Paradigm Shift in the Management of Locally Advanced Rectal Cancer: Role of Preoperative Radiotherapy and Total Neoadjuvant Therapy

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ABSTRACT

Rectal cancer ranks among the most common malignancies globally, with significant challenges in local recurrence and systemic failure despite advances in treatment. Historically, surgery alone was associated with recurrence rates as high as 20–50%, but the integration of preoperative radiotherapy has markedly improved outcomes by reducing recurrence and enabling sphincter preservation. Evidence from landmark trials, including the Swedish, Dutch, and German CAO/ARO/AIO-94 studies, established preoperative radiotherapy and chemoradiotherapy as standards of care. Comparative analyses of short-course radiotherapy (SCRT) and long-course chemoradiotherapy (LC-CRT) demonstrate comparable long-term outcomes, though LC-CRT may be preferable in advanced, distal tumors, while SCRT offers a pragmatic option for smaller, proximal lesions. Persistent systemic failures prompted the adoption of total neoadjuvant therapy (TNT), shifting chemotherapy to the preoperative setting. Trials such as PRODIGE 23 and RAPIDO have confirmed TNT's ability to improve compliance, pathological complete response rates, disease-free survival, and distant metastasis control compared to conventional strategies. Both induction- and consolidation-based TNT regimens have shown efficacy, particularly in high-risk locally advanced rectal cancer (LARC) patients. While organ preservation strategies such as watch-and-wait are being investigated, current evidence supports TNT combined with total mesorectal excision as a robust paradigm shift in LARC management, offering improved oncological outcomes and patient adherence.

Keywords: *oncology, chemoradiation, tumor regression, organ preservation, survival outcomes*

INTRODUCTION

Rectal cancer is reported among the top five common cancers worldwide. Although the incidence is relatively lower in India, worldwide overall colorectal cancer (CRC) ranks third in terms of incidence and mortality. [1,2] Management approach to rectal cancer has undergone a dramatic change in the last few decades. With surgery as the primary treatment modality, the local recurrences were found to be between 20-50%. [3,4] Local recurrence mainly depends on the involvement of regional lymph nodes and the depth of tumour infiltration. The role of radiotherapy in rectal cancer has evolved primarily in a preoperative setting for locally advanced rectal cancer patients.

Preoperative radiotherapy

Preoperative radiotherapy aims to downstage the tumour leading to the preservation of the anal sphincters, maintaining anal continence, and improving quality of life. The Swedish Rectal Cancer Trial was the first to demonstrate the benefit of preoperative radiotherapy compared to surgery alone. Short-course radiotherapy of 5Gy for five fractions was used, followed by surgery. The overall survival improved from 30% to 38%, and the local recurrence rate reduced from 26% to 9%. [5] But the results of this trial were criticized as The surgery undertaken was not total mesorectal excision (TME), so the results were criticised.

A Dutch trial added preoperative short-course radiotherapy to TME surgery, showing a reduction of local recurrence from 11 to 5% when compared to surgery. [6]

The German CAO/ARO/ AIO-94 trial compared preoperative long-course radiotherapy 50.4Gy in 28 fractions with concurrent fluorouracil(5-FU) versus the postoperative setting. The preoperative group showed significant benefits with a 5-years local recurrence rate of 6% vs 13%, respectively (P=0.006). [7,8] The colorectal cancer collaborative group carried out a meta-analysis that included 14 randomized controlled trials. This meta-analysis concluded that preoperative radiotherapy is associated with significantly lower local recurrence rates. [9-11]

Preoperative short-course radiotherapy (SC-RT) vs long-course chemoradiotherapy (LC-CRT)

The Polish rectal cancer group first reported the results of their randomized control trial. The SC-RT (25 Gy in five fractions) was compared with the LC-CRT of 50.4 Gy using 1.8- to 2-Gy per fraction with concurrent chemotherapy for T3/T4 mid to low rectal cancer. A higher pathological complete response rate was reported in the LC-CRT than in the SC-RT arm (16% vs 1%). No differences were observed in the sphincter preservation rate, local control, or overall survival (OS). [12] Trans-Tasman Radiation Oncology Group randomized three hundred twenty-six patients with cT3NxM0 rectal cancer to SC- RT (25 Gy in 5 fractions) followed by surgery within one week or LC-CRT (50.4 Gy in 28 fractions with continuous infusion 5-FU) followed by surgery at 4 to 6 weeks. Both groups received adjuvant 5-FU–based chemotherapy. Both the interventions yielded almost the same results, with a 5-year OS of 74% versus 70% (p = 0.62) and a 3-year local recurrence rate (LRR) of 7.5 versus 4.4% (p = 0.24) for SC-RT versus LC-CRT respectively. [13].

Most recently, the results of the multicenter, randomized, phase III Trial of short-term radiotherapy plus chemotherapy versus long-term chemoradiotherapy in locally advanced rectal cancer (STELLAR) have been published. It was a noninferiority trial designed to see that the short course radiotherapy followed by chemotherapy is not inferior to a standard schedule of long-term chemoradiotherapy in patients with locally advanced rectal cancer. The investigational arm received 25 Gy in 5 fractions of radiotherapy followed by four cycles of chemotherapy, and the standard arm received standard radiotherapy of 50Gy in 25 fractions concurrently with capecitabine. Both the arm received adjuvant Capox chemotherapy; the investigation arm received two cycles, and the standard arm received six cycles respectively. The primary endpoint was 3-year DFS. At a median follow-up of 35.0 months, 3-year DFS was 64.5% and 62.3% in TNT and CRT groups, respectively (hazard ratio, 0.883; one-sided 95% CI, not applicable to 1.11; P < .001 for noninferiority). But acute grade III-V toxicities during preoperative treatment was 26.5% in the investigational arm versus 12.6% in the CRT group (P < .001). The completion rate and full-dose completion of preoperative treatment were 82.6% versus 95.2% (P <0. 001) and 74.8% versus 93.2% (P=0.01) in the short-course RT group and CRT groups, respectively. [14] Table 1 depicts major trials comparing SCRT with LCRT.

Based on the available evidence, it can be concluded that both the SC-RT and the LC-CRT are not inferior to each other. However, LC-CRT may be preferable for patients with distal tumours or advanced T3 and T4 with positive clinical circumferential resection margin (cCRM+) and/or positive lymph nodes to downsize the tumour. SC-RT may be a better alternative for patients with small and relatively proximal tumours without compromising the long-term outcomes. [15, 16]

Total neoadjuvant therapy (TNT): different approaches

With the improved technique, preoperative chemoradiation substantially reduced local recurrence in LARC. Despite improvement in the local control, 30% of patients develop systemic failures. [17]

Several literatures have shown that 25%-50% of eligible patients with LARC never underwent adjuvant chemotherapy. This was attributed to postoperative complications, frailty, debilitation, or patient refusal. [18,19] To address the issues of unidentified micrometastatic disease at the time of presentation and poor patient compliance to adjuvant chemotherapy, it was proposed to move systemic chemotherapy to the neoadjuvant setting. To overcome this problem, many studies were undertaken to investigate if the addition of chemotherapy in the neoadjuvant setting, known as total neoadjuvant therapy (TNT), impacts local recurrence and survival.

Many investigators have explored different ways of administering the chemotherapy cycles in the neoadjuvant setting. Some prefer to deliver chemotherapy cycles by dividing them into two schedules. Half of the chemotherapy cycles are administered before surgery with radiation and the remaining cycles after surgery. While others prefer to deliver the complete chemotherapy cycles with radiation before the surgery.

TNT with Induction chemotherapy approach

A few studies exploring the role of induction chemotherapy as a part of the TNT approach are shown in Table 3. In a prospective trial by Fernandez-Martos et al., 108 LARC patients with distal or middle third, T3-T4 and/or N+ rectal adenocarcinoma were randomly divided to receive preoperative CRT followed by surgery and four cycles of adjuvant capecitabine and oxaliplatin (CAPOX) or four cycles of CAPOX followed by CRT and surgery. No difference in rates of pathologic complete response was observed between the two groups. However, those who received TNT showed significantly reduced toxicities (19% vs 54%, P < 0.001). Further, TNT arm patients were found to be more compliant towards receiving a complete chemotherapy schedule (91% vs 51%, P < 0.001). [20,21]

A retrospective cohort analysis from Memorial Sloan Kettering Cancer Center compared 811 patients treated with either the preoperative chemoradiation and planned postoperative chemotherapy (n = 320) or the TNT (induction FU and oxaliplatin-based chemotherapy

followed by chemoradiation, n = 308). Patients of the TNT arm were found to complete the full chemotherapy schedule without any misses. Moreover, the rate of pathological complete response rate was also higher in the TNT arm than the other arm (36%vs 21%).[22]

The PRODIGE 23, a Phase III multicentre, randomized, the open-label trial, compared induction chemotherapy and TNT with standard preoperative chemoradiotherapy followed by surgery and adjuvant chemotherapy (n=461). The TNT arm received six cycles of neoadjuvant mFOLFIRINOX followed by chemoradiotherapy (50 Gy in 25 fractions concurrently with oral capecitabine) followed by TME and adjuvant three months of mFOLFOX and Capecitabine. The standard-of-care group received chemoradiotherapy, total mesorectal excision, and adjuvant chemotherapy (for six months). The preliminary results of the study were published in May 2021. The primary endpoint was DFS at three years. After a median follow-up of 46·5 months, 3-year DFS rates were 76% (95% CI 69–81) in the TNT group and 69% (95% CI 62–74) in the standard-of-care group (stratified HR 0·69, 95% CI 0·49–0·97; p=0·034). The 3-year overall survival rates were 91% in the TNT group and 88% in the standard-of-care group. No differences between the groups were found in locoregional relapse rates (p=0.56).[23]

The TNT approach is now mainly practised for patients with advanced disease with a higher risk of distant metastasis and difficulty for surgical resection. It is thought that the upfront chemotherapy agents reach tumour cells directly as the vasculature is not disrupted by radiotherapy or surgery. [24-26]

TNT with Consolidated chemotherapy approach

Several studies using consolidation chemotherapy as a part of TNT are shown in Table 2.

A phase II study enrolled locally advanced rectal cancer patients to either surgery or 2, 4, or 6 cycles of modified FOLFOX (mFOLFOX) followed by surgery. It was found that patients who received six cycles of mFOLFOX had significantly improved pathologic complete response compared to patients who underwent surgery 6-8 weeks after completing chemoradiation (P = 0.011). The long-term results of this trial showed that the addition of mFOLFOX after chemoradiotherapy and before surgery increased compliance with systemic therapy and improved disease-free survival. [27, 28]

A Polish phase III randomized over 500 patients to short-course radiation followed by consolidation chemotherapy and surgery vs long-course chemoradiation with consolidation chemotherapy followed by surgery. Both arms showed similar pathological complete response, disease-free survival, local failure rate, and treatment-related toxicities. However, the short-course RT group showed improved 3-year OS and better compliance with treatment.

The RAPIDO trial, a large phase III, multicenter, randomized study, used a similar approach of TNT. A total of 920 LARC patients were randomly assigned to SCRT (5x5 Gy) followed by six cycles of CAPOX or nine cycles of FOLFOX4, then TME (experimental arm) or, Capecitabine-based chemoradiotherapy (50-50.4Gy in 25-28 fractions) followed by TME and adjuvant eight cycles of CAPOX or twelve cycles of FOLFOX4 (standard arm). The primary endpoint was a 3-year disease-related treatment failure. The experimental group had significantly less disease-related treatment failure at three years than the standard of care group (p=0·019). The cumulative probability of distant metastases was 20·0% in the experimental group compared with 26·8% in the standard-of-care group (p=0·0048) at three years. Further, there was a significant improvement in pathological complete response rate (pCR) in the TNT group (27.7% vs 13.8%, P<0.001). The study concluded that SCRT followed by 18 weeks of chemotherapy before surgery significantly reduces disease-related treatment failure in patients with LARC and results in a higher rate of pathological complete response rate. [29]

CONCLUSION

Various approaches to the multimodality management of LARC have been investigated for a better outcome. Preoperative radiotherapy with either SCRT or LC-CRT, followed by TME and adjuvant chemotherapy, became the standard of care based on several large studies. TNT approach has resulted in the good oncological outcome and better patient adherence to treatment. The results of the two recently published phase III studies viz. RAPIDO and PRODIGE 23 have established that TNT with TME surgery is feasible for LARC patients to overcome the difficulties with adjuvant chemotherapy.

Further, TNT helps to assess chemosensitivity and tumour response to chemoradiation before surgery. Newer efforts have also been made to see the effectiveness of the wait-and-watch policy for organ preservation in rectal cancer patients. But the data are not mature enough to recommend this approach outside clinical trials.

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013; 63:11–30.

2. Bray F, Ferlay J, Soerjomataram I, Siegel R, Torre L, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.

3. Pilipshen SJ, et al. Patterns of pelvic recurrence following definitive resections of rectal cancer. Cancer 1984; 53(6):1354–1362.

4. Rich T, et al. Patterns of recurrence of rectal cancer after potentially curative surgery. Cancer 1983; 52(7):1317–1329.

5. Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U: Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 2005; 23: 5644–5650.

6. van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, Rutten HJ, Pahlman L,Glimelius B, van de Velde CJ; Dutch Colorectal CancerGroup: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomized controlled TME trial. Lancet Oncol 2011; 12: 575–582.

7. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004; 351:1731–1740.

8. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, Becker H, Raab HR, Villanueva MT, Witzigmann H, Wittekind C, Beissbarth T, Rodel C: Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 2012; 30: 1926–1933.

9. Hofheinz RD, Wenz F, Post S, et al: Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomized, multicentre, noninferiority, phase 3 trial. Lancet Oncol 2012; 13: 579–588.

10. Häfner M, Debus J. Radiotherapy for Colorectal Cancer: Current Standards and Future Perspectives. Visceral Medicine. 2016;32(3):172-177.

11. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomized trials. Lancet 2001;358(9290):1291–1304.

12. Bujko K, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 2006;93(10):1215–1223.

13. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with t3 rectal cancer: trans-tasman radiation oncology group trial 01.04. J Clin Oncol 2012; 30(31):3827–3833.

14. Jin J, Tang Y, Hu C, Jiang L-M, Jiang J, Li N, et al. Multicenter, randomized, phase III trial of short-term radiotherapy plus chemotherapy versus long-term chemoradiotherapy in locally advanced rectal cancer (stellar). Journal of Clinical Oncology. 2022;40(15):1681–92.

15. Glimelius B, Tiret E, Cervantes A, Arnold D; ESMO Guidelines Working Group: Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24(suppl 6):vi81–88.

16. National Comprehensive Cancer Network (NCCN) [Internet]. Nccn.org. 2020 [cited 17 September 2020]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf

17. Cunningham D, Atkin W, Lenz HJ, et al. Colorectal cancer. Lancet. 2010;375:1030–1047

18. Bosset JF , Collette L , Calais G , et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med . 2006;355:1114–1123 .

19. Bosset JF, Calais G , Mineur L , et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomized study. Lancet Oncol . 2014; 15:184–190.

20. Fernandez-Martos C , Garcia-Albeniz X , Pericay C , et al. Chemoradiation, surgery and adjuvant chemotherapy versus induction chemotherapy followed by chemoradiation and surgery: long-term results of the Spanish GCR-3 phase II randomized trialdagger. Ann Oncol . 2015;26:1722–1728 .

21. Fernandez-Martos C , Pericay C , Aparicio J , et al. Phase II, randomized study of concomitant chemoradiotherapy fol- lowed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol . 2010; 28:859–865 .

22. Cercek A , Roxburgh CSD , Strombom P , et al. Adoption of total neoadjuvant therapy for locally advanced rectal cancer. JAMA Oncol . 2018;4 .

23. Conroy T, Bosset J, Etienne P, Rio E, François É, Mesgouez-Nebout N et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomized, open-label, phase 3 trial. The Lancet Oncology. 2021;22(5):702-715.

24. Hartley A, Ho KF, McConkey C, Geh JI. Pathological complete response following preoperative chemoradiotherapy in rectal cancer: analysis of phase II/III trials. Br J Radiol. 2005;78(934):934–8.

25. Park IJ, You YN, Agarwal A, Skibber JM, Rodriguez-Bigas MA, Eng C, et al. Neoadjuvant treatment response as an early response indicator for patients with rectal cancer. J Clin Oncol. 2012;30(15):1770–6.

26. Cercek A, Goodman KA, Hajj C, Weisberger E, Segal NH, Reidy- Lagunes DL, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. J Natl Compr Canc Netw. 2014;12(4):513–9.

27. Garcia-Aguilar J , Chow OS , Smith DD , et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. Lancet Oncol . 2015;16:957–966 .

28. Marco MR , Zhou L , Patil S , et al. Consolidation mFOLFOX6 chemotherapy after chemoradiotherapy improves sur- vival in patients with locally advanced rectal cancer: final results of a multicenter phase II trial. Dis Colon Rectum . 2018;61:1146–1155 .

29. Bahadoer R, Dijkstra E, van Etten B, Marijnen C, Putter H, Kranenbarg E et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomized, open-label, phase 3 trial. The Lancet Oncology. 2021;22(1):29-42.

30. Bujko K, Wyrwicz L, Rutkowski A, Malinowska M, Pietrzak L, Kryński J, et al. Long-course oxaliplatin-based preoperative chemoradiation versus 5 x 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. Ann Oncol. 2016;27(5):834–42.

31. Gao YH, An X, Sun WJ, Cai J, Cai MY, Kong LH, et al. Evaluation of capecitabine and oxaliplatin administered prior to and then concomitant to radiotherapy in high risk locally advanced rectal cancer. J Surg Oncol. 2014;109(5):478–82.

32. Zhu J, Gu W, Lian P, Sheng W, Cai G, Shi D, et al. A phase II trial of neoadjuvant IMRT-based chemoradiotherapy followed by one cycle of capecitabine for stage II/III rectal adenocarcinoma. Radiat Oncol. 2013;8:130.

33. Chua YJ, Barbachano Y, Cunningham D, Oates JR, Brown G, Wotherspoon A, et al. Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. Lancet Oncol.2010;11(3):241–8.

34. Perez K, Safran H, Sikov W, Vrees M, Klipfel A, Shah N, et al. Complete neoadjuvant treatment for rectal cancer: The Brown University Oncology Group CONTRE Study. Am J Clin Oncol. 2017;40(3):283–7.

35. Gollins S, West N, Sebag-Montefiore D, Susnerwala S, Falk S, Brown N, et al. A prospective phase II study of preoperative chemotherapy then short-course radiotherapy for high risk rectal cancer: COPERNICUS. Br J Cancer. 2018;119(6):697–706.

36. Dueland S, Ree AH, Groholt KK, Saelen MG, Folkvord S, Hole KH, et al. Oxaliplatin-containing preoperative therapy in locally advanced rectal cancer: local response, toxicity and long-term outcome. Clin Oncol. 2016;28(8):532–9.

37. Dewdney A, Cunningham D, Tabernero J, Capdevila J, Glimelius B, Cervantes A, et al. Multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). J Clin Oncol. 2012;30(14):1620–7.

38. Schou JV, Larsen FO, Rasch L, Linnemann D, Langhoff J, Høgdall E, et al. Induction chemotherapy with capecitabine and oxaliplatin followed by chemoradiotherapy before total mesorectal excision in patients with locally advanced rectal cancer. Ann Oncol. 2012;23(10):2627–33.