Triple Test—a Predictor of Anastomotic Integrity in Patients Undergoing Low Anterior Resection After Neoadjuvant Chemoradiotherapy

Madhu Muralee¹ · Nithish R. Acharya¹ · Wagh Mira Sudham¹ ·
Arun Peter Mathew¹ · Kurian Cherian¹ · K. Chandramohan¹ · Paul Augustine¹ ·
M. Iqbal Ahamed¹

Received: 4 August 2016 / Accepted: 27 June 2017 / Published online: 11 July 2017
© Indian Association of Surgical Oncology 2017

Abstract Anastomotic leak after low anterior resection for rectal cancer is a dreaded complication. Diversion stoma helps tiding over this crisis and it is routinely practised in most centres, especially in post chemoradiotherapy setting. But a diversion stoma has got its own problems. In this study, we attempt to use the triple test as a predictor of anastomotic integrity and thereby avoid a diverting stoma, and patients undergoing low anterior resection after neoadjuvant chemoradiotherapy were spared the trouble of a diverting stoma if the on table triple test was negative. Two hundred such consecutive patients were prospectively followed up in the postoperative period. The incidence of anastomotic leak and the factors predicting the same were analysed in this group of patients. The incidence of anastomotic leak in our study was 7%, which is much less when compared to published literature. The triple test was a reliable predictor of the integrity of anastomosis and if the test is negative, a diverting stoma can be avoided. Age more than 60 years and end-to-end anastomosis were found to be associated with increased incidence of leak, and patients with a negative triple test need not routinely undergo diversion stoma after a low anterior resection even in post chemoradiotherapy setting.

Keywords Triple test · Low anterior resection · Diversion stoma · Neoadjuvant chemoradiation · Anastomotic leak

Introduction

The treatment for locally advanced rectal cancers has evolved over the years. Neoadjuvant chemoradiotherapy (NACTRT) followed by surgery has become the standard of care. Better understanding of the mesorectal anatomy has led to the acceptance of total mesorectal excision (TME) as the procedure of choice in rectal cancers [1–3]. Better surgical techniques and the advent of staplers have contributed to a steady increase in the number of patients undergoing sphincter-preserving surgeries. But one of the most dreaded complications associated with a sphincter-preserving surgery is the anastomotic leak. Diverting stoma after a low or an ultra-low anterior resection has become the norm across centres, especially in patients undergoing surgeries after NACTRT. But diversion stomas have their own share of disadvantages. The patient has to live with the stoma and its functional and psychological effects till he/she completes the adjuvant treatment. Furthermore, he/she has to undergo another surgery to revert the stoma and there are complications associated with the reversal surgery as well. There are instances of delayed reversal of stoma [4]. Avoiding a diversion stoma would spare the patients of all the abovementioned effects.

In this study, we tried to avoid a diversion stoma in a select group of patients based on the outcome of a combination of tests—called the triple test. The results of this test were used as a predictor of the integrity of the anastomosis, and a stoma was avoided. The incidence of anastomotic leak and its predictors were also studied.

Materials and Methods

The study was conducted in the Department of Surgical Oncology at Regional Cancer Centre (RCC), Trivandrum,

✉ Madhu Muralee
madhumuralee@gmail.com

¹ Division of Surgical Oncology, Regional Cancer Centre, Trivandrum-11, Kerala, India

between August, 2009, and August, 2014. The patients at presentation were evaluated by full colonoscopy and biopsy of the suspicious lesion (or a slide review of the biopsy if already done outside). The disease status was evaluated by pelvic imaging (MRI/CT—as per the discretion of the operating surgeon) and a CT abdomen and thorax. Only locally advanced cases (T3/T4, N+) were included in the study. All of these cases received neoadjuvant chemoradiation (50.4 Gy in 25 fractions) along with chemotherapy (capecitabine). They were re-evaluated after NACTRT with pelvic and abdominal imaging and taken up for surgery after 6–8 weeks. All patients underwent anterior resection and low anterior resection. A standard operating procedure was followed for all patients. All patients included in the study had undergone open TME. Patients undergoing laparoscopic surgery were not included in the study because as a standard protocol, these patients invariably undergo diversion stoma. Circular stapler was used for anastomosis for all cases. The decision regarding splenic flexure mobilisation and high ligation of inferior mesenteric artery pedicle was left to the operating team and the decision was taken based on the redundancy of the sigmoid loop. Following the anastomosis, a triple test was done for all patients.

Triple test, as the name suggests, is a series of three tests which include the classical air leak test, inspection for completeness of doughnuts, and a digital rectal examination for the integrity of the anastomotic ring. The air leak test involved placement of non-crushing bowel clamps around 10 cm proximal to the anastomosis, followed by insufflation of air by an ‘asepto’ syringe introduced per rectally after filling the pelvis with sterile normal saline. A leak is indicated by air bubbling through the saline.

In cases where all the three tests were negative (no bubbling on air insufflation, intact doughnuts, and intact anastomosis on digital rectal examination), no faecal diversion was done and these patients were followed up prospectively to look for the development of anastomotic leak. Therefore, post NACTRT rectal cancer patients undergoing anterior or a low anterior resection and not undergoing diversion stoma (by virtue of a negative triple test) were included in the study. These patients were then followed up in the postoperative period for anastomotic leak.

The primary end point was development of anastomotic leak. Anastomotic leak was defined in the study as one that required surgical intervention. The detection of an anastomotic leak was essentially clinical and in some cases was supplemented by radiological investigations, namely abdominal and pelvic ultrasound and CT scan.

The study was cleared by the institutional review board.

Statistical Analysis

The aim of our study as mentioned earlier was to determine the rate of anastomotic leak. Our study also involved testing

various patients, tumours, and surgery-related factors for significance, in relation to anastomotic leak. The chi-square test and the Fisher exact test were used for the same. A *p* value of less than 0.05 was considered as significant.

Results

A total of 200 patients who satisfied the inclusion criteria were analysed for the purpose of this study. The profile of the patients is given in Table 1. The average age of patients included in our study was 58.4 years, with the age ranging from 27 to 76 years. The number of males was 103 and the number of females was 97. All the patients included in the study had locally advanced low rectal cancers and the stage distribution is as given in Table 1. The average distance of the tumour on digital rectal examination (DRE) from the anal verge (post CTRT) was 7.9 cm for patients undergoing low anterior resection and was 14.3 cm for patients undergoing anterior resection. Seventy-nine out of a total 200 patients were diabetic and 85 were hypertensive.

Fourteen patients (7%) in the study group had a significant anastomotic leak requiring surgical intervention. All these

Table 1 Patient characteristics

	Number	Percentage
Patient characteristics		
Age wise distribution		
Less than 60 years	132	66
More than 60 years	68	34
Sex wise distribution		
Male	103	51.5
Female	97	48.5
Comorbidities		
Diabetes mellitus	79	39.5
Hypertension	85	42.5
Tumour characteristics		
Stage at presentation		
T2N+	39	19.5
T3N0	67	33.5
T3N+	94	47
Distance from the anal verge		
<5 cm	78	39
5–8 cm	91	45.5
>8 cm	31	15.5
Surgical factors		
Type of anastomosis		
End-to-end	84	42
Side-to-end	116	58

patients were salvaged with a diversion stoma. There was no perioperative mortality in our study.

Incidence of anastomotic leak was correlated with various patients, tumours, and surgical characteristics using chi-square test and Fisher's exact test (Table 2).

Five (5/132) of the patients who developed anastomotic leak were less than 60 years of age and nine (9/68) patients were more than 60 years of age. The correlation between age and anastomotic leak was found to be significant, with age more than 60 being a risk factor (p value 0.03).

There were more number of leaks in females when compared to males (8.2 vs. 5.8%) but the correlation of sex as a factor for leak was not statistically significant (p value 0.5).

We also checked for comorbidities as a risk factor for leak in this group of patients. The number of diabetics included in the study was 79 and patient with known history of hypertension added up to 85. Four out of 79 diabetics and eight out of 85 known hypertensives had an anastomotic leak. The correlation of diabetes (p value 0.57) and hypertension (p value 0.4) were not significantly associated with anastomotic leak.

Two types of anastomosis were used in the study population—end-to-end anastomosis (EEA) and side-to-end anastomosis (SEA). One hundred sixteen patients underwent SEA and 84 patients underwent EEA. The leak rates were 3.4 and 12% for SEA and EEA, respectively. The correlation was significant (p value 0.04) indicating that side-to-end anastomosis has a better integrity than end-to-end anastomosis.

All patients having significant anastomotic leak underwent diversion (transverse colostomy or ileostomy was performed as per the operating surgeon's discretion). As mentioned earlier, there were no perioperative mortalities in the study group.

Table 2 Correlation tables

Variable	Leak rate	p value
Age		
<60 years (132)	5 (3.7%)	0.03
>60 years (68)	9 (13.2%)	
Gender		
Male (103)	6 (5.8%)	0.5
Female (97)	8 (8.2%)	
Diabetes mellitus		
Yes (79)	4 (5%)	0.57
No (131)	10 (7.6%)	
Hypertension		
Yes (85)	8 (9.4%)	0.4
No (115)	6 (5.2%)	
Type of anastomosis		
End-to-side (116)	4 (3.4%)	0.04
End-to-end (84)	10 (12%)	

Discussion

The role of a diverting stoma after an anterior resection is still controversial. The presence of a stoma does not decrease the risk for anastomotic leakage [5–7], and the major advantage of the temporary stoma has less dramatic presentation in case a leak occurs. Diversion stomas have their own disadvantages. The disadvantages of a stoma are related to the stoma itself, the stoma reversal, and possible re-surgeries after stoma reversal. The rate of re-operation is reported to be 7% by Poon et al. [8] and 6% by Hallbook et al. [9]. Half of elderly rectal cancer patients in the USA who undergo low anterior resection (LAR) with temporary stoma do not undergo stoma reversal by 18 months [4]. There is temporary alteration in bowel function, impacting on individuals' physical, social, and psychological health, significantly affecting their quality of life if left untreated [10]. One in three patients undergoing stoma closure developed an incisional hernia as well [11]. Our study has attempted to avoid a diverting stoma in post chemoradiation patients undergoing anterior resection and thereby we have tried to reduce the stoma-related complications. In the bargain, we have made sure that the leak rates are also kept at the lowest possible level by relying on a robust triple test.

The rate of anastomotic leak quoted in various international literatures varies. The rate of anastomotic leakage of any grade was 11% in the NACTRT group and 12% in the postoperative CRTT group in the landmark German Rectal Cancer Trial [12]. In a random analysis of 432 rectal cancer patients operated in Sweden from 1987 to 1995, anastomotic leak was seen in around 12% of patients. The rate of anastomotic leak was far greater in patients who had received preoperative radiation (31 vs. 9%) [13]. In our study, only 14 patients out of a total of 200 had a significant anastomotic leak. A 7% anastomotic leak rate is much below the quoted figures in the international literature. Only those patients who had a negative triple test were spared a diverting stoma. This may be the reason for the low leak rates seen in our study.

Doubt regarding the integrity of the anastomosis is the factor which pushes the operating surgeon to do a diversion stoma. But if the anastomotic integrity can be ascertained in an objective way, the surgeon may be inclined towards not doing a stoma. In our study, we have tried to use the predictive value of the triple test in ascertaining the integrity of the anastomosis. All those patients who had a negative triple test were spared a diverting stoma whereas those who had any of the component of the triple test positive were subjected for a diverting stoma. There are many published literatures stating the use of air leak test as an indicator of integrity of rectal anastomosis [14–16]. But there are no reports of the use of combination of the three tests (used in our study and mentioned above) for predicting anastomotic leaks. From our observation, the triple test seems to be a pretty good predictor of the anastomotic integrity because the incidence of anastomotic leak in those patients in whom the

triple test was negative was only 7%, which is much lower than what is reported in the literature. Based on our observation, we would suggest that diverting stoma can be avoided even in post chemoradiation patients in whom the triple test is negative.

Gender as a factor for anastomotic leakage has also been studied. Rullier et al. [17], Poon et al. [8], and Law et al. [18] have found that male gender is a risk factor. In a study by Matthiessen et al. [19], leakage rates of 17% in males and 8% in women have been reported. Male pelvis generally is deeper and more narrow, consequently making the operation technically more difficult. Rullier et al. [17] and Poon et al. [8] have proposed selective defunctioning in male patients. In our study, the leak rate in males was marginally lower as compared to females (6 vs. 8%) and the correlation was not significant.

Preoperative radiation is considered a factor responsible for anastomotic leak. In a study by Matthiessen et al. [19], the leak rate was 31% in post radiotherapy patients. In our study, all the patients were post NACTRT and the leak rate was 7%.

The type of anastomosis (end-to-end vs. side-to-end) is also an important factor determining anastomotic leak. In a study by Brisinda et al. [20], anastomotic leakage after end-to-end anastomosis was 29.2%, while after side-to-end anastomosis was 5% (p 0.005). This study included T1 and T2 rectal cancer patients. In our study also, we found that there is a significant difference in the incidence of anastomotic leak rates between SEA and EEA, with SEA having lesser leak rates. The reason may be the vascularity of the anastomotic end. The side of the bowel has a better vascularity than the end of the bowel.

Several techniques have been employed to test the integrity of anastomosis. Most surgeons rely on the instillation of air via the colonoscope to test the anastomosis. Data supporting the use of colonoscopy as a method of ensuring anastomotic integrity is, at best, inconclusive [21].

Newer techniques are being used to assess anastomotic integrity. It has been hypothesised that assessment of microperfusion at the time of the creation of an anastomosis may influence the rate of anastomotic leak. Jaffari et al. in their PILLAR II study have demonstrated the utility and feasibility of intraoperative perfusion assessment using near-infrared (NIR) indocyanine green (ICG)-induced fluorescence angiography at the time of anastomosis creation. PINPOINT Endoscopic Fluorescence Imaging System was used to assess perfusion of colonic tissue. They concluded that PINPOINT is a safe and feasible tool for intraoperative assessment of tissue perfusion during colorectal resection [22]. Hellan et al. reported on the use of the firefly technique for determination of transection location in robotic left-sided colorectal procedures. Firefly technique involves fluorescence imaging for the assessment of perfusion of transected bowel ends which in turn was assessed by intravenous injection of indocyanine green. They concluded that additional information is achieved by this technique and stressed on the need for further studies with larger patient cohorts to actually validate its use [23].

Conclusion

The rate of anastomotic leakage was 7% in our study, which was far less than the rates quoted in the international literature. Based on the findings of our study, we recommend that diversion stoma may be avoided in post CTRT low rectal cancer patients undergoing LAR in whom the intraoperative triple test is negative in high-volume centres with experienced hands. We would also like to recommend that the “triple test” serves as a good predictor of anastomotic integrity. Faecal diversion can be done as a reserve for patients who undergo surgery for rectal cancer after NACTRT in those patients in whom any of the component of the triple test is positive and also in patients who fall in the high-risk group, who, according to the findings of our study, are patients undergoing end-to-end anastomosis and with age more than 60 years.

Compliance with Ethical Standards The study was cleared by the institutional review board.

References

1. Heald RJ, Husband EM, Ryall RD (1982) The mesorectum in rectal cancer surgery—the clue to pelvic recurrence? *Br J Surg* 69:613–616
2. Quirke P, Durdey P, Dixon MF, Williams NS (1986) Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumor spread and surgical excision. *Lancet* 2(8514):996–999
3. Scott N, Jackson P, al Jaber T et al (1995) Total mesorectal excision and local recurrence: a study of tumour spread in the mesorectum distal to rectal cancer. *Br J Surg* 82:1031–1033
4. Dodgion CM, Neville BA, Lipsitz SR, et al (2014) Hospital variation in sphincter preservation for elderly rectal cancer patients. *J Surg Res* 191(1):161–168. doi:10.1016/j.jss.2014.03.047
5. Fielding LP, Stewart-Brown S, Hittinger R, Blesovsky L (1984) Covering stoma for elective anterior resection of the rectum: an outmoded operation? *Am J Surg* 147:524–530
6. Mealy K, Burke P, Hyland J (1992) Anterior resection without a defunctioning colostomy: questions of safety. *Br J Surg* 79:305–307
7. Machado M, Hallbook O, Goldman S, Nystrom PO, Jarhult J, Sjudahl R (2002) Defunctioning stoma in low anterior resection with colonic pouch for rectal cancer: a comparison between two hospitals with a different policy. *Dis Colon Rectum* 45:940–945
8. Poon R, Chu K-W, Ho J, Chan C-W, Law W-L, Wong J (1999) Prospective evaluation of selective defunctioning stoma for low anterior resection with total mesorectal excision. *World J Surg* 23: 463–467
9. Hallbook O, Matthiessen P, Leinskold T, Nystrom PO, Sjudahl R (2002) Safety of the temporary loop ileostomy. *Color Dis* 4:361–364
10. Gooszen AW, Geelkerken RH, Hermans J et al (2000) *Dis Colon Rectum* 43:650. doi:10.1007/BF02235581
11. Bhangu A et al. (2012) The surgeon. 10(6): 321–325
12. Sauer R, Becker H, Hohenberger W (2004) Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 351:1731–40
13. Swedish Rectal Cancer Trial (1997) Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med* 336: 980–987

14. Ricciardi R, Roberts PL, Marcello PW, Hall JF, Read TE, Schoetz DJ (2009) Anastomotic leak testing after colorectal resection: what are the data? *Arch Surg* 144:407–411
15. Wu Z, van de Haar RCJ, Sparreboom CL et al (2016) *Int J Colorectal Dis* 31:1409. doi:[10.1007/s00384-016-2616-4](https://doi.org/10.1007/s00384-016-2616-4)
16. Kwon S, Morris A, Billingham R, Frankhouse J, Horvath K, Johnson M, McNevin S, Simons A, Symons R, Steele S, Thirlby R, Whiteford M, Flum DR, Surgical Care and Outcomes Assessment Program (SCOAP) Collaborative FT (2012) Routine leak testing in colorectal surgery in the surgical care and outcomes assessment program. *Arch Surg* 147(4):345–351. doi:[10.1001/archsurg.2012.12](https://doi.org/10.1001/archsurg.2012.12)
17. Rullier E, Laurent C, Garrelon L, Michel P, Saric J, Parneix M (1998 March) Risk factors for anastomotic leakage after resection of rectal cancer. *Br J Surg* 85:355–358
18. Law W-L, Chu K-W, Ho J, Chan C-W (2000) Risk factors for anastomotic leakage after low anterior resection with total mesorectal excision. *Am J Surg* 179:92–96
19. Matthiessen P, Hallbook O, Andersson M, Rutegard J, Sjødahl R (2004) Risk factors for anastomotic leakage after anterior resection of the rectum. *Colorectal Disease* 6(6):462–469. doi:[10.1111/j.1463-1318.2004.00657.x](https://doi.org/10.1111/j.1463-1318.2004.00657.x)
20. Brisinda G, Vanella S, Cadeddu F, Civello IM, Brandara F, Nigro C et al (2009) End-to-end versus end-to-side stapled anastomosis after anterior resection for rectal cancer. *J Surg Oncol* 99:75–79
21. Longo WE (2009) Anastomotic leak testing after colorectal resection—invited critique. *Arch Surg* 144(5):411–412
22. Jafari MD et al (2015) Perfusion assessment in laparoscopic left-sided/anterior resection (PILLAR II): a multi-institutional study. *J Am Coll Surg* 220:82–92
23. Hellan M et al. The influence of fluorescence imaging on the location of bowel transection during robotic left-sided colorectal surgery. *Surg Endosc* 28(5):1695–1702