

Continuing Professional Development



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Dr Brian Bird



Dr Liam O'Callaghan

- 1. REFLECT** - Before reading this module, consider the following: Will this clinical area be relevant to my practice?
- 2. IDENTIFY** - If the answer is no, I may still be interested in the area but the article may not contribute towards my continuing professional development (CPD). If the answer is yes, I should identify any knowledge gaps in the clinical area.

- 3. PLAN** - If I have identified a knowledge gap - will this article satisfy those needs - or will more reading be required?
- 4. EVALUATE** - Did this article meet my learning needs - and how has my practise changed as a result? Have I identified further learning needs?
- 5. WHAT NEXT** - At this time you may like to record your learning for future use or

assessment. Follow the 4 previous steps, log and record your findings.

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The Emerging Role of Total Neoadjuvant Therapy in The Treatment of Locally Advanced Rectal Cancer

Colorectal cancer is the second most common cancer in Ireland (excluding non-melanoma skin cancer) accounting for 11% of all invasive cancers in women and 14% in men.¹ Approximately 1 in 4 of these (26%) are rectal in origin. Locally advanced rectal cancer, defined as stage II (T3-4, node negative) or stage III (node positive) disease, has experienced a fundamental shift in management over the past few decades.² Advances in surgical technique, namely total mesorectal excision (TME), and the development of combined modality therapy have led to markedly improved disease-related outcomes. A comprehensive trimodality approach involving neoadjuvant chemoradiotherapy, total mesorectal excision and systemic chemotherapy has been the standard of care for patients with locally advanced rectal cancer without distant metastases. Advances in all three treatment modalities has led to a marked reduction in local recurrence rates – from as high as 25% to less than 5-10%.³ However, despite these advances, distant failure rates remain as high as 35% and constitute the leading cause of death in this population.⁴ This has spurred increasing interest in a new approach called total neoadjuvant therapy with the

addition of systemic chemotherapy in the preoperative period with the aim of eradicating subclinical micrometastases and improving long-term survival. The purpose of this article is to evaluate emerging evidence regarding the role of induction chemotherapy in combination with standard neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer.

TNM Staging of Rectal Cancer:

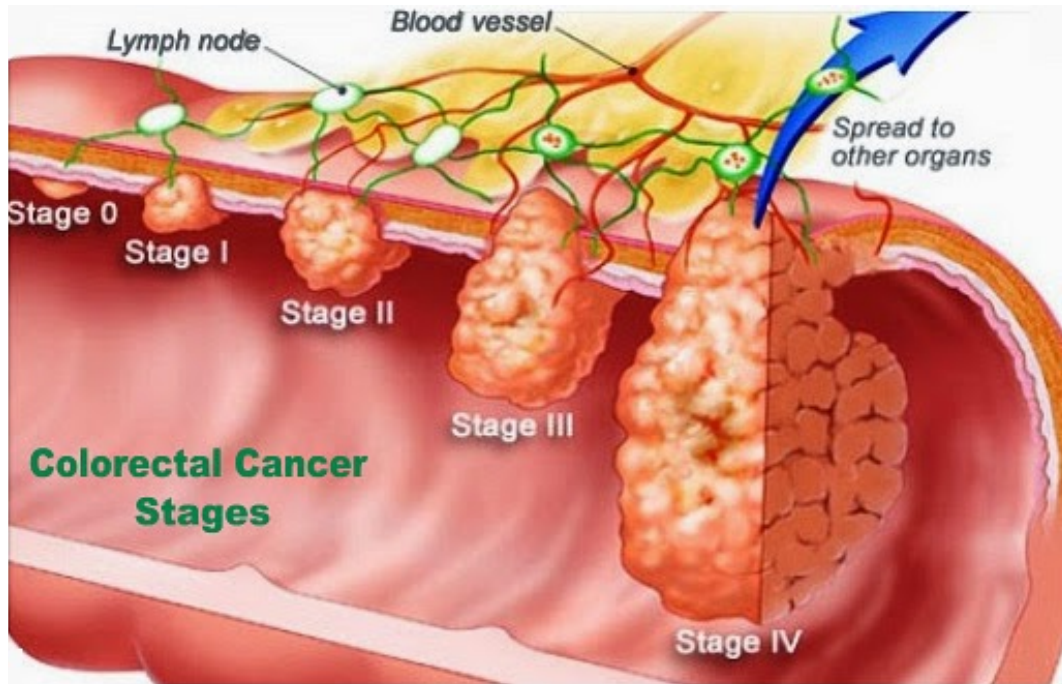
Current Treatment Approach:

Surgery has long been regarded as the only curative treatment for rectal cancer, but non-operative management (NOM) is gaining ground. The principle components for a curative resection include performing a wide resection of the cancer by achieving histologically negative margins

and performing a sharp total mesorectal excision – this includes resection of local lymph nodes with transabdominal procedures e.g. low anterior resection (LAR) or abdominoperineal resection (APR).⁵

Total mesorectal excision (TME) refers to the excision of the rectum and the tumour en bloc with its mesenteric blood and lymphatic

Stage	Level of Involvement
Tumor	
T1	Limited to mucosa and submucosa
T2	Extension into but not through muscularis propria
T3	Invasion of pirectal fat
T4	Invasion of adjacent structures
Nodes	
N0	No involved lymph nodes
N1	Fewer than four regional nodes positive for tumor
N2	More than four regional nodes positive for tumor
Metastasis	
M0	No metastasis
M1	Distant metastasis



supply. That is, the mesenteric rectum or mesorectum along with its envelope, the mesenteric fascia, was established as the gold standard for surgical management of rectal cancer in 1986 when Professor RJ Heald first described the procedure as a means to remove the discontinuous tumour deposits in the mesorectum that are most likely to cause local treatment failure.⁵

Deciding on the optimal treatment of a patient with rectal cancer is usually complicated because of the two competing major outcome measures. Curative intent of surgery must be balanced against the functional results of treatment. These include the restoration of normal bowel function / anal continence and the preservation of genitourinary functions. Contrary to colon cancer, rectal cancer has a high risk of locoregional recurrence. This is due to a number of factors including surgical difficulties in obtaining a wide excision margin (especially in tumours close to the anal verge) and the absence of a rectal serosa. The peritoneal reflection means that the lower 2/3 of the rectum are not covered in peritoneum making it easier for cancer to spread into the mesorectum.

Tumours in the upper and middle rectum can usually be managed with a sphincter-sparing

procedure, such as LAR, provided that a curative resection can be achieved and adequate anorectal function preserved. Tumours in the lower rectum (i.e. tumours within 5cm of the anal verge) may require an APR if a curative resection cannot be achieved with sphincter-sparing procedures. For patients with larger or more invasive rectal tumours, preoperative (neoadjuvant) radiation therapy and chemoradiotherapy have been utilised to promote tumour regression in an attempt to convert a planned APR into a sphincter-sparing surgical procedure. Locally advanced tumours involving adjacent pelvic organs or bony structures may require multivisceral resection (e.g. pelvic exenteration) even as a part of multidisciplinary management that includes preoperative chemoradiotherapy with or without preoperative chemotherapy.⁵

All patients with invasive rectal cancer (with the exception of those with cT1N0 disease after biopsy and local imaging) should be referred for multidisciplinary evaluation (surgery, radiation oncology, medical oncology, with joint review of radiology and pathology findings). Although surgical resection is the cornerstone of curative therapy for patients with potentially resectable rectal cancer, radiation therapy with concurrent

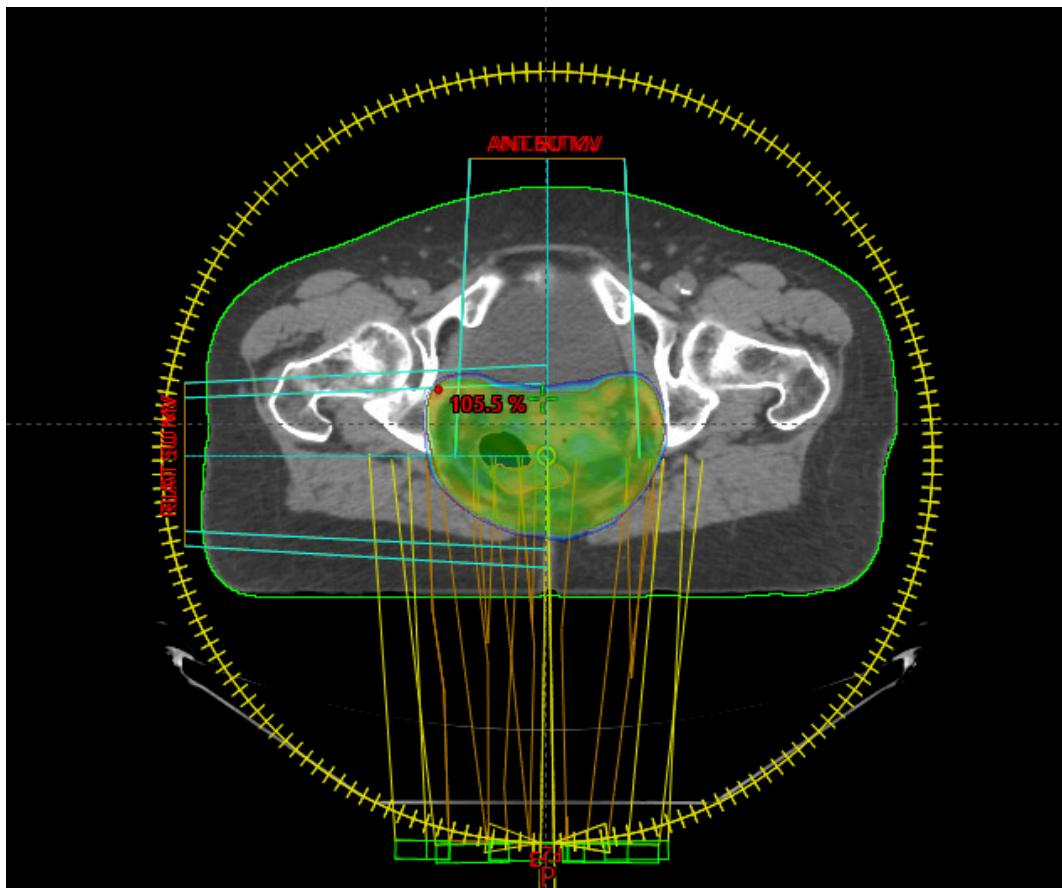
fluoropyrimidine chemotherapy (termed chemoradiotherapy or CRT) has emerged as an important component of curative therapy for transmural or node-positive rectal cancers. In contrast to colon cancer (in which the failure pattern is predominantly distant), the site of first failure in patients undergoing surgery for rectal cancer is equally distributed locally (i.e. pelvis) and in distant sites (e.g. liver, lung). For patients who undergo initial surgery, postoperative (adjuvant) therapy (usually a combination of chemoradiotherapy and chemotherapy alone) is started approximately four to six weeks postoperatively for those with transmural (i.e. T3 or T4) or node-positive tumours.⁵

Currently, chemoradiotherapy is preferentially given preoperatively (neoadjuvant chemoradiotherapy) for the following patient groups:

- Clinically staged T3 or T4, or node-positive tumours.
- Distal tumours, even if cT2N0, for which tumour regression may allow successful conversion of a planned APR into a sphincter-sparing surgical procedure.
- If the preoperative staging evaluation suggests invasion of the mesorectal fascia or a threatened circumferential resection margin.

As was demonstrated in the German Rectal Cancer Study,⁶ the benefits of neoadjuvant (as compared with adjuvant) chemoradiotherapy include a superior sphincter preservation rate, a lower rate of anastomotic stenosis as a long-term complication of pelvic radiotherapy, and better local control while providing similar long-term survival. Neoadjuvant chemoradiotherapy is generally administered over 5.5 weeks (1.8 Gray per day, five fractions per week) with concurrent infusional fluorouracil or daily oral capecitabine (long-course chemoradiotherapy). Two other types of neoadjuvant or induction therapy may be considered under specific circumstances:

- Short-course radiotherapy alone – Short-course radiotherapy (25 Gray in five fractions over one week) has been adopted in many institutions as the standard preoperative approach for operable rectal cancer. As seen in the MRC CRO7 Trial, short-course radiotherapy is as effective as traditional full-course chemoradiotherapy in patients with locally advanced rectal cancer.⁷ Short-course radiotherapy also offers additional benefits in specific patient groups, such as those who are thought unlikely to tolerate full-course



Radiotherapy Planning Image using RapidArc IMRT of T3N0 Rectal Cancer

chemoradiotherapy, or prior to rectal surgery in the setting of metastatic disease to minimize delays in initiation of systemic therapy.

- Total neoadjuvant therapy (TNT) consists of either neoadjuvant SCT or CRT followed by neoadjuvant chemotherapy (typically an oxaliplatin-based regimen, such as oxaliplatin plus short-term infusional fluorouracil and leucovorin [FOLFOX]) and then surgery. Sometimes the chemotherapy is given first, termed induction and sometimes after radiotherapy, termed consolidation. Total neoadjuvant therapy may be considered for patients with locally advanced or bulky primary tumours or in the setting of extensive nodal disease. The rationale is that the likelihood of a positive margin at the time of surgery may be diminished if the patient experiences significant downstaging using a preoperative regimen that includes both chemoradiotherapy and

chemotherapy. Further, there is a greater likelihood of completing systemic chemotherapy if given before surgery rather than after surgery due to postoperative morbidity and treatment-related toxicity. The hope of TNT is the ability to treat occult micro metastatic disease and decrease death from distant metastases. Furthermore, it provides an opportunity to assess the inherent biological profile of the tumour. Disease progression during high-dose chemotherapy is suggestive of unfavourable treatment-resistant biology, in which case resection may be futile. In contrast, in patients with marked tumour regression, organ preservation may be an appropriate option, thereby facilitating a more selective practice of surgery.⁵

Trials presented at American Society of Clinical Oncology 2020 Annual Meeting:

Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME)

in locally advanced rectal cancer – the randomized RAPIDO trial. G Hospers, RR Bahadoer, EA Dijkstra, et al:

- The aim of this study was to reduce distant metastases without an increase in local failure in high risk locally advanced rectal cancer.
- The standard arm received 5.5 weeks of chemoradiotherapy comprised of 50 Gray of radiotherapy given over 25 fractions combined with oral capecitabine chemotherapy. Surgical resection was performed ~8 weeks later with adjuvant chemotherapy 6-8 weeks postop (8 Cycles of CAPOX or 12 Cycles of FOLFOX).
- The experimental arm received 5x5 Gray radiotherapy followed by 18 weeks of neoadjuvant chemotherapy (6 Cycles of CAPOX or 9 Cycles of FOLFOX) finishing 2-4 weeks before surgical resection (total neoadjuvant therapy).
- The primary endpoint was Disease-related Treatment Failure (DrTF) defined as distant metastases, locoregional failure or treatment-related death.
- The experimental arm saw a 6.7% reduction in disease-related treatment failure after 3 years (23.7% vs 30.4%) and a 6.8% reduction in distant metastases (20% vs 26.8%)
- There was also a 2.7% increase in locoregional failure after 3 years in the experimental arm but this was not statistically significant. (6% vs 8.7%)
- Of note the short-course radiotherapy received by the experimental arm was not tested in isolation as this group also received neoadjuvant chemotherapy. A study comparing different neoadjuvant radiotherapy regimens is needed to identify the optimal radiation modality.

Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiation in patients with

locally advanced rectal cancer: Final results of the PRODIGE 23 phase III trial, a UNICANCER GI trial. T Conroy, N Lamfichekh, P-L Etienne, et al:

- The aim of this study was to improve disease-free survival in patients with locally advanced rectal cancer.
- The CRT arm received neoadjuvant chemoradiotherapy (50.4 Gray over 5 weeks with oral capecitabine) followed by total mesorectal excision and adjuvant chemotherapy (12 Cycles of mFOLFOX6 or 8 Cycles of capecitabine).
- The TNT arm received 6 Cycles of mFOLFIRINOX and neoadjuvant chemoradiotherapy followed by total mesorectal excision and adjuvant chemotherapy (6 Cycles of mFOLFOX6 or 4 Cycles of capecitabine).
- The primary endpoint was disease-free survival (defined as the first occurrence of any tumour recurrence or metastases, second cancer or death from any cause)
- The TNT arm had greater disease-free survival (75.7% vs 68.5%) and metastasis-free survival (78.8% vs 71.7%) along with lower symptom scores.
- They conclude that neoadjuvant chemotherapy with mFOLFIRINOX significantly increases the probability of pathological complete response and the probability of curative-intent surgery. It also improved disease-free survival and metastasis-free survival.
- They recommend that total neoadjuvant therapy with mFOLFIRINOX should now be considered as a new option of care in the initial management of patients with T3-4 rectal cancers.

Preliminary results of the Organ Preservation in Rectal Adenocarcinoma (OPRA) trial. J Garcia-Aguilar, S Patil, JK Kim, et al:

- The hypothesis was that a treatment approach that incorporates total neoadjuvant therapy (TNT) and selective watch-and-wait (WW) for patients with a clinical

complete response (cCR) will result in better 3-year disease-free survival compared to patients treated with chemoradiotherapy (CRT), total mesorectal excision (TME) and adjuvant chemotherapy.

- This trial compared two different sequences of total neoadjuvant therapy to historical controls – one group in the investigational arm received chemotherapy followed by chemoradiation and the other group received chemoradiation followed by chemotherapy.
- A formal investigation between these two arms and the control arm (neoadjuvant chemoradiation and adjuvant chemotherapy) was not undertaken.
- The primary endpoint was disease-free survival at three years.
- They found no difference in disease-free survival between patients treated with TNT and selective WW or TME, compared to historical controls treated with CRT, TME and adjuvant chemotherapy.
- The order of chemoradiation and systemic chemotherapy did not affect survival or distant metastasis rates.
- With this study design, patients who received CRT followed by systemic chemotherapy are more likely to preserve the rectum compared to patients treated with systemic chemotherapy first.
- Organ preservation may be a safe alternative to TME for patients with a clinical complete response to total neoadjuvant therapy.
- Chemoradiation followed by consolidation chemotherapy may be the preferred TNT approach if organ preservation is a priority.

Summary:

Historically, treatment for clinical stage II or III locally advanced rectal cancer (T3/4, N0, or node-

positive) consisted of preoperative chemoradiotherapy followed by TME and postoperative adjuvant chemotherapy with fluorouracil and oxaliplatin. Emerging evidence from clinical trials is challenging this standpoint and total neoadjuvant therapy is quickly becoming the new standard of care. Improvements in disease-free survival, reductions in distant metastases and a superior sphincter preservation rate have all been attributed to total neoadjuvant therapy. Long-term results of ongoing and future trials will continue to refine the role of TNT in the setting of locally advanced rectal cancer.

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