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The Christie NHS Foundation Trust

Greater Manchester (GM) Cancer: Colorectal Pathway Board

Guideline:

Neoadjuvant and Non-operative Management of Rectal Cancer

Abbreviations

CAPOX	Capecitabine/Oxaliplatin
cCR	clinical Complete Response
DFS	Disease free survival
dMMR	Deficient mismatch repair
EBRT	External beam radiotherapy
ERC	Early rectal cancer
FOLFOX	Oxaliplatin/5-Fluorouracil
FOLFIRINOX	Oxaliplatin/Irinotecan/5-Fluorauracil
LARC	Locally advanced rectal cancer
LCCRT	Long course chemoradiotherapy
GM	Greater Manchester
HGD	High Grade Dysplasia
LRR	Locoregional recurrence
MDT	Multi-disciplinary team
MMR	Mismatch repair
MRF	Mesorectal fascia
mrTRG	MRI based Tumour Regression Grade
MSI-High	Microsatellite instability High
ncCR	Near clinical complete response
nCT	Neoadjuvant chemotherapy
nCRT	Neoadjuvant chemoradiotherapy
NOM	Non operative management
OP	Organ preservation
OS	Overall survival
pCR	pathological Complete Response
pMMR	Proficient mismatch repair
PS	Performance Status
RT	Radiotherapy
SACT	Systemic Anti-Cancer Therapy
SoC	Standard of Care
SCRT	Short Course Radiotherapy
TAMIS	Transanal minimally invasive surgery
TEMs	Transanal endoscopic microsurgery
TME	Total Mesorectal Excision
W&W	Watch and wait

1.Clinical Updates

In this latest version, *v3.0 May 2026*, we have updated our Greater Manchester (GM) guidance in response to emerging clinical data and recommendations.

- *Updated European (ESMO)[1] and North American (NCCN)[2] guidelines, 2025*, have been reviewed and, where appropriate, local guidance amended.

- *Updates in radiotherapy treatment delivery*: As part of long course (chemo)radiotherapy, a synchronous integrated boost (SiB) to gross disease has replaced sequential radiotherapy (RT) boosts; radiotherapy dose & fractionation schedules have been amended in line with UK Royal College of Radiologists (RCR) rectal cancer guidance (National rectal cancer intensity-modulated radiotherapy (IMRT) guidance | The Royal College of Radiologists).

- *NICE Update[3] 11/2025* supporting the use of low-energy contact x-ray brachytherapy (Papillon) and recognising the important of patient counselling and treatment selection, in early rectal cancer (ERC).

- *Maturing Total Neoadjuvant Therapy (TNT) regional GM data*: With a multitude of international TNT regimens reporting matured data & patient outcomes, we acknowledge TNT has become standard of care (SoC) for patients with Performance Status (PS) 0/1 and locally advanced rectal cancer (LARC). There is justification for utilising varying TNT approaches, dependent upon patient & tumour factors alongside the treatment intent. This document provides guidance regarding TNT regimen selection for MDTs, aiming to reduce variation in patient selection and treatment pathways. The Christie continues to maintain a prospective database of GM TNT patients, enabling us to reflect upon our regional experience in alignment with international guidance.

- *Assessment & management of near complete Clinical Response (ncCR):* Several (early & locally advanced) rectal cancer trials have described a 2-stage assessment of near-complete and complete clinical response (ncCR and cCR) which – in a trials setting - replace the single response assessment post neoadjuvant therapy. Whilst not all trials have published their long term outcomes, GM trial recruitment and experience has accumulated. These trials provide a surveillance framework that can be embedded into standard of care (SoC) assessment & management of ncCR, which - with patient involvement & informed decision making - may be considered if the treatment intent is organ preservation (OP). We recognise this is an evolving field and await updates from OnCoRe and ACPGBI, but MDTs value guidance of ncCR for patients who are keen to pursue OP.

- *Implementation of a GM-wide MRI rectum reporting template, June 2025:* A GM multi-disciplinary working group developed an MRI reporting template, to standardise staging reporting. Ensuring complete staging data is pivotal to MDT discussions, amidst a multitude of treatment approaches for early and locally advanced rectal cancer, patient preference and counselling of treatment options.

- *GM Guideline Recognition by NBOCA:* In their State of the Nation Report 2025[4], NBOCA referenced these guidelines as an example of how regional guidelines can be used to address variations in care. This latest version has been adapted for a multi-disciplinary readership.

2. Early Rectal Cancer

Definition: **T1 – T3b (EMVI negative, MRF -, tumours <5cm, pMMR)**

Defining 'early' stage rectal cancer is an area of debate. For the purposes of this oncological guidance, we have adopted the staging criteria used in early rectal cancer (ERC) trials *(table 1)* although we acknowledge:

(i) the surgical definition of ERC differs for the purposes of the Significant Polyp & Early Colorectal Cancer (SPECC) MDT

(ii) there is overlap with the definition of 'intermediate' rectal cancer (page 10)

	T & N inclusion criteria	Tumour size	Exclusion criteria
OPERA	T2 – 3b, N0 – N1 (node < 8mm)	< 5cm	N1 node > 8mm EMVI + Poorly differentiated histology
APHRODITE	T1 – T4b, N0 – N1b	< 5cm	N1c / N2 disease Mucinous MRI features Neuroendocrine histology MRF +
STAR TREC	T1 – 3b, N0	< 4cm	N1 EMVI + Mucinous MRI features MRF +

Table 1: ERC trials and definition of 'early' disease

There are a multitude of surgical and non-surgical approaches for patients with ERC. Tumour location, baseline bowel function and patient preference will determine the treatment selection. Careful endoscopic assessment aligned with MRI characteristics is essential. NICE guidance (2025)[3] mandates that patients should be offered a discussion about all surgical and non-surgical treatment approaches with the appropriate specialist in an era of increasing organ preservation.

Surgery

This oncology guidance acknowledges the role of surgery – alongside neoadjuvant and adjuvant treatments for ERC - but does not provide further surgical details beyond this.

Total Mesorectal Excision (TME)

For patients proceeding directly to Total Mesorectal Excision (TME) there is no role for pre-operative RT for most patients. There may be exceptions including:

- concerns regarding a patient's fitness for surgery, when short course radiotherapy (SCRT), 25Gy/5#, prior to planned **deferral** of surgery can be offered to support:
  - GM prehabilitation programme/optimisation for surgery; undertaken during the downstaging period (8-10 weeks) post RT
  - in this scenario, non-operative treatment approaches as outlined (page 7) should be reconsidered

- adverse histological or radiological features, when SCRT prior to **immediate** surgery may be considered with the intention of reducing the risk of local recurrence
    - *Adverse features may include:* EMVI+ or N+ or poorly differentiated histology. However, these features overlap with indications for TNT, which may be justified in this setting and in our contemporary GM practice have largely replaced SCRT prior to immediate surgery.

Transanal Endoscopic Microsurgery (TEM) and Transanal Microinvasive Surgery (TAMIS)

Local excision, as a definitive (single modality) treatment, may be appropriate for early tumours without adverse features present, as supported by ESMO[1] and NCCN[2] 2025 guidelines. At the time of writing this document (v3, May 2026), a GM ERC working group has been established to discuss care pathways for patients with ≤T2 N0 rectal cancer and review of inclusion criteria; in particular, discussion regarding management of T2 tumours continues.

Careful endoscopic assessment by an MDT endoscopist is important to identify patients suitable for these approaches. Patients must be pre-operatively counselled about the requirement for further surgical or non-operative treatment in the event of adverse histology (including: involved resection margin <1mm, poorly differentiated histology, vascular invasion, high tumour budding score).

If unfavourable characteristics are reported in the excision specimen, salvage TME should be offered. There is limited data to support the role of adjuvant radiotherapy in this setting, and this should only be discussed with the patient following assessment for TME if there are concerns regarding surgical fitness or the patient is stoma averse. We await evolving international trials[5,6,7], investigating the dual treatment approaches (RT in combination with TEMS); this data will likely impact future versions of this GM guidance amidst increasing clinician and patient preference for OP and stoma avoidance. Oncological safety, and long-term disease free (local and distant) survival, remains paramount.

Offering adjuvant RT post local excision can be challenging; in most cases there will be no residual gross tumour to delineate, and the excision site will not be identifiable on radiotherapy planning CT. In this instance, an endoscopy report detailing the height and location of the tumour prior to local excision, including retroflexion images is extremely useful. Whilst ESMO[1] acknowledges the role of adjuvant Papillon to the TEMs site, this has not been adopted in our GM practice; external beam RT is advised to ensure the mesorectum is treated (elective nodal irradiation) in addition to the rectal lumen (excision site).

Adjuvant RT schedules post TEM/TAMIS for high-risk tumours or patient unsuitable for TME:

- Long course chemoradiotherapy (LCCRT): 45Gy/25# with concurrent Capecitabine 825mg/m^2 BD (no SiB should be incorporated unless this can be confidently delineated e.g. gross residual disease, metallic clips[7])
- Short course radiotherapy (SCRT): 25Gy in 5#

Conventional ICTV_Elective volumes should be used[7], whilst we await data from STAR TREC[5] regarding mesorectal only irradiation.

Radiotherapy (RT) aiming for organ preservation

External Beam RT and Papillon

T1 - T3b N0, T < 5cm, EMVI -

The OPERA[8] trial recruited patients with T2-3b N0/1 rectal cancers and investigated RT dose escalation, comparing an external beam boost vs Papillon. Inclusion criteria included: tumours in the low and mid rectum, < 5cm in maximum dimension, and N1 nodes <8mm diameter. All patients received LCCRT, 45Gy/25#, with concurrent Capecitabine, and were randomised to receive either an external beam boost (9Gy/5#) or Papillon boost (90Gy/3#). Within the Papillon boost arm, the size of the primary lesion determined the RT sequence (< 3cm = Papillon 1st, or >3 cm = EBRT 1st). A 3-year OP rate of 97% (T<3cm) vs 68% (T>3cm) was reported in the Papillon arm, compared external beam boost 63% vs 55% (T < or > 3cm respectively). Late rectal bleeding (Grade 1-2) was reported in 12% vs 63% (external beam RT vs Papillon dose escalation) of patients respectively.

NICE[3] endorsed the role of Papillon, in association with external beam RT, in November 2025 for patients who were either (a)surgically unfit or (b) keen to avoid surgery/pursue an OP strategy. This is now SoC for GM patients presenting with T1-3b N0 tumours with maximum craniocaudal dimension <5cm. Patients should be referred via the regional Clatterbridge Papillon pathway. The MDT clinical oncologist should confirm patient suitability and complete the referral form. The Clatterbridge Papillon MDT will confirm a) patient suitability and b) RT sequence.

Papillon treatment :: The Clatterbridge Cancer Centre

Referral Form Contact RT Version 2 .

Referral Form Contact RT Version 2 .

Restaging (MRI & endoscopy*) should be performed 8 weeks post completion of treatment (irrespective of RT sequence), arranged by the local surgical team

There are 3 potential restaging outcomes post combination RT/Papillon:

- Clinical complete response (cCR) – *refer to page 23*
- Near clinical complete response (ncCR)* - *refer to page 25*
- Overt residual disease (on endoscopy or mrTRG 4/5): definitive surgery should be advised

*Endoscopic assessment – by a skilled MDT endoscopist - may identify an ulcer, reflecting either treatment effect or residual disease. This possible radiation effect **should not be biopsied** at the 1st restaging timepoint and should be correlated with the MRI appearances. Endoscopy images can be forwarded to Clatterbridge for clinical advice and guidance about the timing of biopsy. If mrTRG 1-3, the MDT may consider:

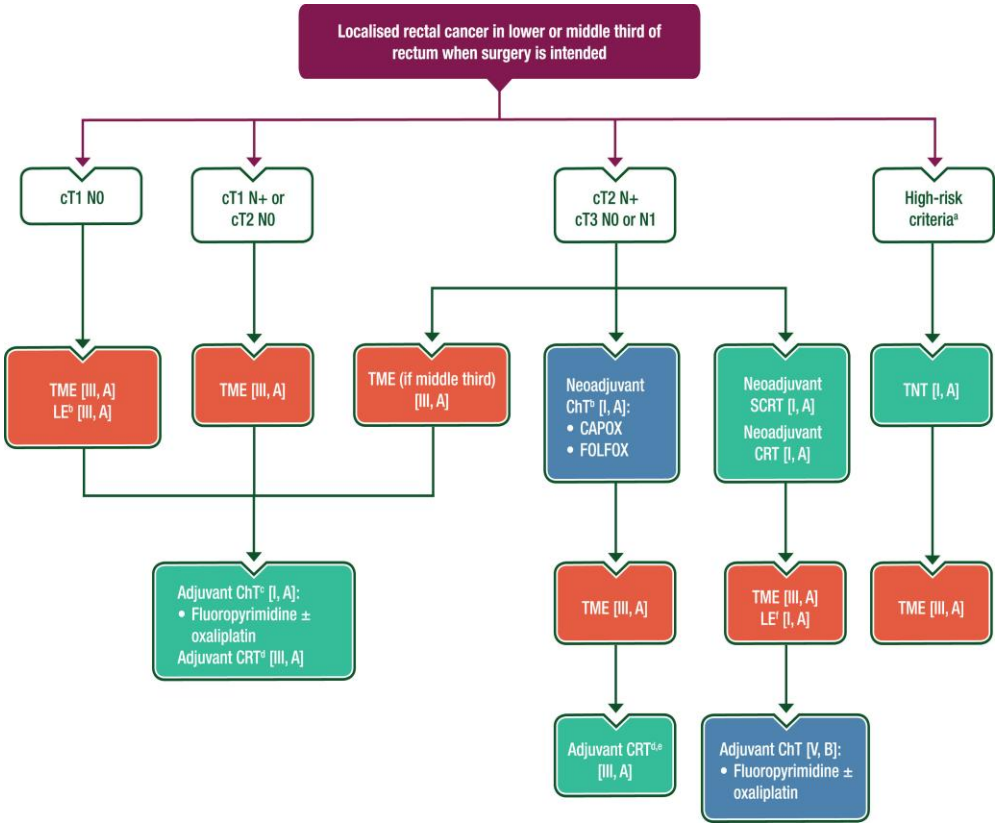
- Early interim endoscopy after 6/52 to reassess the ulcer (**it should not be biopsied at this 2nd assessment)**
- Proceeding to surgery (TME)

External Beam Radiotherapy (RT) alone

<u>T1 - T3b N0, T > 5cm:</u>

Long course chemoradiotherapy (LCCRT)

- 45Gy/25# with Simultaneous Integrated Boost (SiB) to gross disease (50Gy/25#) with concurrent Capecitabine (825mg/m^2 BD on days of RT)
- The role of Papillon should be reconsidered, alongside TME, if restaging investigations confirm residual disease <5cm remains. The regional Papillon pathway *(page 7)* should be followed.
- Several TNT trials have included patients with low T3b N0 disease[9,10,11,12], overlapping with OPERA inclusion criteria. Results from these trials (except for OPRA) are awaited. TNT for ERC is not current SoC in GM for early rectal although we recognise the evolving international landscape and will review our guidance in response to emerging data regarding oncological outcomes and toxicity.



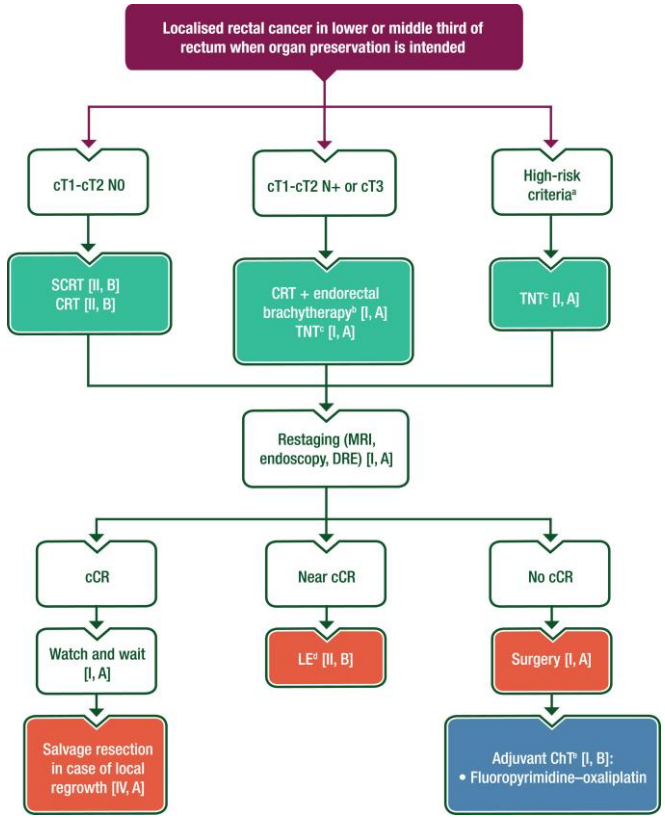


Figure 1: Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of ERC[1]

3. Intermediate Rectal Cancers

Definition: **T3c (MRF >1mm, pMMR) or ≤ T3b N+ disease**

Whilst not broadly recognised as a definition in rectal cancer literature, this entity is recognised in real-world practice; for the purposes of this GM guidance 'intermediate' rectal cancers encompasses tumours:

- ≥T3c or ≤ T3b N+ disease or ≥T3b EMVI+ disease

and

- have a clear MRF (> 1mm) which is <u>not</u> threatened either directly by tumour or by extramural vascular invasion (EMVI) or suspicious lymph nodes

The treatment approach for 'intermediate' risk tumours has become increasingly complex because of the tumour heterogeneity encompassed within this group. Some tumour characteristics overlap with the early & locally advanced definitions (pages 5 and 12) and reflect overlapping trial inclusion criteria exploring non-operative and neoadjuvant approaches:

XRT dose escalation	**TNT**
OPERA (n = 141, published 2023)	OPRA (n = 324, published 2020)
APHRODITE (n = 104, closed to recruitment 2024)	STELLAR (n = 599, published 2022)
XRT/TEM approach	
STAR-TREC (n = 120, closed to recruitment 2024)	JANUS (n = 783, closed to recruitment 2025)
	CAO/ARO/AIO-18.1 (n = 702, closed to recruitment 09/2023)

Table 2: dose escalation vs TNT for intermediate staged rectal cancers

It is likely that the presence of risk factors will determine the treatment approach. In addition to MRF status, other radiological features that will influence the MDT discussion include:

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

Table 3: Adverse intermediate rectal cancer characteristics

The following criteria are for MDT guidance regarding the neoadjuvant approach for intermediate rectal cancer (acknowledging the heterogeneity described previously in this section):

<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="2">If 2+ adverse features (Table 5) present & patient PS 0/1

TNT*</td></tr>
<tr><td>Neoadjuvant chemotherapy 6 x FOLFOX~</td></tr>
<tr><td rowspan="3">Distal</td><td rowspan="2">Immediate surgery</td><td colspan="2">TNT*</td></tr>
<tr><td colspan="2">SCRT, 25Gy in 5# prior to surgery (TME)</td></tr>
<tr><td rowspan="2">Organ preservation</td><td colspan="2">LCCRT</td></tr>
<tr><td colspan="2">TNT*</td></tr>
</table>

Table 4: Neoadjuvant approach for intermediate rectal cancer

*Adverse features as described in *Table 3*

When may radiotherapy be avoided?

~ The PROSPECT[13] trial compared the use of neoadjuvant FOLFOX x 6 vs LCCRT in patients with T2 N+ and T3 N0/+ mid/upper rectal cancers (planned for sphincter-sparing surgery). In the neoadjuvant FOLFOX arm, if tumour regression was >20% then TME was performed without RT; if response was <20% then neoadjuvant RT was mandated. The trial demonstrated that DFS was non-inferior in the experimental arm (5-year DFS: 80% vs 78.6%) and concluded that in presence of a >20% SACT induced regression RT toxicities could be spared. However, the PROSPECT inclusion criteria encompassed patients who would ordinarily proceed to surgery without any neoadjuvant treatment in GM. On balance, the PROSPECT approach may be debated alongside TNT for selected mid/upper rectal cancers if adverse radiological/histological features are present (refer to *Table 3* page 10) and there is a preference to avoid pelvic radiation but is not considered standard of care for low and intermediate risk mid/upper rectal cancers.

Similarly, the FOWARC[14] trial also compared FOLFOX x6, LCCRT alone and LCCRT + FOLFOX x6, in stage II-III rectal cancer. The majority of patients (>60%) had T3 tumours in the low-mid rectum (>95%) and no MRF involvement (>60%). There was no significant difference in 10-year LRR or OS rates with data (collected for patients with no stoma and no local recurrence) suggesting improved long term bowel function in patients who had not received radiotherapy.

In the OCUM[15] trial, patients with a clear MRF (no tumour or nodes or tumour deposits within 1mm of the MRF) proceeded to TME surgery without neoadjuvant chemoradiotherapy (nCRT); patients with low rectal tumours or T4 disease received nCRT. The 5-year local recurrence rate in the straight-to-surgery cohort was 3.8%. The

MERCURY[16] trial support the ongoing work in GM to implement a standardised rectum MRI reporting template to aid patient selection for neoadjuvant treatment. Within MERCURY, patients were defined as “good prognosis” if MRF > 1mm and T2-3b (regardless of MRI nodal staging); in this cohort, neoadjuvant therapy was omitted and a local recurrence rate was 3% was reported.

The CONVERT[17] trial also considered the role of neoadjuvant chemotherapy (nCT): CAPOX x 4) vs LCCRT (50Gy/25#). It is important to note that most 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 observed in the nCRT arm (0.7% vs 3%).

ESMO guidelines[1] suggest that patients with a depth of invasion beyond the muscularis propria that is 5 mm or less are appropriate candidates for upfront surgery rather than neoadjuvant therapy, even if they are node positive, as long as the levators are not threatened, the mesorectal fascia is clear, and there is no extra nodal extension.

4. Locally Advanced Rectal Cancer

***Definition:* T4 or MRF threatened (pMMR)**

Locally Advanced Rectal Cancer (LARC) is defined as:

-T4a/b disease

and/or

- an involved or threatened (< 1mm) MRF by:
  - tumour (T3)
  - extramural vascular invasion (EMVI)
  - morphologically abnormal lymph nodes (N1/2)
  - N1c tumour deposit
- Pelvic side wall node(s)

TNT is standard of care for these patients, unless PS, comorbidities or frailty deem this to be an unsuitable approach (*Table 5*).

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

Table 5: Factors determining neoadjuvant approach for LARC.

Total Neoadjuvant Therapy (TNT)

TNT adopts the use of both (chemo)radiotherapy and neoadjuvant systemic anti-cancer therapy (SACT) for patients with locally advanced, non-metastatic disease.

Published TNT schedules demonstrate varying patient inclusion criteria and different primary endpoints. This heterogeneous evidence base means that a standardised GM approach is important; this guidance aims to provide guidance regarding regimen selection, but MDT discussion and patient assessment is important when determining the optimum approach.

TNT Trial	N =	1st treatment	2nd treatment	3rd treatment	pCR (*+cCR)	5 yr DFS
RAPIDO[18] Bahodoer *Lancet Onc* 2020	920	LCCRT SCRT	- SACT	Surgery Surgery	pCR 14% pCR 28%	80% 81.7%
OPRA[9] Garcia-Aguilar *JCO 2022*	324	SACT LCCRT	LCCRT SACT		39%* 5 yr TME-free survival 54%*	88% 85%
PRODIGE[19] Conroy *Lancet Onc 2021*	461	LCCRT SACT	Surgery LCCRT	Adjuvant SACT Surgery +/- SACT	11.7% 27.5%	67%* 62.5%* *7 yr DFS
STELLAR[20] Jin *JCO 2022*	599	LCCRT SCRT	Surgery SACT	SACT Surgery	14% 28%	58.7% 62.0%

Table 6: TNT trial data summary

Table 6 demonstrates that TNT can result in improved patient outcomes compared with neoadjuvant chemoradiotherapy alone, however, these trials reported significant rates of G3 toxicity. Appropriate patient selection is therefore important.

Patient Selection for TNT

The following criteria are based upon TNT trial eligibility including RAPIDO[18], OPRA[9], PRODIGE[19] and STELLAR[20]. In RAPIDO, over 66% of patients had 2-5 adverse tumour factors (defined in Table 7, page 14) and we have adopted this patient selection approach in our GM practice.

However, there may be instances when the MDT agree that TNT should be offered to patients with 1 adverse feature - 'intermediate' risk disease – on the basis that the patient would have fulfilled the eligibility criteria for one of the highlighted TNT trials. Amidst an international landscape investigating TNT for OP, and patient preference for NOM, we await the results of JANUS[11] and AIO-18.1[12]. Both trials include patients with intermediate risk disease (page 10), which may impact our future TNT patient selection.

Trial inclusion of patients ≥65 years was limited (39% RAPIDO[18], 32% PRODIGE[19]) and pre-treatment assessment of frailty is important. In our GM experience, 24.2% of patients were > 65 years. Offering LCCRT – with or without concurrent Capecitabine - may remain the appropriate neoadjuvant approach and is at the discretion of the MDT.

Patient Factors	*Tumour Factors* ***At least 2 should be present****
PS 0/1	MRF +
Age < 70*	T4
Minimal, well controlled comorbidities (unlikely to compromise ability to complete treatment)	EMVI +
	N2 disease
	Lateral pelvic side wall nodes

*Advancing age is not a contraindication to TNT, but the relatively small proportion of patients > 70 years old in TNT trials should be noted & a frailty assessment documented

Table 7: LARC factors to support TNT indication.

TNT Treatment Intent

Varying TNT trial primary endpoints, and future trial design, remains an area of debate. Clinicians should be clear regarding the treatment intent, to set the expectations of patients and MDT colleagues alike. The following treatment intentions are not mutually exclusive, but their prioritisation sequence may help determine the TNT approach:

- To downstage and achieve an R0 resection
- To reduce risk of local recurrence
- To reduce risk of distant metastases
- Aiming for organ preservation (clinical complete response)

TNT sequence

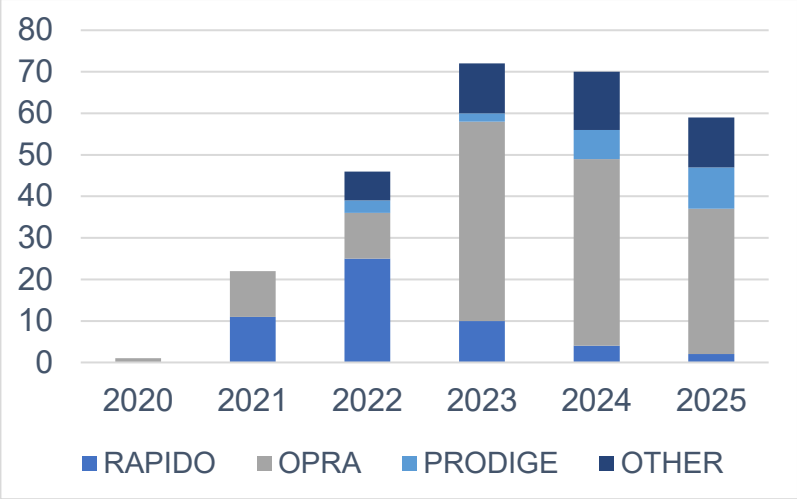


Figure 2: TNT regimen selection in GM

'Other' regimens include: TNT trial inclusion (PRIME-RT, ARTEMIS), other SACT regimens (Oxaliplatin/Tomudex) and OxCap → LCCRT sequence.

The various TNT approaches have different inclusion criteria; the following guide is aimed at ensuring a standardised approach across GM MDTs.

1) OPRA-like approach: *LCCRT → Neoadjuvant SACT → Reassessment*

Indications:
- Low rectal tumours, involving MRF
- T4 tumours
- Treatment intent = organ preservation

2) PRODIGE-like approach: *Neoadjuvant SACT → LCCRT → Reassessment*

Indications:
- Bulky, proximal tumours (e.g. straddling or extending above the peritoneal reflection) where there are concerns regarding radiotherapy treatment volume and anticipated toxicity
- Concerns about risk of distant metastatic disease when the priority is early SACT delivery e.g. EMVI / N2 / pelvic side wall disease

3) RAPIDO-like approach: *SCRT → Neoadjuvant SACT → Reassessment*

- Mid rectal tumours, ≤ T3b, MRF – but other adverse risk features present: N1/2, EMVI

We acknowledge the updated RAPIDO data and a higher rate of locoregional recurrence (LRR) in patients treated in the experimental arm (TNT: SCRT and neoadjuvant SACT) compared with standard of care (neoadjuvant LCCRT)[21]. Subsequent analysis reports a higher incidence of LRR is associated with a distal resection margin ≤10mm (25.4% vs 1.8%) and shares important insights into surgical planning post TNT. In patients who underwent an APR, LRR was 8.5% v 7.5% (TNT and LCCRT arms respectively), whereas LRR rates in patients who underwent sphincter preserving surgery were 12.1% vs 4.8% (TNT and LCCRT arms respectively)[22]. The baseline tumour height prior to TNT should be assessed when considering the surgical approach. The following pathological factors at the time of surgery were also noted to be associated with an increased risk of LRR: enlarged lateral lymph nodes, a positive CRM, N1c tumour deposits. These adverse pathological features have shaped the neoadjuvant treatment selection guidance in *Table 8* – and is at the discretion of the oncology team[21].

	Short course radiotherapy SCRT 25Gy/5#	Long course chemoradiotherapy LCCRT 45Gy/25# with SiB 50Gy/25# boost to gross disease Concurrent Capecitabine 825mg/m^2 Monday - Friday
Trial Regimen	RAPIDO	OPRA, PRODIGE
Location	Proximal/Mid	Distal
T staging	< T4a	T4a or b
CRM status		Positive
EMVI status	Positive*	
N2 disease	Positive*	
Lateral Pelvic Nodes		Involved

Table 8: LARC radiological characteristics to guide XRT schedule selection

**EMVI + and/or N2 disease may be an indication for a PRODIGE-like or RAPIDO-like approach*

OPRA demonstrated higher rates of OP when LCCRT was delivered prior to SACT; 5-year TME-free survival was 54% vs 39%[9] and therefore is the recommended TNT sequence if the treatment intent is OP. However, it should be noted this trial included patients with intermediate risk disease, compared to our GM patients with LARC undergoing TNT. Among patients who underwent TME immediately after TNT, 10% of these patients ultimately had a pathologic complete response (pCR), highlighting the effectiveness of

TNT as well as the challenges in identifying complete responses clinically. Of those patients with a cCR who entered W&W surveillance, the vast majority of regrowths (94%) occurred within two years and 99% within three years of completing TNT[9].

TNT: SACT schedule

Previously, the XRT approach – SCRT or LCCRT – dictated the duration of neoadjuvant SACT, aiming for a TNT period of approximately 24 weeks.

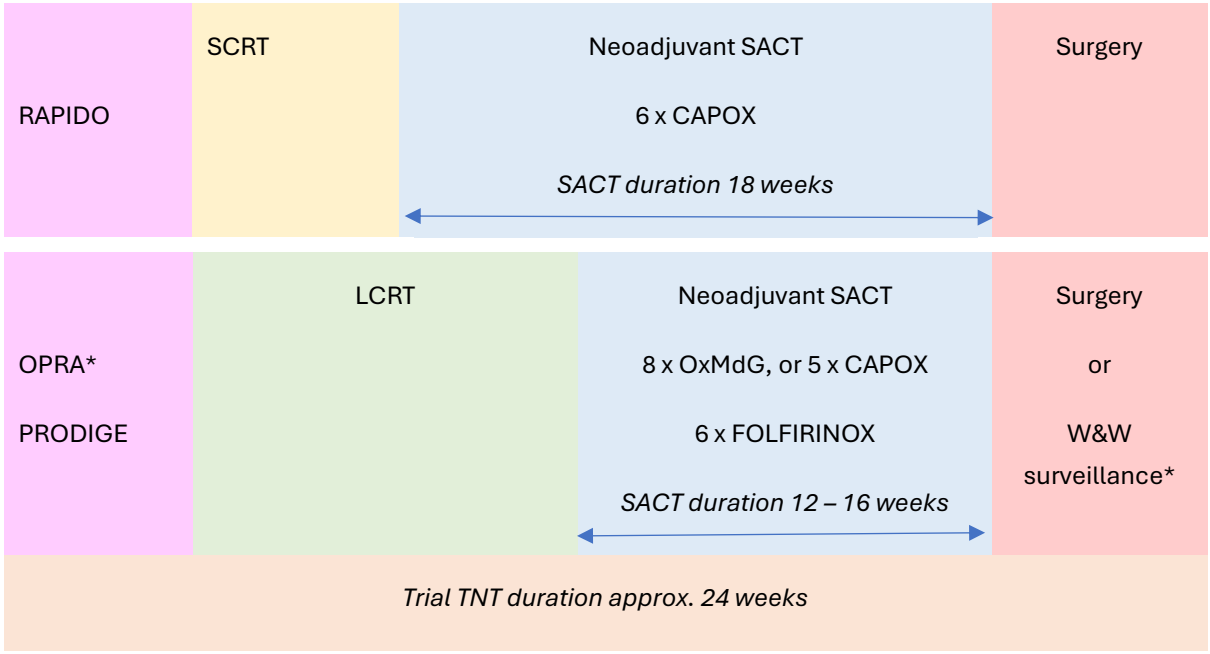


Figure 3: Trial TNT SACT duration

TNT trials used varying SACT durations; sequencing was a key factor (*Figure 3)* but even allowing for this, variation in overall TNT treatment period was observed. Subsequently the SCOT[23] and LARC US[24] studies, and our GM TNT audit, have shaped our adapted SACT TNT approach - aiming to minimise variation in clinical practice – as follows:

	SACT schedule	No. of cycles
RAPIDO-like	FOLFOX	6 x 2 weekly cycles (FOLFOX)
	CAPOX	4 x 3 weekly cycles (CAPOX)
OPRA-like	FOLFOX	
	CAPOX	
PRODIGE-like	FOLFIRINOX*	2 weekly cycles x 6
GM TNT SACT duration = 12 weeks		

Figure 4: GM TNT SACT duration

Most TNT trials utilised a doublet SACT schedule, except PRODIGE 23[19] which adopted neoadjuvant FOLFIRINOX. This schedule may be suitable for fit patients (PS 0-1), with

minimal/no comorbidities and multiple adverse staging characteristics as previously described *(Table 8)*.

In GM, CAPOX is the preferred doublet schedule (*Table 9*), but FOLFOX may be used if there is a concern regarding risk of GI side effects or frailty. In our regional database, patients ≥65 years old were more likely to receive FOLFOX (30%), compared with patients ≤65 years (21%).

GM TNT schedule	SACT regimen	
OPRA-like RAPIDO-like 'OTHER'	CAPOX	70.1%
	FOLFOX	23.7%
	OxTom	1.6%
PRODIGE	FOLFIRINOX	3.7%

Table 9: GM TNT SACT selection (2020-2024)

Long Course Chemoradiotherapy (LCCRT)

Patients with LARC deemed unsuitable for TNT may be considered for LC(C)RT alone as per previous standard of care prior to adoption of TNT.

Treatment Intent: to downstage disease and achieve an R0 resection. A small proportion of patients may achieve a cCR.

Indications for LCCRT alone:

- PS 2
- Age >70
  - This is not an absolute cut-off but side effects & ability to complete treatment should be considered when debating the optimal neoadjuvant approach.
- MRF + but no other adverse radiological or histological features noted.
  - In view of only 1 adverse risk factor, LCCRT may be appropriate although we recognise there is overlap with some TNT trials' inclusion, guiding the MDT to consider TNT also.

Radiotherapy Schedule:

- 45Gy/25#, with 50Gy/25# Simultaneous Integrated Boost (SiB), delivered Monday – Friday for 5 weeks.
  - combined with concurrent Capecitabine, 825mg/m^2 BD, on days of RT only. Consider a dose 20% dose reduction if PS 2-3.

Patients Deemed Unsuitable for Surgery

Patients may be unfit for TME for a variety of reasons, which will also influence the non-operative management (NOM).

The intent of NOM may be to:

1) achieve a cCR
   or
2) to downsize or downstage
   or
3) to offer short term local control whilst patient undergoes prehabilitation prior to surgical reassessment
   or
4) to offer long term control

The treatment intent, patient's symptoms, PS and anticipated side effects will influence the RT volume and prescription.

RT approach	RT volume	RT dose(s)	Role for Papillon*	Restaging	Considerations
Short course RT & 'delay'	Gross tumour & elective (nodal) regions	25Gy/5# (5-7 days)	Yes	8-10 weeks later	Allows time for (pre)habilitation or optimisation of comorbidities
Long course (chemo)radiotherapy		45Gy/25# (5 weeks) +/- SiB (50Gy) to gross disease	Yes		
Palliative	Gross tumour & margin	20Gy/5#/1 week 25Gy/5#/1 week 30Gy/10#/1 week	No	At discretion of clinical team	May palliate: - pain - bleeding

Table 9: RT approaches for patients unsuitable for surgery

**refer to page 7: Patients could receive Papillon as per OPERA sequence: LCCRT → Papillon (for tumours > 3cm at initial staging)*

6. MMR Testing & MMRd Tumours

Further information can also be found in regional laboratory guidance: MMR-information-1.pdf[25]

Mismatch repair (MMR) is reflex tested on all biopsy proven rectal adenocarcinomas across GM. It will not be re-tested on a surgical specimen unless requested. Patients with an MMR deficient (MMRd) rectal cancer - localised or metastatic - should be offered immunotherapy, either via a clinical trial or industry drug access programmes.

On occasion, when invasion is not confirmed and repeat biopsies reveal high grade dysplasia only (despite clear radiological and endoscopic evidence of malignancy) the MDT will decide whether a repeat biopsy is required versus proceeding with treatment. The histopathologist may perform MMR testing on the HGD sample but there is limited evidence to inform this interpretation and therefore our guidance cannot support this.

A) Localised, non-metastatic, 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[24]. Access to Dostarlimab, via a clinical trial or drug access programme, should be considered before offering other surgical or oncological treatments.

Check-mate 8HW[27] (Ipilimumab/Nivolumab) did include patients with localised, non-metastatic disease.

B) Mx or M1 disease

The phase III KEYNOTE-177 trial[28] demonstrated improved overall response rates (43.8% vs 33.1%) and progression free survival (16.5 vs 8.2 months) in metastatic dMMR patients receiving Pembrolizumab vs SACT. First line Pembrolizumab is NICE approved for dMMR/ MSI-High metastatic colorectal cancers (Blueteq application) and should be considered prior to palliative SACT. If there is evidence of response, Blueteq currently supports 2 years duration.

Alternatively, in response to the Checkmate-8HW trial[27], is NICE approved as an alternative 1st line SACT approach in metastatic rectal cancer.

If a patient with MMRd metastatic rectal cancer did not receive 1st line immunotherapy (for whatever reason) access to 2nd line Ipilumumab/Nivolumab is available. If this is unsuitable, single agent Pembrolizumab should be considered.

7. Reassessment post neoadjuvant/non-operative 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	 2 – 3 weeks 8 – 10 weeks

Table 10: Restaging timelines following neoadjuvant treatment.

**Restaging MRI Pelvis and CT TAP should be performed after the last cycle of SACT*

8. Clinical Complete Response (cCR)

A clinical complete response (cCR) is a triad of evidence including:

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

The management of patients who achieve a cCR is complex, requiring careful patient counselling and an MDT who are confident to assess and restage. It is likely to be influenced by:

- the patient's preference
- baseline bowel function
- the tumour location, and whether a permanent stoma is anticipated with surgery
- the patient's ability to comply with a watch and wait surveillance schedule

Patients should be counselled regarding their treatment options:

1) the patient and surgical team may still wish to proceed with surgical resection. The patient should be counselled regarding the possibility of a pathological Complete Response (pCR) being confirmed.
2) patients may be keen to proceed with watch and wait (W&W) surveillance, in which case, the GM complete responder pathway schedule should be adopted *(Table 11)* and the patient should be recruited to the OnCoRe registry[29].

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

Table 11: Follow-up schedule, taken from GM Colorectal Cancer Complete Responder Guidelines (2018)[30]

Early Rectal Cancer (T1 – T3b (EMVI negative, CRM negative, tumours <5cm)

There is increasing clinical evidence to support W&W surveillance for patients presenting with early stage rectal cancer[6,8,31].

Intermediate- and Locally Advanced Rectal Cancer

The data supporting W&W, and oncological safety, is still evolving for patients with advanced disease. To date, OPRA[9] is the only TNT trial to offer W&W surveillance, whilst other TNT trials proceeded to surgery within the treatment pathway. However, there is an evolving shift in the TNT landscape with current UK & international trials investigating OP as a primary endpoint[10, 11, 12, 32]. It is important that rates of regrowth and long-term oncological outcomes (distant DFS and OS) are reviewed alongside the primary endpoint (cCR). Patients should be informed that this data is still maturing, and their preference to avoid surgery must be balanced with these oncological uncertainties. Our GM TNT experience (2020-2024, n=190) demonstrates a cCR rate of 21.5% in our LARC population; 22% had local relapse, of which with 89% underwent surgery and 11% underwent Papillon. 7% developed distant metastases. There was no statistically significant difference in OS between patients undergoing W&W versus surgery post TNT (n=190, median duration of follow up 3 years).

9. Near Clinical Complete Response (ncCR)

Near cCR (ncCR)

- DRE and rectoscopy: the presence of small and smooth regular irregularities including residual ulcer, or small mucosal nodules or minor mucosal abnormalities, with mild persisting erythema of the scar.
- MRI: obvious downstaging with residual fibrosis but heterogeneous or irregular aspects and signal or regression of lymph nodes with no malignant enhancement features, but with a size of >5 mm.
- Endoscopic biopsy[c]: not mandatory to define ncCR.

[33] *Figure 5: Definition of Near Clinical Complete Response*

In many respects, assessment and management of a ncCR is more challenging for the MDT; this is a relatively new clinical entity, arguably a more subjective assessment than cCR and requires confident endoscopic and MRI assessment.

Several clinical trials of early rectal cancers - T1–T3b (MRF -, T < 5cm) have utilised a 2-stage approach to response assessment *(Table 12)*. APHRODITE results were presented at ESTRO 26 and our trial experience has fostered MDT awareness and confidence with ncCR assessment. We await STAR TREC outcomes.

	1st timepoint (from *start* of XRT)		2nd timepoint (from *start* of XRT)		3rd timepoint (from *start* of XRT)
OPERA[8]	Week 14 MRI & endoscopy	ncCR = Yes	Week 20 MRI & endoscopy	If a cCR NOT achieved	Week 24 MRI & endoscopy
STAR-TREC[6]	Week 11 -13 MRI & endoscopy	ncCR = Yes	Week 16-20 Endoscopy		
APHRODITE[29]	3 months MRI & endoscopy	Evidence of response	6 months MRI Endoscopy		

Table 12: ERC OP trial 2-stage assessment schedules

Extrapolating from the ERC experience, recent TNT trials (PRIME RT[32], ARTEMIS[10], JANUS[11], AIO-18.1[12]) with the aim of OP have also adopted a 2-stage response assessment. We await maturing trial data to determine the safety of this approach in patients with LARC, however, patients may be reluctant to proceed to TME and achieve a pCR (particularly if a permanent stoma is required). We therefore propose the following timelines, and management plan, are considered with the patient *(Table 13):*

<table>
<tr><td>Neoadjuvant approach</td><td colspan="2">Time from completion of neoadjuvant treatment until 1st restaging timepoint</td><td rowspan="3">2nd restaging timepoint
6 weeks later
Repeat endoscopy</td></tr>
<tr><td>SCRT, or,
LC(C)CRT alone</td><td>8 – 10 weeks</td><td rowspan="2">MRI, CT TAP & endoscopy
Near Clinical Complete Response (ncCR) identified</td></tr>
<tr><td>TNT*:
RT → SACT
SACT → RT</td><td>2 – 3 weeks
8 weeks*</td></tr>
</table>

Table 13: 2-stage reassessment of ncCR timelines

*TNT trials selectively restaged patients at different timepoints post TNT. To minimise confusion amidst an array of neoadjuvant approaches, the above GM timelines reflect a pragmatic decision to standardise the 1st restaging timepoint.

If a cCR is not achieved by the 2nd timepoint, the patient should be advised to proceed to TME. Beyond STAR TREC[6] and TAUTEM[5] for ERCs, the role of local excision (TAMIS) following neoadjuvant treatment had not yet been established and should not be offered to a) patients who have received Papillon or b) patients treated with TNT (by definition, with intermediate and advanced disease).

10. Functional outcomes / Late toxicity and ePROMs

Poor functional outcomes and low anterior resection syndrome (LARS) are common after surgery for rectal cancer. Risk factors for LARS include low tumour height and previous pelvic RT[32]. At present, there is insufficient data on the functional outcomes for patients undergoing TNT and should be a focus for future research and GM-based audit. Electronic Patient Reported Outcomes (ePROMS) is becoming increasingly utilised and could offer the potential for future outcome reporting.

The functional outcome for each patient should be considered when counselling a patient regarding their NOM and surgical management options. The balance between maintaining oncological efficacy against acceptable long-term effects is individual to each patient's preference and their tumour characteristics.

11. Adjuvant SACT following neoadjuvant therapy

Indications for adjuvant SACT will be influenced by:

- Neoadjuvant treatment (or not)
- Resection Histopathology
- The patient's fitness and post-operative recovery

	Indication(s) for adjuvant SACT	Proposed SACT regimen
No neoadjuvant treatment	N+ disease EMVI + T4 tumour Poorly differentiated histology	Consider CAPOX x 4
Neoadjuvant XRT alone		
TNT*	Clinician discretion, but not standard of care. Based upon adverse histology / evidence of minimal downstaging	
cCR	No	

Table 14: Adjuvant SACT indications and regimens

*The benefit of adjuvant SACT following TNT is uncertain. Based on data from the SCOT[23] study it appears unlikely that extending the duration of Oxaliplatin/Capecitabine chemotherapy beyond 12 weeks will impact on DFS or OS in this high-risk patient group. Therefore, if the patient has received this duration of neoadjuvant SACT, further adjuvant therapy is unlikely to provide any further benefit. From a subset analysis of RAPIDO data[18], patient outcomes were the same, irrespective of whether they received adjuvant SACT or not. PRODIGE[19] advised 8 weeks adjuvant SACT (CAPOX or FOLFOX) although only 60% of expected patients received this and there were concerns about the cumulative Oxaliplatin dose and risk of neurotoxicity. We do not advise routine adjuvant SACT as SoC post TNT but acknowledge there may be individual factors when adjuvant SACT post resection may be considered on a case-by-case basis.

ESMO guidance[1] recommends adjuvant fluoropyrimidine/oxaliplatin can be offered on an individual basis if a cCR is achieved after (chemo)radiotherapy alone if there was initial N+ disease, but this is not standard practice in GM currently. This decision should be made within an MDT.

12. Locoregional recurrence and pelvic reirradiation

The GM pathway for the multidisciplinary management of locoregional recurrent disease is shown on page 30. There are several clinical scenarios when pelvic reirradiation may be considered:

a) locoregional recurrence, unsuitable for up front resection (surgical margin)
b) previously treated non-rectal pelvic malignancy e.g. prostate

Each of the above scenarios will require a personalised approach but important factors to consider include:

- the location, and volume, of disease
- lumen, vascular or adjacent organ involvement
- the previous radiotherapy schedule & irradiated volume
- the time elapsed since previous radiotherapy treatment
- the intent of pelvic reirradiation (neoadjuvant prior to surgery vs palliative, offering 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) if reirradiation were to occur.
- alternative treatment modalities e.g. SACT
- presence of extra-pelvic disease (metastases), the patient's prognosis & PS

There are several GM reirradiation approaches *(links to files below may not be accessible to external viewers, the file can be shared upon request)*:

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

XRT.CLP.19 -
Abdominal and Pelvic

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

XRT.CLP.11 -
Hyperfractionated acc

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

20Gy / 10# 20 – 25Gy / 5# 30 – 10 / 15#

The radiotherapy prescription, and treatment volumes (gross disease alone vs elective volume) will be influenced by the clinical and radiobiological factors outlined above.

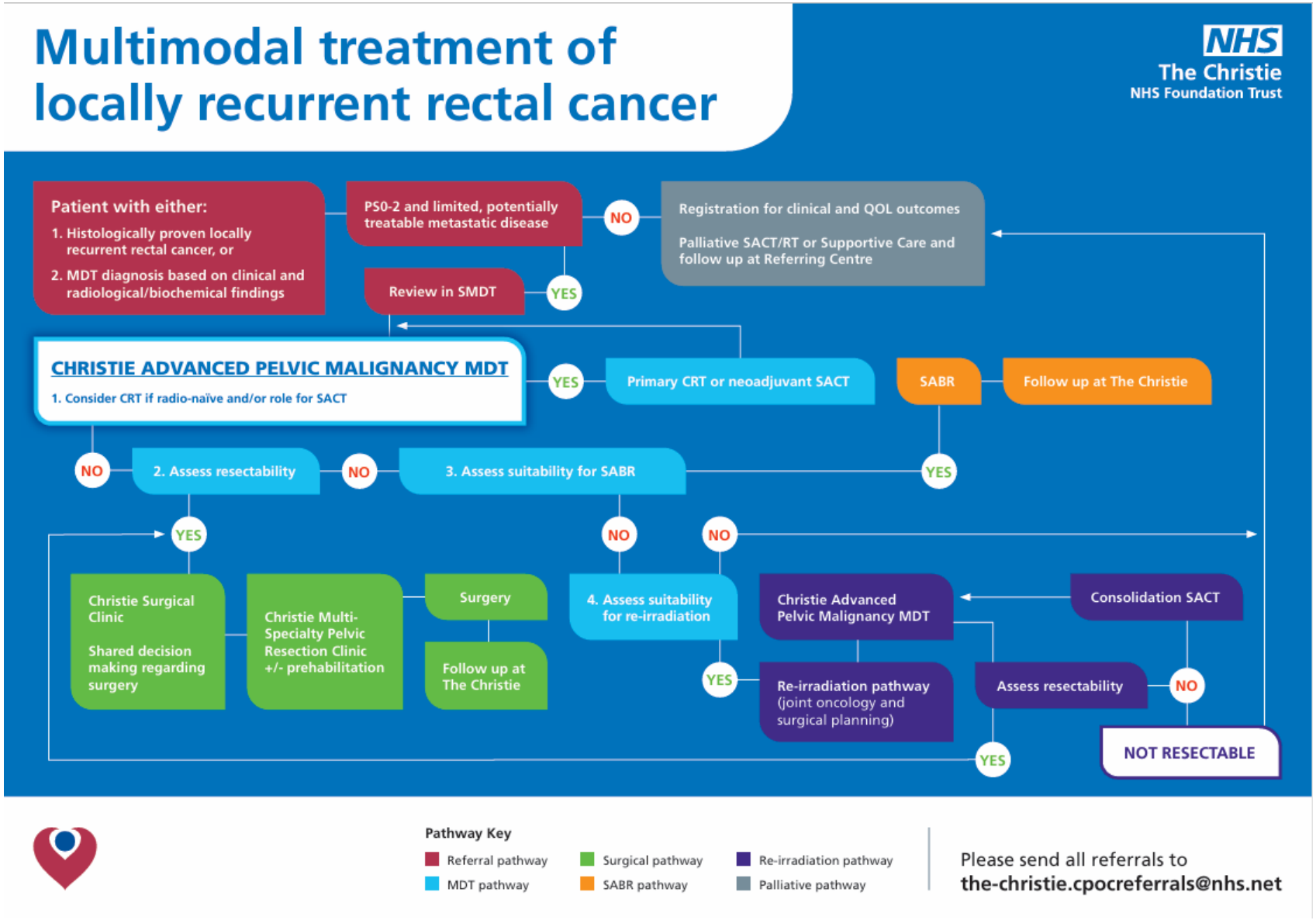


Figure 4: GM locoregional recurrence pathway

13. Future Updates

We acknowledge the ongoing regional and national collaborations that will need incorporated into future versions of this GM guidance, including:

- GIRFT Lower GI programme

Lower GI cancer - Getting It Right First Time - GIRFT

This national review is focussed on rectal cancer pathways, equity of access to different treatment approaches and attempting to understand variations in rectal cancer pathways

- OnCoRe-led Delphi consensus statement regarding organ preservation treatment strategies, patient counselling and assessment and management of ncCR and CR.

- An updated version of the RCR UK IMRT rectal cancer guidance

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