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# Update in localized rectal cancer

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## Introduction

The management of rectal cancer requires a multidisciplinary approach with individual treatment based on a careful assessment of tumour location, stage and resecability (Fig. 1). The use of preoperative chemoradiotherapy and the widespread implementation of total mesorectal excision (TME) (1) have concurred to improve the prognosis of locally advanced rectal cancer with local recurrences decreasing from 40 to <10% and overall survival increasing from 50 to 75% in the last 40 years . Acute and long-term toxicity and

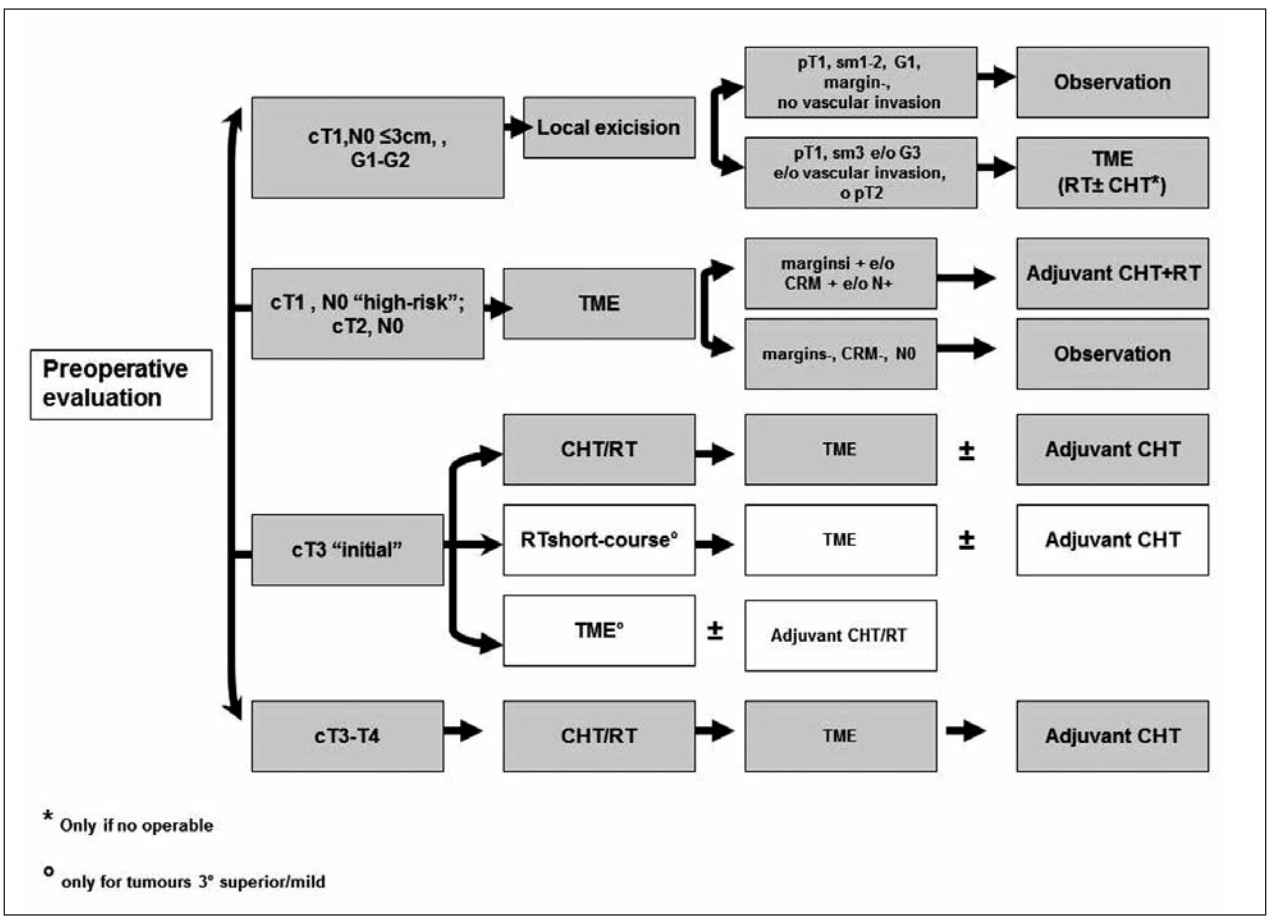


**Figure 1**. **CRM**: circumferential resection margin; **CHT**: chemotherapy; **RT**: radiotherapy; **TME**: total mesorectal excision

treatment related morbidities, however, may be relevant and significantly affect quality of life. For these reasons , it is crucial to carefully identify the patients who are candidate to receive adjuvant or neoadjuvant chemoradiation (1). Chemoradiation and total mesorectal excision are in fact recommended for rectal cancers with extramural penetration and/or involvement of the regional lymph nodes (2). Pelvic magnetic resonance (MRI) is the standard tool to identify these patients preoperatively (3).

**Adjuvant and/or neoadjuvant treatment**

Radiotherapy is used in rectal cancer to sterilize local foci of microscopic disease and decrease the risk of local failure. TME has been developed to decrease the rate of pelvic recurrences due to inadequate excision of all the mesorectal tissue and lymphonodes. Given the increase in local control with more aggressive surgery, the role of radiotherapy to reduce pelvic recurrences has been questioned. However, a randomized Dutch study that has compared preoperative radiotherapy followed by optimal surgery (TME) versus optimal surgery alone, has shown a significant reduction in the rate of local recurrences in the radiotherapy arm (4).

Concomitant radiosensitizing chemotherapy is required to maximize these effects. Two large randomized studies have demonstrated the superior activity of preoperative chemoradiation compared with preoperative radiation alone (5,6), with a significant 3-4 fold increase in the rates of pathological complete response (pCR). Furthermore, the addition of chemotherapy to radiation reduced local recurrence, which were observed in 17.1 and 16.5 versus 7.6 and 8.6 % of patients, in the radiation-alone and chemoradiation arms, respectively (5, 6). Neoadjuvant use of short-term hypofractionated pre-operative radiation therapy (25 Gy in 5 daily fractions within one week from surgery) is also effective in reducing local falilures with an impact on overall survival in a single study performed in the pre-TME era (7). The value of short-term intensive pre-operative radiotherapy has been confirmed in a recent study and may represent an alternative to chemoradiotherapy in patients with mid-high tumors with a limited locoregional spread (8).

In the post-operative setting, chemoradiation consistently halved the rates of local failure compared with surgery alone in a series of randomized clinical trials (9, 10). Preoperative radiation, however, is more efficacious than post-operative radiotherapy (11). In addition, radiotherapy administered before surgery may induce an objective tumour shrinkage and/or salvage of the anal sphincter for large or low-lying tumours. A randomized study indeed showed both a superior outcome (local failure reduced from 13 to 6%) and reduced toxicity with preoperative compared to postoperative chemoradiation (1) setting the current standard for the treatment of locally-advanced rectal cancer.

**Chemotherapy**

In the standard combined-modality treatment programs for locally advanced rectal cancer, chemotherapy is administered both concomitantly and sequentially to radiation with additional chemotherapy courses delivered either before or after concurrent treatment for a total of 6 monthly cycles (12). In fact, in the first studies investigating combined modality treatment, local control and overall survival were improved but no effect on distant metastases was obtained when chemotherapy was administered exclusively during radiation (9). Further support for the use of adjuvant chemotherapy is provided by a pooled analysis of five randomized studies that showed a 20% absolute survival benefit with post-operative chemotherapy, administered for 6-18 months with or without post-operative radiotherapy, compared with observation or post-operative radiation alone following surgery (13). Given the greater efficacy of preoperative compared with post-operative radiation, the need of a formal proof of efficacy for the use of adjuvant chemotherapy has been advocated particularly for patients that receive radiation or chemoradiation pre-operatively. Although statistical significance was not reached, higher rates of DFS and OS were observed in a European randomized study testing adjuvant chemotherapy in patients treated with RT or CRT neoadjuvantly ( 14). Of

interest, a subset analysis of this study showed that patients responding to neoadjuvant treatment (ypT0-pT1-pT2, ypN0) are those more likely to benefit from adjuvant chemotherapy (15).

## Ongoing research

In the preoperative setting, oral or infused fluoropyrimidines administered continuously during radiation provide optimal radiosensitization with equivalent outcome (16). The addition of oxaliplatin to fluoruracile or capecitabine and concurrent radiotherapy did not improve pCR rates (17, 18) nor local control (19) while increasing toxicity in four recent randomized studies. Alternative strategies are thus being explored to potentiate preoperative treatment including induction chemotherapy (before CT/RT), neoadjuvant chemotherapy (without RT), "consolidation" chemotherapy (after CT/RT), FP-free chemoradiation regimens and modulated treatment programs based on early response assessment with MRI and/or PET-TC (Fig. 2). In parallel, indications to preoperative treatment are being refined with a more accurate risk stratification based on the site and location of the tumor, T3 substaging, circumferential resection margin (CRM) status and assessment of extramural venous invasion. Micro-array DNA technologies and pharmacogenomics may provide further help in modulating treatment intensity, based on the risk of recurrence, and also in the choice between different drugs, based on prediction of response and toxicity.

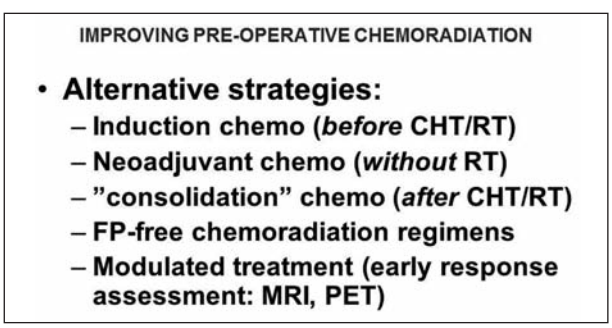


**Figure 2**. **CHT**: chemotherapy; **RT**: radiotherapy; **FP:** fluoropyrimidine

## References

1. Sauer R, Becker H, Hohenberger W, *et al*. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004; 351 (17): 1731-40.
2. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA 1990; 264 (11): 1444-50.
3. Brown G, Davies S, Williams GT, *et al*. Effectiveness of preoperative staging in rectal cancer: digital rectal examination, endoluminal ultrasound or magnetic resonance imaging? Br J Cancer 2004; 91 (1): 23-9.
4. Kapiteijn E, Marijnen CA, Nagtegaal ID, *et al.* Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001; 345 (9): 638-64.
5. Cammà C, Giunta M, Fiorica F, *et al*. Preoperative radiotherapy for resectable rectal cancer: A meta-analysis. JAMA 2000; 284 (8): 1008-15.
6. Gérard JP, Azria D, Gourgou-Bourgade S, *et al.* Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. J Clin Oncol 2010; 28 (10): 1638-44.
7. Swedish Rectal Cancer Trial. Improved survival with preoperative radIation in resectable rectal cacner. N Engl Med 1997; 27: 360-311.
8. 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): 3827-33.
9. Tveit KM, Guldvog I, Hagen S, *et al*. Randomized controlled trial of postoperative radiotherapy and short-term time-scheduled 5-fluorouracil against surgery alone in the treatment of Dukes B and C rectal cancer. Norwegian Adjuvant Rectal Cancer Project Group. Br J Surg 1997; 84 (8): 1130-5.
10. Krook JE, Moertel CG, Gunderson LL, *et al.* Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med,1991;324(11):709-715.
11. Madoff RD. Chemotherapy for rectal cancer-when, why andhow. N Engl J Med 2004; 351 (17): 1790-2.
12. Gunderson LL, Sargent DJ, Tepper JE, *et al.* Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: a pooled analysis. J Clin Oncol 2004; 22 (10): 1785-96.
13. Bosset JF, Collette L, Calais G, *et al*. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006; 9; 355 (11): 1114-23.
14. Collette L, Bosset JF, den Dulk M, *et al.* Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organisation for Research and Treatment of

Cancer Radiation Oncology Group. J Clin Oncol 2007; 25 (28): 4379-86.
14. Roh MS, Yothers GA. The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP-RO4. J Clin Oncol 2011; 29: abstr 3503.
16. Rödel C, Liersch T, Becker H, *et al.* Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer:initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol 2012; 13 (7): 679-87.
17. Aschele C, Cionini L, Lonardi S, *et al.* Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol 2011; 29 (20): 2773-80.
18. Gérard JP, Azria D, Gourgou-Bourgade S, *et al.* Clinical Outcome of the ACCORD 12/0405 PRODIGE 2 Randomized Trial in Rectal Cancer. J Clin Oncol 2012; 20; 30 (36): 4558-65.