical examination, Carcinoembryonic antigen (CEA), colonoscopy and Contrast enhanced Computerised Tomography (CECT) / Magnetic Resonance Imaging (MRI) Abdomen and Pelvis to look for recurrence as per National Comprehensive Cancer Network (NCCN) guidelines.

Disease free Survival (DFS) was defined as time from the date of operation to date of first recurrence.

Rectal Cancer: Tumours within 15cm from the anal Verge

Recto-sigmoid Cancer: Tumour between 16 and 20 cm from the anal Verge.

Low tie was defined as ligation of the IMA distal to the take-off of Left Colic artery (LCA).

Clinical leak was defined as the presence of intestinal content in pelvic drain or wound; or Systemic Inflammatory Response Syndrome (SIRS) with either contrast extravasation on imaging or radiologic evidence of pelvic collection requiring percutaneous drainage / laparotomy (with or without diverting stoma / Hartmann's procedure).

Neoadjuvant Chemoradiotherapy (NACRT) protocol: All patients with mid and lower rectal T3 and higher stage, mesocolic nodules and/or lymphadenopathy on CECT/MRI or restricted mobility on rectal examination were subjected to NACRT. 5-Fluorouracil (FU) infusional / capecitabine based radiosensitizer dose with long course 5040cGy in 28 fractions was the protocol followed for NACRT. Rectal tumours above peritoneal reflection and rectosigmoid tumours were taken up for upfront surgery.

Mechanical bowel preparation was not used in any of the patients. The Department protocol being followed is to keep the patient on low residue diet for three days prior to surgery. Low residue diet schedule was defined as semisolid diet without leafy vegetables or coarse grains.

Objectives

The primary objective was to assess the 3-year Disease Free Survival (DFS) following Low Tie in Rectal Cancer surgery. The secondary objectives were to evaluate the Lymph Node (LN) yield in histopathology specimens

and the clinical anastomotic leak rates following low tie without mechanical bowel preparation.

Statistical Analysis

The results were analysed using Statistical Package for Social Sciences (SPSS) version 16.0. Data are expressed in its frequency and percentage. Quantitative variables were summarized as mean and standard deviation; and qualitative variables as proportions. Three-year Disease-free Survival and overall median survival rates among rectal cancer patients were assessed using Kaplan–Meier survival analysis. For all statistical evaluations, a two-tailed probability of value, <0.05 was considered significant.

Ethical Considerations

It was ensured that participants were fully informed and gave their written consent to participate in the study. Institutional ethics committee clearance was obtained before starting the study. No expenses were incurred from the participants.

Results

There were 254 patients during the study period, of which 53 patients were lost to follow up and 29 patients expired while on follow up due to other causes (14-Cardiac cause, 6-chemotherapy associated toxicity, 5-Renal co-morbidities and 4-unknown cause). The remaining 172 patients were included for analysis (**Figure 1**).

In this study, 131 (76.2%) patients were more than 50 years. Pathologic complete response was seen in 5/82 (6.1%). The median LN yield in those patients who underwent upfront surgery and those following NACRT was 14 (8-24) and 5 (0-20) respectively (**Table 1)**.

Open surgery was done in 140 (81.4%) patients and Laparoscopic surgery in 32 (18.6%). Though we started doing Laparoscopic Colorectal resections from 2010, as the numbers were small compared to open surgeries no comparison between open and laparoscopic resection was done. In 5 (2.9%) patients Hartmann procedure was done. In two patients it was done due to

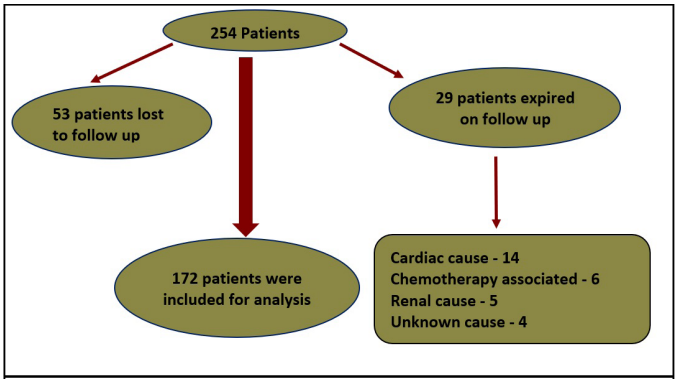

Figure 1: Inclusion algorithm.

failure of stapling device with wide defect at anastomosis and the remaining were done in obstructing tumours. There was no anastomosis in 51 (29.7%) patients (APR-46 and Hartmann procedure -5).

In the remaining 121 (70.3%) patients (LAR- 61, AR-54, and uLAR-6) in whom anastomosis was done, 48 (39.7%) patients had proximal defunctioning stoma. In these 121 (70.3%) patients who underwent resection with anastomosis, 6/121 (4.9%) patients had clinical leak. The surgery performed in these patients were LAR-3, AR-2 and uLAR-1. Proximal defunctioning stoma was there in three patients and the anastomotic leak in these patients were managed conservatively. Among the remaining three patients, two underwent relaparotomy, lavage and proximal stoma; and the other patient underwent relaparotomy, lavage and Hartmann procedure. The median post-operative stay in these patients was 22.5 (SD-8.96) days. Over a median follow up of 61.5 months; two patients in the leak group had recurrence out of which one patient expired due to recurrence.

In this study, six patients required relaparotomy; three patients for anastomotic leak and the other three patients for post-operative adhesive obstruction (Clavein-Dindo score-3B). Overall the median hospital stay in the study was 11days (mean=11.92 +/- 3.77).

Recurrence and Survival

The median follow-up of the patients was 61 months (8-117 months). The mean DFS was 81.6 months [standard error (SE): 3.2; 95% Confidence Interval (CI): 75.35-87.91]. The mean OS was 90.7months (SE:2.78, 95%

Table 1: Demographic characteristics.

Variables	n (%) (total=172)
Gender	
Male	93 (54.07%)
Females	79 (45.93%)
Age (years)	
Median, Range	58.5 (32-85)
Primary site of tumour	
Rectum (up to 15cm from anal verge)	149 (86.6%)
Rectosigmoid (16-20 cm from anal verge)	23 (13.4%)
Distance from anal verge for Rectal Tumours (Mean, Range, SD)	7.64, 0-15, 4.3
Distance from anal verge for Sigmoid Tumours (Mean, Range, SD)	19.1, 16-20, 1.58
Pre-operative tumour differentiation	
Well differentiated	102 (59.3%)
Moderately differentiated	66 (38.4%)
Poorly differentiated	4 (2.3%)
Carcinoembryonic antigen (CEA) Levels (ng/ml) (Median, range)	
Pre NACRT/ Pre-Operative	3.8 (0.2-260)
Post NACRT	2.97 (0.5-20.2)
Rectal cancer patients who received NACRT	82/149 (47.7%)
Upfront surgery	90 (52.3%)
cTNM stage	
Stage I	19 (11.1%)
Stage II	54 (31.4%)
Stage III	99 (57.5%)
Median interval from the completion of NACRT to surgery, weeks (Range)	8 (4-23)
Achievement of Pathological complete response (PCR) after NACRT	5/82 (6.1%)
Surgery performed	
Low Anterior Resection (LAR)	61 (35.5%)
Anterior Resection (AR)	54 (31.4%)
Abdomino-perineal Resection (APR)	46 (26.7%)
Ultra-Low Anterior Resection (uLAR)	6 (3.5%)
Hartmann Procedure (HP)	5 (2.9%)
Open procedure	140 (81.4%)
Laparoscopic procedure	32 (18.6%)
Technique of anastomosis	
Rectal cancer resections	Double stapled anastomosis
Rectosigmoid resections	End to end hand sewn anastomosis-15 Double stapled anastomosis-8
Resection and anastomosis Double stapled anastomosis Hand sewn anastomosis	121 106 15
No anastomosis (APR/Hartmann procedure)	51
Proximal diversion stoma Loop Ileostomy Transverse loop Colostomy	48 37 11
Anastomosis without diversion stoma	73
Clinical leak rate	6/121 (4.9%)
LN yield, Median (range) NACRT patients Upfront surgery patients	 5 (0-20) 14 (8-24)
Median duration of Laparoscopic surgery (minutes)	380
Median duration of open surgery (minutes)	210
Drain removal (median day)	6 (3-21)
Urinary bladder catheter removal (median day)	6 (1-20)
Median hospital stay (days)	11 (6-39)
Clavein- Dindo score	
Uneventful post-operative period	150 (87.2%)
Score 1	6 (3.5%)
Score 2	5 (2.9%)
Score 3	9 (5.2%) [3A:3, 3B-6]
Score 4	2 (1.2%)
30-day mortality (Clavein- Dindo score 5) (*excluded from study)	2 (cardiac cause)

CI 85.2 – 96.1). The 3-year DFS and the 3-year OS was 76.9% and 83.5% respectively (**Figure 2 and 3**). In a subset of 69 patients who had at least 60 months follow-up, 5-year DFS and 5-year OS was 73.9% and 79.7% respectively. On comparing the DFS between rectum and rectosigmoid, the mean DFS was 81.6months (SE: 3.45, 95% CI: 74.9-88.4) and 71.8months (SE: 6.65, 95% CI: 58.8-84.9) respectively for rectum and rectosigmoid cancers (**Figure 4**). There was no significant difference in DFS between the two sites (p=0.947). On subgroup analysis, the stage of the tumour and the LN positivity had significant impact on DFS and OS; p= 0.006 and p <0.001 respectively (**Table 2 and 3**). However, there was no statistically significant impact of the number of positive LNs on DFS (0.931) and OS (p=0.783) (**Figure 5-10**), (**Table 2 and 3**).

Analysis of Recurrence

The Loco-regional recurrence (LRR) was seen in 11 (6.3%) patients. Distant failure was more common than locoregional recurrence with liver being the most common site of recurrence. Lung only metastasis was least common and seen in 2 (4.4%) patient (**Table 4**).

Discussion

Miles and Moynihan respectively proposed low tie and high tie techniques for rectal cancer surgery around the same time, in 1908[3,4]. High tie has the presumed advantage of easily creating mesenteric windows in laparoscopy, gain in length of the proximal anastomotic colonic limb and hence the resultant tension free anastomosis, as well as, clearance of apical LN[5-12]. However, the incidence of metastatic LNs at the origin of IMA has

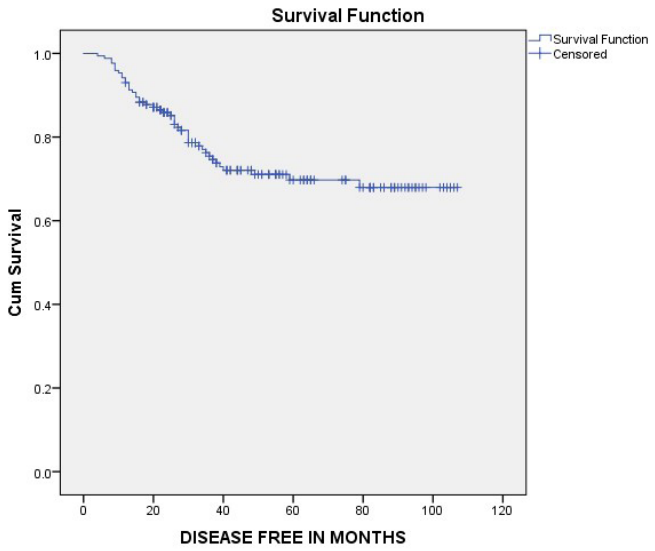

Figure 2: Kaplan Meier analysis of DFS as 81.6months (SE: 3.2, 95% CI: 75.4-87.9)

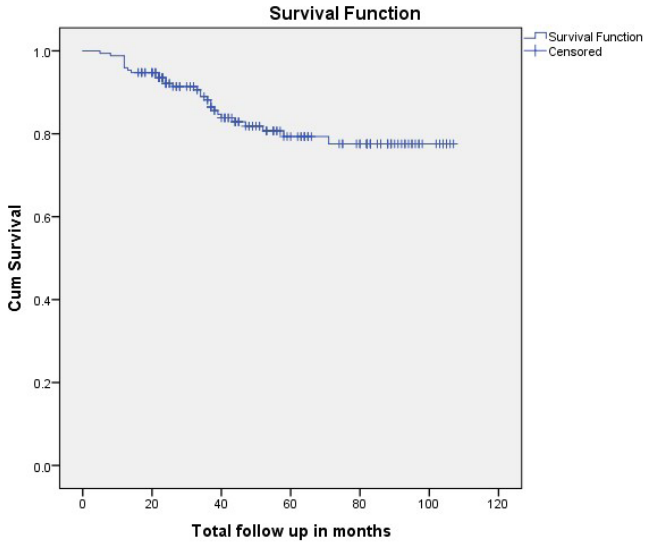

Figure 3: Kaplan Meier analysis of OS as 90.7months (SE: 2.78, 95% CI: 85.2-96.1)

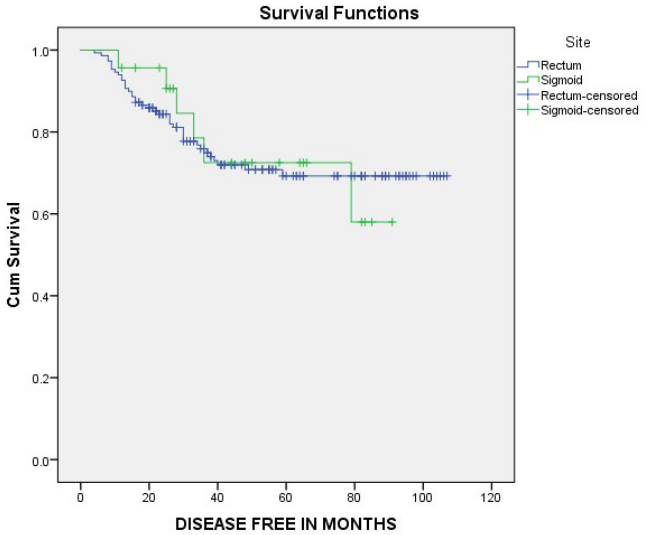

Figure 4: Kaplan Meier analysis of DFS based on the site as Rectum vs Sigmoid (DFS:81.6 vs 71.8 months); the mean DFS was less for sigmoid cancers however, there was no significant difference between the two (0.947).

Table 2: Disease Free Survival (DFS) among various variables.

	Variables	Total no. (n)	Recurrence	DFS(%)	DFS (mean, SE, (95% CI)
Site	Rectum	149	39	73.8	81.6, 3.45, 74.8 - 88.4
	Sigmoid	23	6	73.9	71.8, 6.6, 58.8 - 84.9
Stage	Stage I	19	1	94.7	99.9,4.97, 90.2 – 109.6
	Stage II	54	9	83.3	88.9, 4.55, 79.9 – 97.8
	Stage III	99	35	73.8	73.1, 4.53, 64.2 – 81.9
Leak (n=121)	Yes	6	2	66.7	81.4, 11.9, 57.9 – 104.9
	No	115	26	77.4	84.7, 3.81, 77.2 – 92.1
LN	Positive	51	24	52.9	61.6, 6.15, 49.6 – 73.7
	Negative	121	21	82.6	89.9, 3.4, 83.3 – 96.4
Blood transfusion	Yes	18	5	72.2	84.6, 8.6, 67.7 – 101.5
	No	154	40	74	80.7, 3.20, 74 – 87.3

Table 3: Overall Survival (OS) among various variables.

	Variables	Total no. (n)	Death	OS (%)	OS (mean, SE, (95% CI)
Site	Rectum	149	26	82.6	89.6, 3.05, 83.6 – 95.6
	Sigmoid	23	2	91.3	84, 4.6, 74.9 – 93
Stage	Stage I	19	1	94.7	99.5, 5.34, 88.9 – 109.9
	Stage II	54	3	94.4	98.8, 2.88, 93.2 – 104.5
	Stage III	99	24	75.8	82.7, 4.28, 74.6 – 90.9
Leak (n=121)	Yes	6	1	83.3	94.4, 9.4, 75.8 – 112.9
	No	115	14	87.8	94.2, 3.15, 88.1 – 100.4
LN	Positive	51	19	62.7	70.8, 5.8, 59.2 – 82.3
	Negative	121	9	92.6	99.4, 2.4, 94.7 – 104.1
Blood transfusion	Yes	18	5	72.2	85.9, 7.9, 70.3 – 101.6
	No	154	23	85.1	90.9, 2.82, 85.3 – 96.5

been reported to be relatively low in several studies, ranging from 0.3 to 8.6%[1,2]. The disadvantages of high tie are the possible impaired perfusion[13-15] and impaired innervation of the proximal anastomotic limb, thereby resulting in a probable higher chance of anastomotic leak rate and bowel dysfunction respectively[16]. Whereas in low tie, the advantages are perfusion to the anastomotic limb is attenuated by left colic artery (LCA), there is less invasive dissection, lesser need for splenic flexure mobilisation and less chance of hypogastric nerve injury. The reported disadvantages are possibility of tension at anastomotic site and lack of apical LN clearance[12-14,17-19] (**Table 5 and 6**).

Several studies have reported that high IMA ligation did not improve the 5-year survival rates of patients with rectosigmoid or rectal cancers as compared to low IMA ligation [17-19,21]. In this study the 3-year DFS and the 3-year OS was 76.9% and 83.5% respectively. In a subset of 69 patients who had at least 60 months follow-up, 5-year DFS and 5-year OS was 73.9% and 79.7% respectively. Various studies have reported 5-year OS of high tie ranging from 50-73.4%[14,22]. In the RCT by Matsuda *et al*, the 5-year DFS and OS of high ligation was 74.9 and 79.3%, respectively; the 5-year DFS and OS of low ligation was 80.7 and 83.0%, respectively. Hence, there was no statistical difference in DFS and OS[23].

The median LN yield in our study of patients who underwent upfront surgery and surgery following NACRT was 14 (8-24) and 5 (0-20) respectively. There is significant decrease in the LN yield following NACRT[24-27]. This has been reported in various other studies as well and the median LN yield after NACRT ranges from 4-14[24,28]. According to study by Won-Suk Lee *et al* the absence of recovered LN in resected specimens

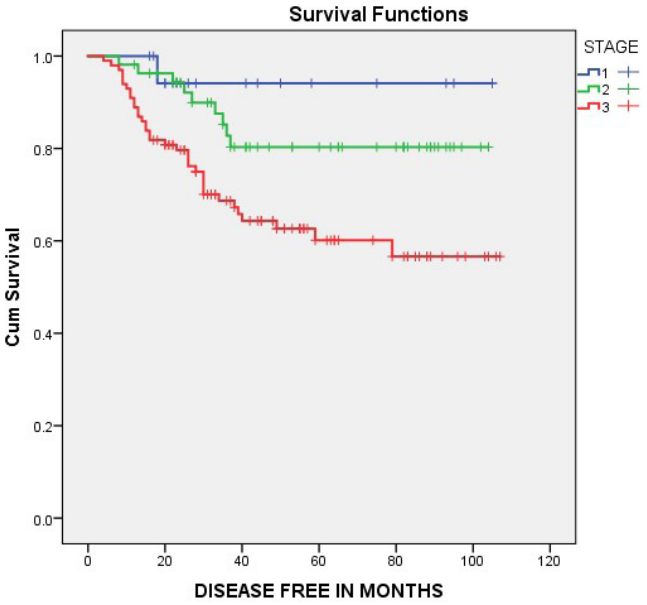

Figure 5: Kaplan Meier analysis showing the DFS was significantly low for Stage III cancers. (Stage I vs Stage II vs Stage III: 99.9 vs 88.9 vs 73.1, p = 0.006)

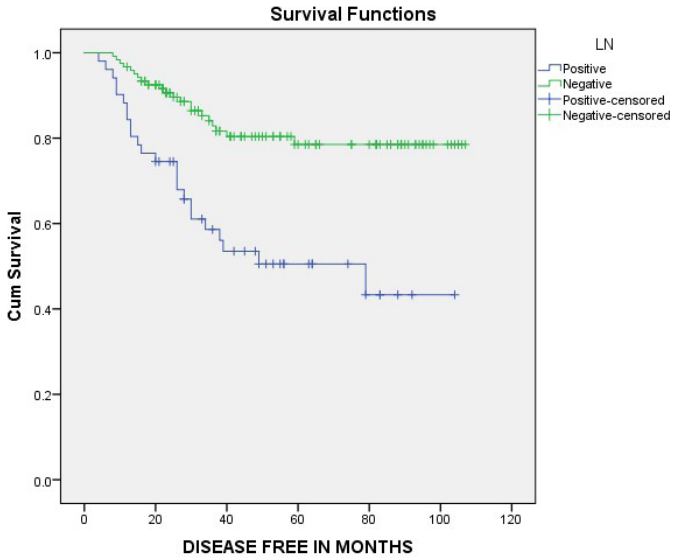

Figure 7: Kaplan Meier analysis showing the DFS was significantly low for LN positive cancers. (LN positive vs LN negative: 61.6 vs 89.9, p = <0.001)

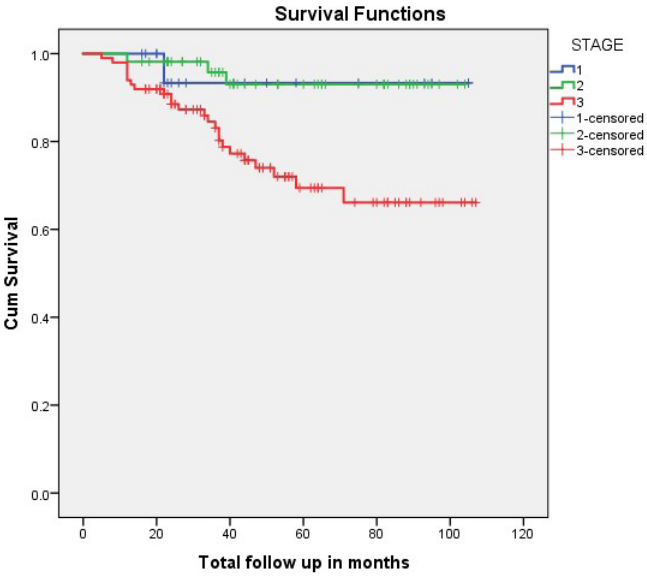

Figure 6: Kaplan Meier analysis showing the OS was significantly low for Stage III cancers. (Stage I vs Stage II vs Stage III: 99.5 vs 98.8 vs 82.7, p = 0.005)

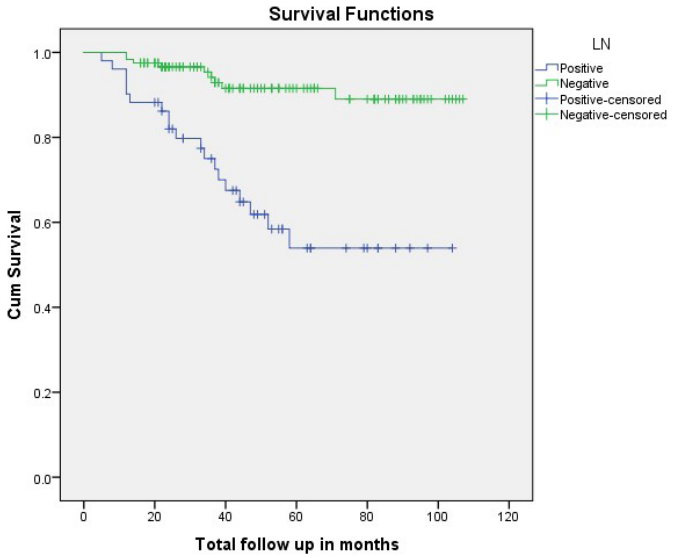

Figure 8: Kaplan Meier analysis showing the OS was significantly low for LN positive cancers. (LN positive vs LN negative: 70.8 vs 99.4, p = <0.001)

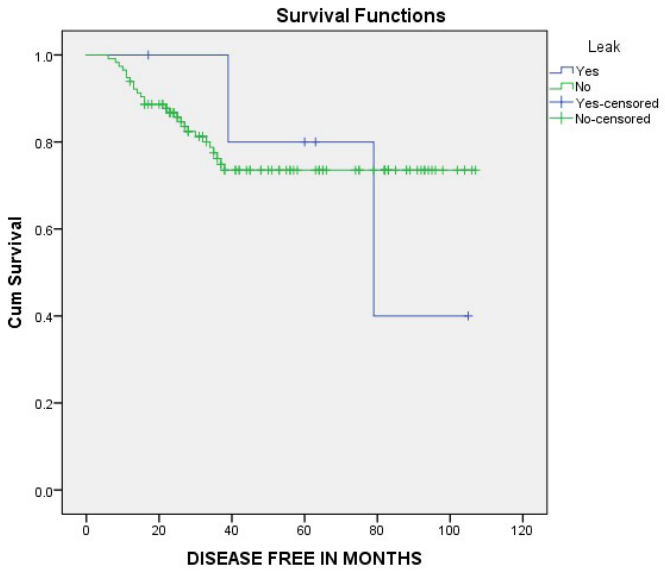

Figure 9: There was no statistically significant difference in DFS among those patients who had anastomotic leak in post-operative period. (Leak vs No leak: 81.4 vs 84.7, p = 0.817)

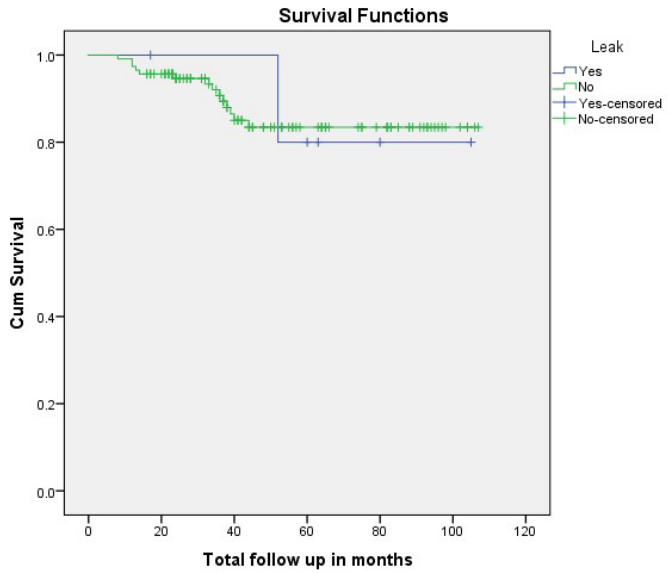

Figure 10: There was no statistically significant difference in OS among those patients who had anastomotic leak in post-operative period. (Leak vs No leak: 94.4 vs 94.2, p = 0.987)

Table 4: Sites of recurrences.

Variables	n=45
Locoregional recurrence (LRR)	11 (24.4%)
Liver only	16 (35.6%)
LRR + Liver	4 (8.9%)
Liver + Lung	3 (6.7%)
Lung only	2 (4.4%)
Widespread Metastasis	9 (20%)

Table 5: Pros and Cons of Low Tie.

Pros	
1.	Vascular compromise of the proximal anastomotic limb is less as the vasculature is based on both middle colic artery (MCA) and LCA
2.	Routine splenic flexure mobilisation not required
3.	Less dissection and less operating time
4.	Less chance of hypogastric nerve injury
Cons	
1.	Tension at the anastomotic line and reach of proximal Limb may be an issue but with judicial IMV ligation /splenic flexure mobilisation /cutting descending branch of LCA, the same may be solved
2.	Apical LN sampling not done routinely (may be done separately- Dunphy's modification) [20]

Table 6: Pros and Cons of High Tie.

Pros	
1.	For Ultra low resections, high tie may be helpful for Coloanal / J pouch anastomosis by reducing tension of mesocolic vasculature and gain of length of proximal limb.
2.	Apical LN clearance (D3 Lymphadenectomy) is part of the procedure.
Cons	
1.	Descending colon ischemia is a possibility especially in elderly patients and those with atherosclerotic disease as the vascularisation is solely based on MCA and collaterals.
2.	More dissection and more operating time.
3.	Chance of injury to Hypogastric nerve is high.

Table 7: Comparison anastomotic leak rates with other study

Rolf Sauer *et al* (German trial)[22]	11%
M. Rutegard *et al*[32]	High tie-9.9% Low tie-9.8%
Jun-Zhong Lin *et al*[33]	4.9%
Present study	4.9%

after neoadjuvant chemoradiation was observed in 7.6% of specimens; and the absence of LN following NACRT should not be regarded as a risk factor for poor survival or as a sign of less radical surgery[29]. The NACRT has a significant effect on the adequacy of lymph node sampling and a negative impact on the lymph nodes retrieved. This negative effect was more prominent with the long term rather than the short-term NACRT[30]. The LN yield and status following NACRT were not significant predictors of overall survival[31].

The anastomotic leak rate in the present study without mechanical bowel preparation was 4.9%. The reported leak rates after anterior resection with TME ranges from 3-27%[32] (**Table 7**). Low tie rectal cancer surgery assumes significance in this era of Laparoscopic surgery where low tie without routine mobilisation of splenic flexure may decrease the operating time and make the procedure simpler yet oncologically adequate enough.

Conclusion

Low tie in rectal cancer surgery provides comparable 3-year and 5-year DFS and OS with that of high tie reported in literature. Adequate LN yield can be achieved in low tie rectal cancer surgery with a low clinical anastomotic leak rate (without mechanical bowel preparation) compared to that of other studies reported.

References

1. Pezim ME, Nicholls RJ. Survival after high or low ligation of the inferior mesenteric artery during curative surgery for rectal cancer. Ann Surg 1984;200:729–33.
2. Uehara K, Yamamoto S, Fujita S, Akasu T, Moriya Y. Impact of upward lymph node dissection on survival rates in advanced lower rectal carcinoma. Dig Surg 2007;24:375–81.
3. Miles WE. A method of performing abdominoperineal excision for carcinoma of the rectum and of the terminal portion of the pelvic colon. Lancet 1908; 2: 1812-3
4. Moynihan BG. The surgical treatment of cancer of the sigmoid flexure and rectum. Surg Gynecol Obstet 1908;463.
5. Zhou ZG, Hu M, Li Y, *et al*. Laparoscopic versus open total mesorectal excision with anal sphincter preservation for low rectal cancer. Surg Endosc 2004;18:1211–5.
6. Wexner SD. Invited editorial. Dis Colon Rectum 1998;41:987–9.Hartley JE, Mehigan BJ, Qureshi AE, Duthie GS, Lee PW,Monson JR. Total mesorectal excision: assessment of the laparoscopic approach. Dis Colon Rectum 2001;44:315–21.
7. Leroy J, Jamali F, Forbes L, *et al*. Laparoscopic total mesorectal excision (TME) for rectal cancer surgery: longterm outcomes. Surg Endosc 2004;18:281–9.
8. Morino M, Parini U, Giraudo G, Salval M, Brachet CR, Garrone C. Laparoscopic total mesorectal excision: a consecutive series of 100 patients. Ann Surg 2003;237:335–42.
9. Pikarsky AJ, Rosenthal R, Weiss EG, Wexner SD. Laparoscopic totalmesorectal excision. Surg Endosc 2002;16:558–62.
10. Guraya SY. Modern oncosurgical treatment strategies for synchronous liver metastases from colorectal cancer. Journal of Microscopy and Ultrastructure 2013; 1: 1-7.
11. Kang J, Hur H, Min BS, Kim NK, Lee KY. Prognostic impact of inferior mesenteric artery lymph node metastasis in colorectal cancer. Ann Surg oncol 2011; 18: 704-710.
12. Ikeda Y, Shimabukuro R, Saitsu H, Saku M, Maehara Y. Influence of prophylactic apical node dissection of the inferior mesenteric artery on prognosis of colorectal cancer. Hepatogastroenterology 2007; 54: 1985-1987.
13. Nano M, Dal Corso H, Ferronato M, Solej M, Hornung JP, Dei Poli M. Ligation of the inferior mesenteric artery in the surgery of rectal cancer: anatomical considerations. Dig Surg 2004; 21: 123-126.
14. Titu LV, Tweedle E, Rooney PS. High tie of the inferior mesenteric artery in curative surgery for left colonic and rectal cancers: a systematic review. Dig surg 2008; 25: 148-157.
15. Kendal WS. Lymph node-based prognostics: limitations with individualized cancer treatment. Am J Clin Oncol 2006; 29: 298-304.
16. Kang J, Hur H, Min BS, Kim NK, Lee KY. Prognostic impact of inferior mesenteric artery lymph node metastasis in colorectal cancer. Ann Surg oncol 2011; 18: 704-710.
17. Cirocchi R, Trastulli S, Farinella E, Desiderio J, Vettoretto N, Parisi A, *et al*. High tie versus low tie of the inferior mesenteric artery in colorectal cancer: a RCT is needed. Surg Oncol 2012; 21: e111-e123.
18. Surtees P, Ritchie JK, Phillips RK. High versus low ligation of the inferior mesenteric artery in rectal cancer. Br J Surg 1990; 77: 618-621.
19. Hida J, Yasutomi M, Maruyama T, Fujimoto K, Nakajima A, Uchida T, *et al*. Indication for using high ligation of the inferior mesenteric artery in rectal cancer surgery.

Examination of nodal metastases by the clearing method. Dis Colon Rectum 1998; 41: 984-987.

20. Dunphy JE, Pikula JV: Sphincter-saving procedures: the anterior resection. In Diseases of the Colon and Anorectum. Volume 1. Edited by: Turell R. W. B.Saunders; 1959:491-502
21. Lee AW. Review of mixed treatment comparisons in published systematic reviews shows marked increase since 2009. J Clin Epidemiol 2014; 67: 138-143.
22. Rolf Sauer, M.D., Heinz Becker, M.D *et al* Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer. N Engl J Med 2004;351:1731-40.
23. Matsuda K, Yokoyama S *et al* Oncological Outcomes following Rectal Cancer Surgery with High or Low Ligation of the Inferior Mesenteric Artery. 2017 Sep Gastrointest Tumors, 2017 Jul 5; 4(1-2):45-52
24. Rinkus KM, Russell GB, Levine EA. Prognostic significance of nodal disease following preoperative radiation for rectal adenocarcinoma. Am Surg 2002; 68: 482-487
25. Stefano Scabini, Valter Ferrando. Number of lymph nodes after neoadjuvant therapy for rectal cancer: How many are needed. World J Gastrointest Surg 2012 February 27; 4(2): 32-35
26. Monirath Hav *et al*. Pathologic Assessment of Rectal Carcinoma after Neoadjuvant Radio(chemo)therapy: Prognostic Implications. BioMed Research International Volume 2015, Article ID 574540, 11 pages
27. James R McDonald, Andrew G Renehan *et al*. Lymph node harvest in colon and rectal cancer: Current Considerations. World Journal of Gastrointestinal Surgery.2012 January 27; 4(1): 9-19
28. Sobin LH. TNM classification: clarification of number of regional lymph nodes for pN0. Br J Cancer 2001; 85: 780
29. Won-Suk Lee, Seok Ho Lee *et al* What does absence of lymph node in resected specimen mean after neoadjuvant chemoradiation for rectal cancer Radiation Oncology 2013, 8:202
30. Somaia Elsheikh and Abed Zaitoun M. Factors Influence Lymph Node Retrieval after Resection for Rectal Cancer. Journal of Adenocarcinoma. 2016, 1:2.13.
31. Sherif R.Z. Abdel-Misih, Lai Wei *et al*. Neoadjuvant Therapy for Rectal Cancer Affects Lymph Node Yield and Status Without Clear Implications on Outcome: The Case for Eliminating a Metric and Utilizing Preoperative Staging to Guide Therapy. Journal of National Comprehensive Cancer Network. 2016 December; 14(12): 1528–1534
32. M. Rutegard, O. Hemmingsson, *et al*. High tie in anterior resection for rectal cancer confers no increased risk of anastomotic leakage. British Journal of Surgery 2012; 99: 127–132.
33. Lin JZ, Peng JH, Qdaisat A, *et al*. Preoperative chemoradiotherapy creates an opportunity to perform sphincter preserving resection for low-lying locally advanced rectal cancer based on an oncologic outcome study. Oncotarget. 2016;7(35):57317-57326.