GM Colorectal Pathway Board

Guideline:

Neoadjuvant and Non-operative Management of Rectal Cancer

1. Clinical Updates

In this latest update, *v2.0 November 2023*, we aim to adapt our guidance in response to emerging data including:

- Maturing TNT data
    - With a multitude of international TNT regimens reported in the data, we acknowledge there is justification for utilising varying TNT approaches, dependent upon patient and tumour factors. In this document, we aim to offer guidance regarding TNT regimen selection alongside MDT discussions.

- The emerging role of neoadjuvant chemotherapy, and omission of radiotherapy, for selected intermediate and locally advanced rectal cancers

- MMR testing
    - MMR status is routinely performed on all rectal biopsies across GM
    - For MMR deficient rectal cancers, neoadjuvant immunotherapy (including trial entry) should be considered

2. Early Rectal Cancer

Definition: T1 – T3b (CRM negative, tumours < 5cm in size, pMMR)

1.1 There is no role for pre-operative radiotherapy prior to Total Mesorectal Excision (TME) in early T1-T3b rectal cancers. These may be treated by immediate surgery unless there are:

- adverse histological or radiological features, when 25Gy/5# prior to immediate surgery may be considered
- concerns regarding a patient's suitability for surgery, when 25Gy/5# prior to delayed reassessment
    - prehabilitation/optimisation for surgery can be undertaken during the downstaging period

Patients who may proceed straight to surgery, without neoadjuvant treatment:

Location	mid or upper
T stage	T3 a/b
N stage	N0 (mid) N0/1 (upper)
CRM	Not involved
EMVI	Negative

ESMO Clinical Practice Guidelines: Gastrointestinal Cancers[1]

1.2 In low rectal cancers, requiring an abdominoperineal resection (APR) and permanent stoma formation, the patient may be keen to attempt organ preservation, and in these cases a number of treatment approaches may be considered:

1.2.1 **T1 tumours**: a combined TEMS / radiotherapy approach, as adopted in the TREC trial[2], aiming for organ preservation may be offered

1.2.2 Long course chemoradiotherapy (LCCRT) may be offered with the aim of achieving a clinical Complete Response (cCR).

Schedule: 45Gy/25# +/- a boost to the primary tumour, 5.4 – 9Gy/ 3-5#.

Patients should be informed that the likelihood of this is, at best, 30-40%, and if achieved they should be willing to comply with the GM Colorectal Cancer Complete Responder Guidelines[3] COLORECTAL CLINIC SUBGROUP (gmcancer.org.uk)

1.2.3 The OPRA study recruited patients with T2-3b N0/1 rectal cancers, < 5cm and offered LCCRT 45Gy/25# with concurrent Capecitabine) alongside a Papillon boost (90Gy/3#). A 3 year organ preservation (OP) rate of 97% (T<3cm) vs 68% (T>3cm) was reported when compared with LCCRT with external beam boost (9Gy/5#) – 63% vs 55% (T < or > 3cm respectively)[4].

In accordance with NICE guidance[5] (2020), all patients should be offered recruitment to the OnCoRe registry[5] www.complete-response.com

3. Intermediate Rectal Cancers

Definition: T3c (CRM not threatened, pMMR)

For the purposes of our GM guidance 'intermediate' rectal cancers encompassed tumours:

- ≥T3c

and/or

- have a clear Circumferential Resection Margin (CRM > 1mm) which is not threatened either directly by tumour, or by extramural vascular invasion (EMVI) or suspicious lymph nodes

The treatment approach for these 'intermediate' risk cancers has become increasingly more complex because of the heterogeneity of tumours encompassed within this group. It is recognised that, in addition to CRM status, other radiological features will also influence the MDT decision.

Tumour Location	Distal vs Mid/Upper
Adverse Radiological features	EMVI
	N1 or N2 disease
	N1c deposits
Adverse Histological features	Poorly differentiated

Table 1: Adverse rectal cancer characteristics

The following criteria are for MDT guidance of the neoadjuvant approach (acknowledging there may be exceptions agreed by the MDT):

<table>
<tr><th>Tumour Location</th><th>Adverse features* absent</th><th colspan="2">Adverse features* present</th></tr>
<tr><td rowspan="2">Mid/Upper</td><td rowspan="2">Immediate surgery</td><td>SCRT, 25Gy in 5#, prior to immediate surgery</td><td rowspan="4">If 2+ adverse features present & patient PS 0/1

TNT</td></tr>
<tr><td>Neoadjuvant chemotherapy, 6 x FOLFOX~</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Distal</td><td>Immediate surgery</td><td>SCRT, 25Gy in 5# prior to immediate surgery</td></tr>
<tr><td colspan="2">LCCRT with the aim of organ preservation and achieving a cCR</td></tr>
</table>

Table 2: Neoadjuvant approach for intermediate rectal cancer

*Adverse features as described in Table 1

~ The recently published PROSPECT trial compared the use of neoadjuvant FOLFOX x 6 vs LCCRT in patients with T2, node positive and T3, node positive/negative mid/upper rectal cancers (planned for sphincter-sparing surgery). The trial demonstrated that disease-free survival was non-inferior in the experimental arm (5 year DFS: 80% vs 78.6%)[6]. This approach may be considered for mid/upper rectal cancers.

The CONVERT trial has also considered the role of neoadjuvant chemotherapy (nCRT: CAPOX x 4) vs LCCRT (50Gy/25#). It is important to note that the majority of trial patients had locally advanced disease and therefore the results should be applied with caution to this intermediate patient group. However, patients with T2 N1 disease were eligible (T2 = 4.6%). A pathological (pCR) rate of 11.0% vs 13.8% (nCRT vs LCCRT) was reported, with a reduced rate of peri-operative distant metastases was observed in the nCRT arm (0.7% vs 3%)[7].

4. Locally Advanced Rectal Cancer

Definition: T4 or CRM threatened (pMMR)

Locally Advanced Rectal Cancer (LARC) is defined as:

- an involved Circumferential Resection Margin (CRM ≤ 1mm) which is threatened either directly by:

  - tumour (T3)
  - tumour involvement of adjacent structure/organ (T4a/b)
  - extramural vascular invasion (EMVI)
  - morphologically abnormal lymph nodes
  - N1c tumour deposit

There are a multitude of treatment approaches for these patients, based upon patient and tumor factors. Any treatment plan will require a robust MDT discussion and patient assessment:

Patient Factors	Tumour Factors
Performance Status	T & N stage
Age	EMVI N1 or N2 disease N1c deposits
Comorbidities	Location eg. distal / proximal
Patient preferences e.g organ preservation	

Table 3: Factors determining neoadjuvant approach for LARC

Treatment options for LARC include:

1) **Long Course Chemoradiotherapy (LCCRT)**

Schedule: 5-6 weeks of radiotherapy (total dose: 45–54 Gy/25–28#) combined with concurrent Capecitabine chemotherapy (825mg/m^2 Monday-Friday)

The aim is to downstage disease, and enable an R0 resection, but a small proportion of patients may achieve a cCR.

We propose long course radiotherapy (LCCRT) alone (rather than a TNT approach) is considered for the following patient groups:

- PS 2
- Age >70 - this is not an absolute cut-off but toxicity and ability to complete treatment should be considered when debating the role of TNT (see below). Offering LCCRT – with or without concurrent Capecitabine - and restaging may remain the appropriate neoadjuvant approach but is at the discretion of the MDT.
- CRM + but no other adverse radiological or histological features noted. In selected cases, this single risk factor may be adequate for the MDT to recommend TNT (please refer to TNT indications, below).

2) Total Neo-adjuvant Therapy (TNT)

Total Neoadjuvant Therapy – TNT- adopts the use of both (chemo)radiotherapy and neoadjuvant chemotherapy prior to surgery in patients with locally advanced, non-metastatic disease. There are various TNT schedules published, with overlapping patient inclusion criteria and different endpoints. This guideline aims to offer a structured approach to TNT regimen selection but MDT discussion and patient assessment is important when determining the optimum approach.

Trial Author	N =	1st treatment	2nd treatment	3rd treatment	pCR (*+cCR)	3 yr DFS
RAPIDO Bahodoer Lancet Onc 2020	920	LCCRT SCRT	- Chemotherapy	Surgery Surgery	pCR 14% pCR 28%	69.6% 76.4%
OPRA Garcia-Aguilar JCO 2022	324	Chemotherapy LCCRT	LCCRT Chemotherapy		41%* 3 yr TME-free survival 53%*	76% 76%
PRODIGE Conroy Lancet Onc 2021	461	LCCRT Chemotherapy	Surgery LCCRT	Adjuvant chemotherapy Surgery +/- chemo.	11.7% 27.5%	69% 76%
STELLAR Jin JCO 2022	599	LCCRT SCRT	Surgery Chemotherapy	Chemotherapy Surgery	14% 28%	64.5% 62.3%

Table 4: TNT trial data summary

Table 4 demonstrates that TNT can result in improved patient outcomes compared with chemoradiotherapy alone, however, these trials reported significant G3 toxicity (in approximately 60% of patients). Therefore, selecting suitable patients and justifying a TNT approach is key.

Q1: Who should be considered for TNT?

The following criteria are based upon eligibility criteria for TNT trials including RAPIDO[8], OPRA[9], PRODIGE[10] and STELLAR[11]. In RAPIDO, over 66% of patients had 2-5 adverse factors (defined in *Table 5*) present and we have adopted this approach in our guidelines. However, there may be instances when the MDT agree TNT should be offered to patients with 1 adverse feature (and the patient would still have been eligible for the one of the above mentioned TNT trials)*.

Patient Factors	*Tumour Factors* ***At least 2 should be present****
PS 0/1	CRM +
Age < 70* (this is not an absolute cut-off)	T4
Minimal, well controlled comorbidities (unlikely to compromise ability to complete treatment)	EMVI +
	N2 disease
	Lateral pelvic side wall nodes

Table 5: LARC factors to support use of TNT

Q2: What TNT sequence should be adopted?

Radiotherapy → Neoadjuvant chemotherapy → Reassessment

In the majority of patients receiving TNT, neoadjuvant radiotherapy will precede chemotherapy, in line with the RAPIDO and STELLAR trials. OPRA also demonstrated higher rates of OP when LCCRT was delivered prior to chemotherapy (5 year TME-free survival 54% vs 39%).

Neoadjuvant chemotherapy → Radiotherapy → Reassessment

Similar to the PRODIGE approach, chemotherapy may precede radiotherapy:

- For bulky, proximal tumours (for example, straddling or extending above the peritoneal reflection) where there are concerns regarding radiotherapy field size and anticipated toxicity
- There are concerns about risk of distant metastatic disease and a priority to deliver SACT e.g. EMVI + or multiple abnormal nodes

Q3: Which radiotherapy approach should be used?

We acknowledge the updated RAPIDO data and a higher rate of locoregional recurrence (LRR) in patients treated in the experimental arm (SCRT and neoadjuvant chemotherapy). Ongoing analysis continues but the following pathological factors at the time of surgery were noted to be associated with an increased risk of LRR: enlarged lateral lymph nodes, a positive CRM, N1c tumour deposits[12]. These adverse pathological features have shaped the neoadjuvant treatment selection guidance in *Table 5.*

	Short course radiotherapy SCRT 25Gy/5#	Long course chemoradiotherapy LCCRT 45-50.4Gy/25-28# Concurrent Capecitabine 825mg/m^2 Monday - Friday
Location	Proximal/Mid	Distal
T staging	< T4a	T4a or b
CRM status		Positive
EMVI status	Positive	
N2 disease	Positive	
Lateral Pelvic Nodes		Involved

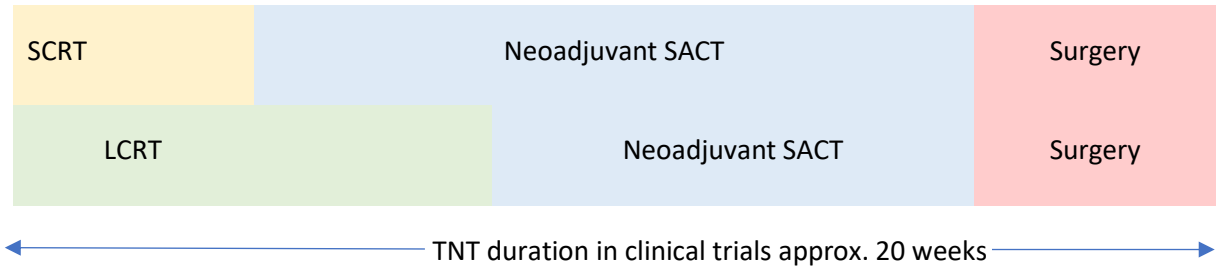
Table 6: LARC radiological characteristics to guide XRT schedule selection

Other issues which may influence the XRT approach:

- The anticipated radiotherapy field size and irradiated small bowel volume
- If the primary intent is to achieve a cCR, the OPRA regime using a LCCRT approach may be preferred
    - Indication for radiotherapy boost (5.4-9Gy/3-5#) to:
        - Involved lateral pelvic side wall nodes, beyond the mesorectal fascia
        - The primary tumour, when the treatment aim is to achieve a cCR

Q4: Which chemotherapy regimen should be adopted in the TNT schedule?

The XRT approach – SCRT or LCRT – may dictate the duration of neoadjuvant chemotherapy, aiming for a TNT period of approximately 20 weeks.



However, there is still debate about the optimal duration of neoadjuvant therapy. We therefore suggest a pragmatic approach whereby all patients receive a 3/12 duration of neoadjuvant chemotherapy although we accept there may be specific situations where a varying duration (12-18 weeks) is proposed.

	Chemotherapy	Duration
Short course radiotherapy (SCRT)	FOLFOX CAPOX	3 months
Long course radiotherapy (LCRT)	FOLFOX FOLFIRINOX* CAPOX	

*The majority of TNT trials have utilised a doublet chemotherapy schedule, with the exception of PRODIGE 23[10] which adopted neoadjuvant FOLFIRINOX. This schedule may be suitable for fit patients, with minimal/no comorbidities and multiple adverse staging characteristics.

We would propose the following group of tumour characteristics are considered for FOLFIRINOX:

- PS 0/1
- T4b, or, disease beyond the mesorectal fascia
- Features difficult to encompass in a radiotherapy field

5. Patients deemed unsuitable for surgery

Patients may be unfit for surgery for a variety of reasons, which will also influence the non-surgical treatment approaches offered.

The intent of non-operative management may be to:

- achieve a cCR
- to downsize or downstage, aiming to offer long term local control
- palliate local symptoms

The treatment indication, patient's symptoms, ECOG Performance Status and anticipated toxicity will influence the radiotherapy prescription.

a) Short course radiotherapy and delay

Schedule: 25Gy/5# (delivered over 5-7 days) followed by an 8-10 week delay before re-staging

b) Long course (chemo)radiotherapy and restage

c) Palliation of symptoms: 20Gy/5#, 25Gy/5#, 30Gy/10#

Low Energy Contact Brachytherapy (Papillon) can be considered for surgically unfit patients with early rectal cancer. This treatment approach should be discussed at the MDT and the patient referred to Clatterbridge Cancer Centre.

Referral Form
Contact RT Version 2 .

6. MMR testing & MMRd tumours

MMR testing is routinely performed on rectal cancer biopsies. Ideally, MMR should be performed on an adenocarcinoma specimen rather than high grade dysplasia (HGD). The dysplastic component will frequently mirror the MMR status of the invasive tumour, but not always. A MMRd high grade dysplastic biopsy is likely to reflect the malignancy but an MMRp dysplastic biopsy may not.

If the 1st rectal biopsy does not confirm adenocarcinoma, a 2nd biopsy should be considered. If repeat biopsies demonstrate high grade dysplasia only, the pathology report should clearly state that dysplasia only has been tested.

Patients with an MMR deficient rectal cancer, localised or metastatic, should be offered immunotherapy as primary treatment.

A) Localised, non-metastatic disease, MMR deficient rectal cancer

A phase II trial using Dostarlimab in MMR deficient stage II and III rectal cancer reported a 100% cCR rate, avoiding the need for pelvic radiotherapy or surgery[13]. Access to Dostarlimab, via a clinical trial or compassionate access, should be considered before offering other surgical or oncological treatments.

B) Mx or M1 disease, MMR deficient rectal cancer

The phase III KEYNOTE-177 trial demonstrated improved overall response rates (43.8% vs 33.1%) and progression free survival (16.5 vs 8.2months) in metastatic dMMR patients receiving Pembrolizumab vs standard chemotherapy. First line Pembrolizumab is NICE approved for dMMR/ MSI-High metastatic colorectal cancers (Blueteq application) and should be considered prior to palliative chemotherapy[14]. If there is evidence of response, Blueteq currently advocates 2 years duration.

For patients who did not receive 1st line immunotherapy for metastatic disease, for whatever reason, access to 2nd line Ipilimumab/Nivolumab combination is available. If this is unsuitable, single agent Pembrolizumab should be considered.

7. Reassessment post neoadjuvant treatment

Timing of restaging investigations following neoadjuvant treatment

Neoadjuvant approach	**Time from *completion* of neoadjuvant treatment until restaging**
Short course or Long course chemoradiotherapy alone	8 – 10 weeks
TNT: XRT → chemotherapy Chemotherapy → XRT	 5 - 6 weeks[$] 7 weeks*

[$]Taken from the STELLAR[11] protocol, also incorporating OPRA[9] trial = 8 weeks (+/- 4 weeks)

**Based upon PRODIDGE[10] schedule*

Reassessment of Early Rectal Cancers - T1 – T3b (CRM negative, tumours < 5cm in size)

If the intent of treatment is to achieve a cCR, an adapted – 2 stage – assessment can be considered if there is evidence of response on the 1st restaging investigations. This merits careful MDT and patient discussion at the 1st restaging timepoint, as described below. Further guidance on the cCR f/u pathway is shown in section 8 (page 17)

	1st timepoint (from *start* of XRT)		2nd timepoint (from *start* of XRT)		3rd timepoint (from *start* of XRT)
OPERA[3]	Week 14 MRI & endoscopy	ncCR = Yes	Week 20 MRI & endoscopy	If a cCR NOT achieved	Week 24 MRI & endoscopy
STAR-TREC Ph III [15]	Week 11 -13 MRI & endoscopy	ncCR = Yes	Week 16-20 Endoscopy		

8. Clinical Complete Response (cCR)

cCR is a triad of evidence including:

- no palpable tumour on digital rectal examination (DRE)
- fibrosis/no visible residual disease on MRI (TRG 1/2)
- a flat white scar on endoscopy

If a cCR is identified following radiotherapy alone or TNT, patients should be counselled regarding their treatment options:

- the patient and surgical team may still wish to proceed with TME. The patient should be counselled regarding the possibility of a pathological Complete Response (pCR) being confirmed.
- patients may be keen to purse organ preservation and stoma avoidance, in which case, they may be offered surveillance. The GM complete responder pathway schedule should be adopted[2] and the patient should be recruited to the OnCoRe registry[5] **www.complete-response.com**

Groups	Time (months)											
	3	6	9	12	18	24	30	36	42	48	54	60
1. Low risk (endoscopically removed T1 polyp cancers)	Endoscopic visualisation of scar [a]	CEA		CEA CT TAP Colon*	CEA	CEA CT TAP	CEA	CEA		CEA Colon		CEA
2. Intermediate (Stage 1-3, Dukes A-C) tumours with curative resections **		CEA		CEA CT TAP Colon*	CEA	CEA CT TAP	CEA	CEA CT TAP		CEA Colon		CEA
3. High risk (Stage 4 disease) at presentation with primary & metastatic sites resected (liver, lung, peritoneum)		CEA CT TAP		CEA CT TAP Colon*	CEA CT TAP	CEA CT TAP	CEA	CEA CT TAP		CEA CT TAP Colon		CEA CT TAP
4. 'Watch and Wait' for Clinical complete response after chemoradiotherapy for rectal cancer (recruit to OnCoRe)	MRI F Sig	MRI F Sig CT TAP	MRI F Sig	MRI Colon* CT TAP	MRI F Sig CT TAP	MRI F Sig CT TAP	MRI F Sig	MRI F Sig CT TAP		F Sig CT TAP Colon		CT TAP

[a] Frequency of further investigation of scar depends on findings at the 3-month flexi sig or colonoscopy

* Patients will have year 1 and 4 colonoscopy as per 2019 BSG guidelines

** High risk patients in this group may have an additional scan at 60 months if clinically indicated

Follow-up schedule, taken from GM Colorectal Cancer Complete Responder Guidelines (2018) [2]

9. Functional outcomes / Late toxicity and ePROM

Poor functional outcomes and low anterior resection syndrome is common after surgery for rectal cancer. Risk factors for LARS include low tumour height and previous pelvic radiotherapy. At present there is insufficient data on the functional outcomes for patients undergoing total neoadjuvant treatment.

The potential functional outcome for each patient should be considered where more than one treatment strategy is viable, with the aim of maintaining oncological efficacy whilst minimising the risk of dysfunction. Any discussion of different treatment options with the patient should include the risk of LARS as well as sexual and urinary dysfunction.

10. Adjuvant SACT

Post-operative SACT may be considered:

1) following neoadjuvant radiotherapy alone

2) following TNT

The benefit of adjuvant chemotherapy following TNT is uncertain. Based on data from the SCOT study and IDEA collaborative it appears unlikely that extending the duration of Oxaliplatin/ Capecitabine chemotherapy beyond 12 weeks will impact on Disease Free or Overall Survival in this high-risk patient group. Therefore, if the patient has received this duration of neoadjuvant chemotherapy, further post-operative adjuvant chemotherapy is unlikely to provide any further benefit. From a subset analysis of RAPIDO data, patient outcomes were the same irrespective of whether they received adjuvant chemotherapy or not[8]. However, the benefits of further adjuvant chemotherapy can be debated in the MDT when the pathology from the resection specimen is available.

If a patient has had a cCR and has not had surgery, no further adjuvant chemotherapy is recommended since there is no evidence to support this.

11. Pelvic Reirradiation

There are several clinical scenarios when pelvic reirradiation may be considered:

a) oligometastatic or localised disease recurrence

b) recurrent disease, unsuitable for up front resection due to concerns regarding the surgical margin

c) previously treated non-rectal pelvic malignancy e.g prostate

Each of these scenarios will require an individual approach but are likely to consider:

- the location, and volume, of disease
- the previous radiotherapy schedule and irradiated volume
- the time elapsed since previous radiotherapy treatment
- the intent of pelvic reirradiation (neoadjuvant prior to surgery vs palliative, aiming for local control)
- the equivalent dose in 2Gy /# (EQD2), as a measure of the total dose of radiation delivered by both treatments (to both the tumour and adjacent normal tissues)
- alternative treatment modalities to radiotherapy
- presence of extra-pelvic ie. metastatic disease and patient's prognosis

There are agreed GM protocols regarding:

A) SABR for the treatment of oligometastatic or localised disease recurrence

SABR Pelvic Reirradiation protocol

B) BD pelvic reirradiation, for patients who are unsuitable for SABR. The aim of reirradiation is to downstage and achieve a radical, R0, resection

Hyperfractionated pelvic re-irradiation p

For patients unsuitable for A) or B) above, the following prescribed radiotherapy doses may be considered:

i) 20Gy /10#
ii) 20 – 25Gy/5#
iii) 30 – 10/15#

The radiotherapy prescription will be influenced by the clinical and radiobiological factors outlined above.

References

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5 Overview | Colorectal cancer | Guidance | NICE

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