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Background

Rectal cancer is less common than colon cancer but presents difficult treatment decisions because, while it is frequently curable, treatment may involve radical surgery including the need for a colostomy, which can have a profound effect on a survivor's quality of life.

Equally, recurrent rectal cancers produce distressing symptoms and are difficult to treat and frequently require reirradiation for symptom control, exenterative surgery or both.

The aim of radiotherapy in rectal cancers is to allow radical treatment to take place for more advanced cancers or to reduce the risk of relapse for early-stage cancers (neoadjuvant therapy).

Total neoadjuvant therapy (TNT) uses chemotherapy in addition to radiotherapy in the neoadjuvant setting.

In recurrent or incurable disease, radiotherapy can reduce the disease burden and help control symptoms.

NICE guidance published in 2020 recommends preoperative radiotherapy with or without chemotherapy for rectal cancer staged as cT1–T2, cN1–N2 or cT3–T4, any N0–2, M0, as the evidence from several randomised controlled trials shows that this approach reduces local recurrence and has better overall and disease-free survival compared with no preoperative radiotherapy.[1]

Neoadjuvant therapy

Risk-reducing radiotherapy

Preoperative radiotherapy is preferred to postoperative treatment as the preoperative technique is more effective and less toxic (Level 1a).[2–5]

Preoperative short-course rectal radiotherapy (SCRT) has been evaluated in several prospective randomised controlled trials (RCTs). The Dutch total mesorectal excision (TME) versus SCRT (25 Gray [Gy] in 5 fractions) plus TME trial demonstrated a reduction in local recurrence rate, though with a longer median follow-up of 6.1 years the benefit appears to decrease (10.9% versus 5.6%; 49% relative reduction in risk).[6,7] The overall survival was the same in both groups (Level 1b).[4] The MRC-07 trial demonstrated the advantage of SCRT (25 Gy in 5 fractions) for operable rectal cancer over selective postoperative (chemo-) radiation, in terms of reducing the relative risk of local recurrence after a median follow-up of 4 years by 61% (hazard ratio [HR] 0.39, confidence interval [CI] 0.27–0.58). This translates to an absolute reduction in risk of local relapse of 6.2% at 3 years. There is also an absolute improvement in disease-free survival of 6% at 3 years with no effect on overall survival (Level 1b).[4,8]

The Stockholm III trial evaluated SCRT (25 Gy in 5 fractions) followed by immediate surgery versus delayed surgery after 4–8 weeks or long-course radiotherapy (50 Gy in 25 fractions).

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The rate of local recurrence was similar in all arms but the rate of postoperative complications was significantly higher in the SCRT and immediate surgery compared with the delayed surgery arm.[9]

SCRT, however, increases long-term toxicity, with poorer functional outcomes, especially in terms of continence (Level 1b).[4,10,11]

Recommendation

Short-course preoperative radiotherapy:

- 25 Gy in 5 daily fractions (Grade A)
- Followed by definitive surgery either within a week or delayed surgery

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[4]

Down-staging radiotherapy

For inoperable cancers, cancers that involve or threaten the circumferential margin or cancers deemed to be at high risk of relapse, down-staging treatment is recommended.[12,13]

Doses of >30 Gy improve the response rate, and long-course chemoradiotherapy (LCCRT) has been shown to improve response rate and the likelihood of R0 resection compared with long-course radiotherapy alone (Level 1a), though the sphincter preservation rate and long-term outcomes appear to be similar.[2,4,12,13] A dose of 45–50.4 Gy in 1.8 Gy per fraction with concurrent chemotherapy is commonly used in the UK.

Fluorouracil (5-FU)-based chemotherapy has been used in all major trials since the 1980s, and more recently capecitabine has been shown to have similar efficacy in several phase 2 studies (Level 2b); it has replaced infusional 5-FU as the drug of choice for LCCRT to the rectum.[4,14,15] Addition of a second agent such as irinotecan or oxaliplatin has not demonstrated improvement in outcomes and is not recommended (Level 1A).[4,16–19]

TNT has been shown in multiple trials to reduce local recurrence rates (STELLAR/Prodige 23), reduce distant free metastasis (STELLAR, RAPIDO, Prodige 23) and improve clinical and pathological complete response (RAPIDO, OPRA, Prodige 23) for high-risk rectal cancers. Two studies have found an overall survival benefit at 3 years, with one showing at 8 years that benefit was not maintained.[20–23]

Some authors have reported a 'boost' of 5.4 Gy in 3 fractions to the gross tumour volume plus margin following 45 Gy in 25 fractions to a larger volume.[15] The efficacy and toxicity of this remains unknown (Level 2b).[4] A simultaneous integrated boost of 50 Gy in 25 fractions is recommended. A dose of 52 Gy in 25 fractions is an alternative and is equivalent to 54 Gy in 30 fractions used in the EXPERT study, with minimal acute toxicity.[24,25] Higher doses correlate to improved response rates rather than local relapse rate and hence doses of greater than 50 Gy should only be considered for boosting disease that lies outside the resection margin or for an organ-preservation approach.[26]

Retrospective series from Sweden and the UK, looking at patients with locally advanced unresectable rectal cancer who are unfit for standard LCCRT, treated with 25 Gy in 5 fractions, have reported significant tumour regression, with 60–80% of patients going on to have delayed surgery (Level 2c).[4,27,28]

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Recommendations

For down-staging LCCRT:

- 45 Gy in 25 daily fractions with concurrent chemotherapy (Grade A); optional boost of 5.4 Gy in 3 fractions to smaller volume (Grade C) or
- 50 Gy in 25 fractions simultaneous integrated boost (SIB) (Grade C)

For patients not suitable for chemotherapy:

- 45 Gy in 25 daily fractions (Grade A) with or without boost
- 25 Gy in 5 daily fractions (Grade B)

For total neoadjuvant therapy:

- 25 Gy in 5 daily fractions (Grade A)
- 45 Gy in 25 daily fractions with concurrent chemotherapy (Grade A); optional boost of 5.4 Gy in 3 fractions to smaller volume (Grade C) or
- 50 Gy in 25 fractions SIB (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[4]

Brachytherapy

Low-energy contact brachytherapy[29,30] (Papillion technique) and high-dose-rate (HDR) brachytherapy have both been used, generally in combination with external beam radiotherapy (EBRT), for the treatment of rectal cancers. In patients unfit for surgery or who choose to not have surgery, these techniques can be used to improve local control.

For tumours less than 5 cm in size (T2–T3b, N0-1, node <8 mm), LCCRT plus contact radiotherapy significantly improves the 3-year organ-preservation rate, especially with tumours <3 cm where contact boost was delivered before LCCRT (Level 1b).[31]

There is one published RCT evaluating a neoadjuvant 10 Gy in 2 fractions HDR brachytherapy boost (endoluminal) along with 50.4 Gy in 28 fractions of EBRT (Level 1b).[4,32] This trial showed no improvement in pathological complete response (pCR) or long-term survival despite a better R0 resection rate for T3 tumours.

Contact radiotherapy can be used following endoscopic resection if there are adverse pathological features (CONTEM 1).

Contact radiotherapy can be used for the palliative treatment of patients with a recurrence or metastases.

Dose recommendations are derived from published trials and current consensus among UK centres offering brachytherapy.[33–37]

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Recommendations

Postoperative:

- pT1 or pT2 with adverse pathological features: 60 Gy in 2 fractions over 2 weeks followed by EBRT (Grade B)

Radical treatment (<3 cm):

- cT1/cN0: 90–110 Gy in 3–4 fractions (30 Gy ×3 and final boost 20 Gy) over 3–6 weeks (Grade C)
- cT1/cN1 or cT2–T3b cN0/cN1 (node <8 mm): 90–110 Gy in 3–4 fractions (30 Gy ×3) and optional final boost (20 Gy) over 3–6 weeks, followed by EBRT (Grade A)

Radical treatment (>3 cm):

- cT1/cN1 or cT2–T3b cN0/cN1 (node <8 mm): EBRT followed by contact radiotherapy or HDR boost if regression to <3 cm: 90 Gy in 3 fractions (30 Gy ×3) and optional final boost (20 Gy) over 3–6 weeks (Grade A) or
- HDR brachytherapy 12 Gy in 2 fractions (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[4]

Palliative treatment

There are no good-quality trials evaluating different dose fractionation schedules for palliative treatment. An appropriate regime should be chosen after considering the patient's likely prognosis, disease burden, symptoms and performance status.

Recommendations

- 30 Gy in 10 daily fractions (Grade D)
- 20–25 Gy in 5 daily fractions (Grade D)
- HDR brachytherapy 10 Gy at 1 cm single dose (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[4]

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Reirradiation

Following previous SCRT or LCCRT, some patients will experience a local or regional relapse. Such patients should be discussed in specialist multidisciplinary team meetings (MDTMs) with the relevant expertise in treating recurrent rectal cancer.

Where possible, recurrences after neoadjuvant radiotherapy should be treated with surgery or systemic therapy, avoiding further radiation. However, if surgery is not feasible with clear margins or holds excess risks, reirradiation should be considered for limited volumes, including the use of stereotactic ablative body radiotherapy (SABR) techniques. This may yield good symptomatic relief as a palliative treatment, and long-term control is possible.

When curative resection is to be considered but reirradiation is required to achieve this, currently hyperfractionated chemoradiotherapy should be preferred to limit late toxicity (Grade D).[3]

References

1. National Institute for Health and Care Excellence. Colorectal cancer. NICE guideline [NG151]. NICE, 29 January 2020. www.nice.org.uk/guidance/ng151
2. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from randomised trials. *Lancet* 2001; **358**(9290): 1291–1304.
3. Frykholm GJ, Glimelius B, Påhlman L. Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final results of a randomised trial and an evaluation of late secondary effects. *Dis Colon Rectum* 1993; **36**(6): 564–572.
4. www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009 (last accessed 28/11/2023).
5. Song JH, Jeong JU, Lee JH *et al*. Preoperative chemoradiotherapy versus postoperative chemoradiotherapy for stage II–III resectable rectal cancer: a meta-analysis of randomized controlled trials. *Radiat Oncol J* 2017; **35**(3): 198–207.
6. 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): 638–646.
7. Peeters KC, Marijnen CA, Nagtegaal ID *et al*. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg* 2007; **246**(5): 693–701.
8. Sebag-Montefiore D, Stephens RJ, Steele R. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet* 2009; **373**(9666): 811–820.
9. Erlandsson J, Holm T, Pettersson D *et al*. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. *Lancet Oncol* 2017; **18**(3): P336–346.
10. Peeters KC, van de Velde CJ, Leer JW *et al*. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients – a Dutch colorectal cancer group study. *J Clin Oncol* 2005; **23**(25): 6199–6206.
11. Bregendahl S, Emmertsen KJ, Lous J, Laurberg S. Bowel dysfunction after low anterior resection with and without neoadjuvant therapy for rectal cancer: a population-based cross-sectional study. *Colorectal Dis* 2013; **15**: 1130–1139.
12. Braendengen M, Tveit KM, Berglund A *et al*. Randomised phase II study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. *J Clin Oncol* 2008; **26**(22): 3687–3694.
13. Ceelen WP, Van Nieuwenhove Y, Fierens K. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer. *Cochrane Database Syst Rev* 2009; **1**: CD006041.

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14. De Bruin AF, Nuyttens JJ, Ferenschild FT, Planting AS, Verhoef C, de Wilt JH. Preoperative chemoradiation with capecitabine in locally advanced rectal cancer. *Neth J Med* 2008; **66**(2): 71–76.
15. De Paoli A, Chiara S, Luppi G *et al*. Capecitabine in combination with preoperative radiation therapy in locally advanced, resectable, rectal cancer: a multicentric phase II study. *Ann Oncol* 2006; **17**(2): 246–251.
16. Sebag-Montefiore D, Adams R, Gollins S *et al*. ARISTOTLE: A phase III trial comparing concurrent capecitabine with capecitabine and irinotecan (Ir) chemoradiation as preoperative treatment for MRI-defined locally advanced rectal cancer (LARC). *J Clin Oncol* 2020; **38**: 15_suppl, 4101–4101.
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): 2773–2780.
18. Gerard 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): 1638–1644.
19. Rodel C, Graeven U, Fietkau R *et al*. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2015; **16**(8): 979–989.
20. Jin J, Liu S, Zhu Y *et al*. The updated results for the phase 3 study of 5×5 Gy followed by chemotherapy in locally advanced rectal cancer (STELLAR trial). *Int J Radiat Oncol Biol Phys* 2017; **99**: e157.
21. Bahadoer RR, Dijkstra EA, van Etten B *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 randomised, open-label, phase 3 trial. *Lancet Oncol* 2021; **22**(1): P29–42.
22. Conroy T, Bosset JF, Etienne PL *et al*. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2021 May; **22**(5): 702–715.
23. Aguilar JC, Patil S, Gollub MJ *et al*. Organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy. *J Clin Oncol* 2022; **40**(23): 2546–2556. doi: 10.1200/JCO.22.00032.
24. Chua YJ, Barbachano Y, Cunningham D *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):241–248.
25. Owens R, Mukherjee S, Padmanaban S *et al*. Intensity-modulated radiotherapy with a simultaneous integrated boost in rectal cancer. *Clin Oncol (R Coll Radiol)* 2019; **32**(1): 35–42.
26. The Royal College of Radiologists. *National rectal cancer intensity-modulated radiotherapy guidance*. London: The Royal College of Radiologists, 2021.
27. Radu C, Berflund A, Påhlman L, Glimelius B. Short-course preoperative radiotherapy with delayed surgery in rectal cancer: a retrospective study. *Radiother Oncol* 2008; **87**(3): 343–349.
28. Hatfield P, Hingorani M, Radhakrishna G *et al*. Short-course radiotherapy, with elective delay prior to surgery, in patients with unresectable rectal cancer who have poor performance status or significant co-morbidity. *Radiother Oncol* 2008; **92**(2): 210–214.
29. National Institute for Health and Care Excellence (NICE). *Low energy contact X-ray brachytherapy (the Papillon technique) for early stage rectal cancer*. London: NICE, 2015.
30. Ortholan C, Romestaing P, Chapet O, Ferard JP. Correlation in rectal cancer between clinical tumor response after neoadjuvant radiotherapy and sphincter or organ preservation: 10-year results of the Lyon R 96-02 randomized trial. *Int J Radiat Oncol Biol Phys* 2012; **83**(2): e65–e71.
31. Gerard JP, Barbet N, Schiappa R *et al*. Neoadjuvant chemoradiotherapy with radiation dose escalation with contact x-ray brachytherapy boost or external beam radiotherapy boost for organ preservation in early cT2–cT3 rectal adenocarcinoma (OPERA): a phase 3, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2023: **1253**(22): 00392-2.
32. Appelt AL, Vogelius IR, Pløen J *et al*. Long-term results of a randomized trial in locally advanced rectal cancer: no benefit from adding a brachytherapy boost. *Int J Radiat Oncol Biol Phys* 2014; **90**(1): 110–118.

14
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33. Sischy B, Hinson EJ, Wilkinson DR. Definitive radiation therapy for selected cancers of the rectum. *Br J Surg* 1988; **75**(9): 901–903.
34. Gerard JP, Romestaing P, Chapet O. Radiotherapy alone in the curative treatment of rectal carcinoma. *Lancet Oncol* 2003; **4**(3): 158–166.
35. Sun Myint A, Grieve RJ, McDonald AC *et al*. Combined modality treatment of early rectal cancer: the UK experience. *Clin Oncol (R Coll Radiol)* 2007; **19**(9): 674–681.
36. Dhadda A, Cast J, Hunter I. Organ preservation using contact radiotherapy for early rectal cancer: outcomes of patients treated at a single centre in the United Kingdom. *Ann Oncol* 2014; **25**(suppl 2): ii12.
37. Stewart AJ, Van Limbergen, EJ, Gerard JP *et al*. GEC ESTRO ACROP consensus recommendations for contact brachytherapy for rectal cancer. *Clin Transl Radiat Oncol* 2021; **33**: 15–22.

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