Colorectal Clinical Subgroup:

Non-Surgical Oncology Guidelines

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MOLECULAR ASSESSMENTS IN COLORECTAL CANCER

Mismatch repair/ Microsatellite Instability testing

Mismatch repair (MMR) is an essential process in all cells of the body. In the context of colorectal cancer we recognize two specific scenarios where loss of MMR protein function occurs:

1. Patients with Lynch Syndrome ~3-4% of all colorectal cancer cases
2. Sporadic loss of MMR expression ~10% of all colorectal cancer cases

Two techniques can be used to assess the presence or function of MMR processes:

1. Immunohistochemical (IHC) expression of MMR proteins - Formalin-fixed paraffin-embedded (FFPE) tumour and control material are assessed for expression of MLH1, MsH2, MSH6, and PMS2. Results from this testing define patients as MMR proficient i.e. there is retained expression of all assessed proteins, or MMR deficient based on the loss of IHC expression of a specific protein. This can define which protein(s) have lost expression and can direct germline testing for Lynch Syndrome if that is suspected.
2. Microsatellite instability (MSI) testing - Microsatellites are DNA repeat sequences which show increased variability in the number of repeats if cells don't have effective MMR function. Tumour DNA can be assessed for MSI with results defining the tumour as MSI-high (e.g. has defective MMR function), MSI-low or Microsatellite Stable (MSS).

Results from the two alternative techniques are highly correlated but 1-2% of patients may have normal (proficient) expression of MMR proteins but are MSI-high. IHC testing has been favoured as the initial diagnostic test, particularly in stage 2- 3 cancers. For stage 4 patients who will be having additional mutation testing performed MSI testing is preferred option.

NICE guidance recommends that all patients diagnosed with colorectal cancer have mismatch repair IHC testing performed.[1] This guidance is based on the identification of patients with Lynch Syndrome and subsequent screening to detect cancers at an early stage, and the use of prevention strategies resulting in cost savings to the NHS. Current regional policy predates the NICE guidance and selects patients for testing based on age, family history, clinical or pathological features, and at an oncologist's request.[2] There isn't currently agreement to implement the 2017 NICE guidance due to issues funding MMR testing for all patients. The regional guidance includes a helpful flow chart for MMR testing and interpretation.

MSI testing for patients with advanced disease to identify patients who are candidates for immunotherapy is recommended.[3] It is key that MSI test results are available prior to commencing first-line treatment for patients with advanced disease as patients who have already commenced first-line chemotherapy cannot be switched to Pembrolizumab immunotherapy based on current NICE guidance. It is therefore important that each MDT works to ensure that MSI testing is requested at the earliest opportunity for patients identified to have advanced disease. This is to avoid subsequent delays in commencing palliative treatment.

[1] https://www.nice.org.uk/guidance/dg27/chapter/1-Recommendations

[2] https://mft.nhs.uk/app/uploads/2018/09/mmr-guidelines-v2-inc-flow-chart-and-form.pdf

[3] https://www.nice.org.uk/guidance/gid-ta10420/documents/final-appraisal-determination-document

Clinically MMR deficiency has been associated with an improved prognosis compared to MMR proficient tumours in stage 2 and 3 colorectal cancer. Clinical trial data shows that 22% of stage 2 and 12% of stage 3 cancers are MMR deficient.[4] However, for the 3-4% of patients with advanced colorectal cancer who are MMR deficient the prognosis may be reduced compared to patients with MSS cancers. Pre-clinical data suggests that MMR deficiency can result in a reduced benefit from 5FU chemotherapy. There is some uncertainty over how effective standard chemotherapy is in MMR deficient compared to MSS patients. MMR deficiency is recognized as a predictive factor associated with benefit from immunotherapy treatment in the advanced disease setting.[5]

In clinical decision making MMR/ MSI status affects treatment decisions in the following situations:

1. Stage 2 colorectal cancer and MMR deficient – Patients have an improved prognosis due to MMR deficiency and the benefit of standard adjuvant capecitabine is uncertain. Standard treatment would be surveillance.

2. Stage 4 colorectal cancer and MMR deficient/ MSI-high – These patients should be considered for immunotherapy treatment

Tumour mutation testing

Sporadic mutations occurring in RAS genes (KRAS and NRAS) and BRAF are routinely tested in all patients with stage 4 colorectal cancer as recommended by NICE guidance.[6] Mutations in the RAS genes are associated with shorter prognosis and lack of benefit from EGFR targeted treatment. The BRAF V600E mutation is also associated with significantly shorter survival and meta-analysis performed as part of developing NICE guidance also confirmed that it is a predictor of lack of benefit from EGFR targeted treatment. A full list of approved molecular tests approved is available in the national genomic test directory on the NHS England website.[7]

Assessment of these genes in stage 2 or 3 colorectal cancer is not known to be beneficial so is not part of the routine assessment of early stage tumours. BRAF V600E mutation testing does have a specific role in the assessment of MLH1 deficient tumours to determine whether MMR deficiency is likely to be sporadic, or may be due to Lynch Syndrome.

All stage 4 patients being considered for systemic treatment should have an assessment of RAS and BRAF mutation status. It should be noted that the benefits of EGFRi treatment in RAS wild-type patients is uncertain in patients with right colon cancer (proximal to splenic flexure) and clinicians may take this into consideration when making treatment decisions

Histopathological material from a either the primary tumour or a metastasis could be analysed. Assessment by the North West regional Genomic Laboratory Hub (GLH) based at Manchester Foundation Trust is preferred. The request form can be accessed via the following link: https://mft.nhs.uk/app/uploads/2021/04/Genetic-Testing-Request-Form.pdf

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[4] Roth AD, et al., Stage-specific prognostic value of molecular markers in colon cancer: Results of the translational study on the PETACC 3-EORTC 40993-SAKK 60-00 trial. J Clin Oncol, 2009. 27(15S): p. Abstract 4002.

[5] Dung T. Le, et al., PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 2015; 372:2509-2520

[6] https://www.nice.org.uk/guidance/NG151

[7] https://www.england.nhs.uk/publication/national-genomic-test-directories

NTRK fusions can be assessed in patients who do not have mutations in RAS or BRAF, and are PS 0/1 in a 3rd/ 4th line setting.

It is likely that additional sporadic tumour abnormalities, beyond those currently recommended for testing, which are known to be treatable with targeted agents may be considered for compassionate use applications e.g. Her2 amplification.

Germline DPYD testing

Patients treated with fluoropyrimidine (5FU or capecitabine) have a 10–30% risk of severe treatment-related toxicity, which is lethal in 0·5–1% of patients. Dihydropyrimidine dehydrogenase (DPD), encoded by the gene DPYD is known to be mutated in approximately 5% of the population resulting in partial or complete DPD enzyme deficiency. Complete DPD enzyme deficiency is rare and is found in <0.5% of patients. The DPD protein is responsible for 80-90% of fluoropyrimidine metabolism and reduced enzyme function can therefore result in a build-up of active metabolites and severe or life-threatening chemotherapy toxicity. All patients planned to receive a regimen containing 5FU or capecitabine should be tested for DPYD mutations as per local policy.

It should be noted that many rare DPYD mutations have been demonstrated and their effects on DPD protein function and the subsequent risk of fluoropyrimidine toxicity are uncertain. The DPD testing performed assesses 6 of the commonest mutations in Caucasian populations which have been associated with fluoropyrimidine toxicity. Severe fluoropyrimidine toxicity after a “normal” DPD test result is possible due to the presence rare unassessed DPYD mutations, or rare mutations in other unassessed genes. Patient should therefore still be warned regarding the risks of severe toxicity even if they have a normal DPD test result.

PRE-OPERATIVE TREATMENT FOR PRIMARY RECTAL CANCERS

cT1 / T2 disease (CRM clear from any tumour) *Table 1*

Radiotherapy should not routinely be given for these tumours. The only exception is low rectal tumours whereby an APR and stoma formation is the Standard of Care (SOC).

- After MDT discussion, **T1 tumours** could be considered for SCRT followed by TEMS to try to achieve a complete local resection without stoma formation (ala the "TREC" trial).

- After discussion **T2 tumours** could be treated with a Long course of chemoradiotherapy (LCCRT) with an aim of a Complete Clinical Response (cCR) without surgery / stoma formation. Patients will need to be informed that the chances of this are at best 30-40% and if achieved patients must be willing to comply with the surveillance schedule (Please refer to OnCoRe data-base and ensure patients are managed using the latest surveillance recommendations - www.complete-response.com)

Table 1

Rectal Cancer management based on T-stage, position and CRM involvement

C: chemotherapy; "Surgery": Surgery alone without radiotherapy / chemotherapy

Distance from tumour to CRM	T1	T2	T3 >1mm*	T3 <1mm* T4
Upper 10-15cm from verge	Surgery	Surgery	Surgery SCRT (T3c/d)	C *** LCCRT (±C) SCRT + C
Mid 5-10cm from verge	Surgery	Surgery	SCRT	LCCRT (±C) SCRT + C
Low <5cm from verge	Surgery SCRT*	Surgery LCCRT**	Surgery LCCRT**	LCCRT (±C) SCRT + C

SCRT and delayed surgery could be considered in elderly / frail

* SCRT + TEM (ala TREC) for pts with high -risk features where APR current SOC (preferably as part of trial)
** LCCRT with chance of cCR to prevent APR / stoma
*** Chemotherapy, especially if too high for RT. Then possibly followed by LCCRT, SCRT or SCRT + C with associated pelvic surgery (order defined after MDT discussion)

cT3 disease where CRM is **not** threatened (> 1mm) *Table 1 / Plan 1*

These tumours 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.

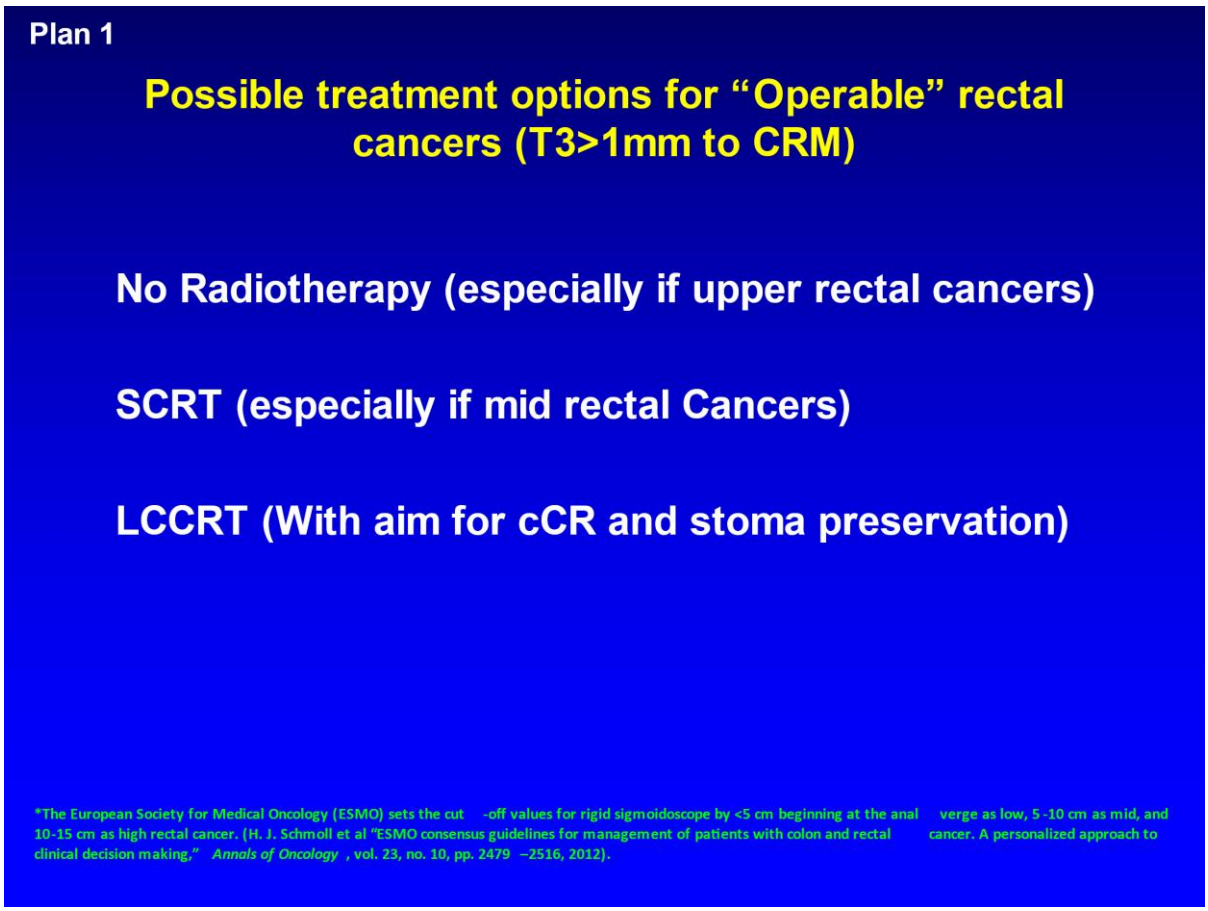
Upper-rectal cancers (10-15cm from anal verge*) with a clear CRM should be considered for immediate surgery. If these tumours are locally advanced (T3c/d), then they could be treated with a short course of radiotherapy (SCRT) prior to surgery. The UK pre-operative short course schedule is 25Gy/5# although 20Gy/4# is used in Manchester following previous data reporting similar local recurrence rates.

Mid-rectal tumours (5-10cm from anal verge*) should be considered for immediate surgery or be treated with pre-op SCRT.

Low-rectal tumours (<5cm from anal verge*) can be treated in a similar manner followed by APR / stoma formation. After discussion, T3 CRM negative tumours could be treated with a LCCRT with an aim of a cCR without surgery / stoma formation. Patients will need to be informed that the chance of this is at best 20%.

*The European Society for Medical Oncology (ESMO) sets the cut-off values for rigid sigmoidoscope by <5 cm beginning at the anal verge as low, 5-10 cm as mid, and 10-15 cm as high rectal cancer. (H. J. Schmoll et al "ESMO consensus guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making," *Annals of Oncology*, vol. 23, no. 10, pp. 2479–2516, 2012).

The radiobiological effect of a SCRT and LCRT are similar. SCRT delivers a higher dose per fraction - 500cGy per fraction (5#) whereas the LCRT gives 180cGy per fraction (25#). SCRT should **not therefore, be considered as a reduced dose of radiotherapy and a "lesser" treatment that can be repeated.



cT3 / T4 disease where crm **is** threatened (≤ 1mm) Tables 1-3 / Plan 2

These tumours have an involved Circumferential Resection Margin (CRM ≤ 1mm) which is threatened either directly by tumour (T3/4), or by extramural vascular invasion (EMVI) or suspicious lymph nodes.

There are a series of treatment options which are presented below. They will all overlap, and it is difficult to precisely define which option each individual should be offered. Any treatment plan will require a robust discussion in the MDT followed by presentation of the MDT decision to the patient for their consent.

Treatment options for these patients include:

1) **LCCRT** involves 5-6 weeks of radiotherapy (total dose: 45 – 54Gy) combined with concurrent Capecitabine chemotherapy. This is the conventional treatment for these patients and has been a treatment options for more than a decade. The pCR rate is in the region of 15%.

2) **Total Neo-adjuvant Therapy (TNT)**

Total Neoadjuvant Therapy – TNT- refers to the use of both (chemo)radiotherapy and neoadjuvant chemotherapy prior to surgery. *Tables 2-3* show that TNT can improve the treatment endpoints (pCR (approx. 20-30%)/cCR/DFS and stoma free survival) but at the expense of greater treatment related toxicity. Therefore, a TNT treatment strategy should only be recommended, after MDT discussion, to patients who are able to tolerate such therapies (PS 0-1, minimal co-morbidities and patients may be younger as are often included in clinical trials). The cohort of patients in these trials are often more advanced cases where a more intensive treatment was deemed appropriate. The RAPIDO trial for example included high-risk patients with at least one of the following criteria: cT4a/cT4b, EMVI, cN2, involved CRM or enlarged "lateral" lymph nodes.

Both radiotherapy approaches – LCCRT or SCRT – may be appropriate for this cohort of patients and it is hard to dictate which of the two options an MDT should recommend. Sometimes if the tumour is high or bulky, or there are concerns regarding adjacent small bowel, a LCCRT may be preferable due to the smaller, better tolerated daily fraction size. Also, if the aim is for cCR and stoma-free-survival, then the smaller fraction size with a LCCRT may reduce late effects on the normal tissues. On-the-other-hand, a SCRT is a lot more convenient for the patient and may improve radiotherapy department efficiencies. It also allows the introduction of chemotherapy earlier to provide a systemic effect. Both LCCRT and SCRT with chemotherapy are good options and the "real-world" usage / toxicity and benefits of each therapy will need to be audited over the coming years. However, it is important that the MDT does not "over-treat" patients with earlier/less extensive tumours, to those described above, with TNT. A LCCRT without post-radiotherapy chemotherapy may be more appropriate for these patients.

a) SCRT / chemo: SCRT, 25Gy in 5#, followed by systemic chemotherapy with Oxaliplatin and Capecitabine/5-FU for 18 weeks before surgery (see below). This regimen has been associated with an increased chance of pCR (14 vs 28%) and a lower rate of distant metastases (26.8% vs 20%) compared to standard LCCRT. The treatment is associated with a higher risk of severe toxicities due to the extended course of chemotherapy (G3 toxicity 48%). This treatment is therefore an option for fit patients (PS 0-1) without significant co-morbidity.

b) LCCRT / chemo: LCCRT involves 5 - 6 weeks of radiotherapy (total dose of 45 - 54Gy in 25 – 30#) combined with concurrent Capecitabine chemotherapy. Post-radiotherapy Oxaliplatin-based chemotherapy (6-16 weeks pre-operative – see below) can be considered for high risk tumours (as described above) to try to maximise downsizing and increase the chance of a pCR / cCR (Fokas et al pCR 25%).

3) SCRT and delay

SCRT and delay involves 25Gy/5# of radiotherapy (delivered over 1 week) followed by an 8-10 week delay before re-staging. Patients with significant co-morbidities, frail patients or those with a relatively poor PS can be offered this treatment with an aim to down-size the tumour either definitively (if medically inoperable) or prior to surgery. The pCR rate is in the region of 10%.

Table 2

Recent TNT publications (1)

Lead author	Journal	Number pts	1st treatment	2nd treatment	3rd treatment	pCR (*+cCR)
Garcia-Aguilar	Lancet 2015	292	LCCRT	- C 2 cycles C 4 cycles C 6 cycles (FOLFOX)	 S S S	18% 25% 30% 38% Sig
Cercek (retrospective)	JAMA 2018	811	C LCCRT (FOLFOXx8/CAPOXx5 /FLOX)	LCCRT S	S C	36%* Sig 21%*
Fokas	JCO 2019	306	C LCCRT (OxFU) (FOLFOX x 3)	LCCRT (OxFU) C (FOLFOX x 3)	S S	17% 25% Sig
Jin (STELLAR)	IJROBP 2017	238	LCCRT SCRT (25/5)	- C (CAPOX x 4)	S S	5% 30%* Sig (19% pCR)
Cisel (Polish2)	Annals 2019	515	LCCRT (OxFU) SCRT (25/5)	- C (FOLFOX x 3)	S S	12% 16% NS (8yr OS 41/43% NS)

LCCRT: Long course chemoradiotherapy SCRT: Short course radiotherapy, C: chemotherapy, S: Surgery

Table 3 Recent TNT publications (2)

Lead author	Journal	Number pts	1st treatment	2nd treatment	3rd treatment	End-point
Garcia-Aguilar (OPRA) Organ Preservation	ASCO 2020	324	C LCCRT (C: FOLFOX x 8 / CAPOX x 5)	LCCRT C (C: FOLFOX x 8 / CAPOX x 5)	S S	43% 58% (p=0.01) Organ pres (3yr DFS 78/77%)
Fernandez-Martos (GEMCAD1402)	ASCO 2020	180	C C (+aflib) (C: FOLFOX± aflib)	LCCRT LCCRT	S S	75.2% 81.2% NS 3yr DFS
Conroy (PRODIGE23)	ASCO 2020	461	LCCRT C (C: FOLFIRINOX x 6)	S LCCRT	C S….. C (C: FOLFOX or Cap)	68.5% (pCR 11.7%) 75.7% (pCR 27.5%) (p=0.034) 3yr DFS
Hospers (RAPIDO)	Lancet Onc 2020	920	LCCRT SCRT (25/5)	S C (C: FOLFOXx9 / CAPOXx6)	C S	13.8% 27.7% (p=0.001) pCR

RAPIDO
- 3yr DrTF (Disease related treatment failure) was 23.7% in the Exp arm and 30.4% in the S arm (HR 0.76 [0.60–0.96]; $p = 0.02$).
- 3yr distant metastasis 19.8% in the Exp arm and 26.6% (HR 0.69 in the S arm [0.53–0.89]; $p = 0.004$)
- 3yr LF were, in the Exp and S arms, 8.7% vs 6.0% (HR 1.45 [0.93–2.25]; $p = 0.10$). No diff in DrTF for diff hosp post-op adj chemo policy (p=0.37)
- Tox ≥grade 3 occurred in 48% of pts in the exp arm, comp to 25% of patients in the standard arm. Only 84% of all patients in exp arm received at least 75% of the prescribed chemo. No stat sign diff in surgical procedures or postop complications were observed. (Rad Onc 3/20)

4) Neo-adjuvant chemotherapy

It may be difficult to encompass bulkier tumours (especially if in the upper rectum (10-15 cm from anal verge) in a reasonable radiotherapy volume. If the volume is large, or a significant volume of small bowel is in close proximity to the anticipated treatment volume, there is often increased treatment-related toxicity. It may be best to consider neoadjuvant chemotherapy to down-size the tumour prior to surgery, the role of subsequent pre-operative SCRT/LCCRT can be reconsidered thereafter.

Chemotherapy duration for option 2) above

The duration and type of chemotherapy used in the pivotal studies assessing preoperative chemotherapy either before or after (chemo)radiotherapy varied considerably. This is highlighted in *Tables 2-3*.

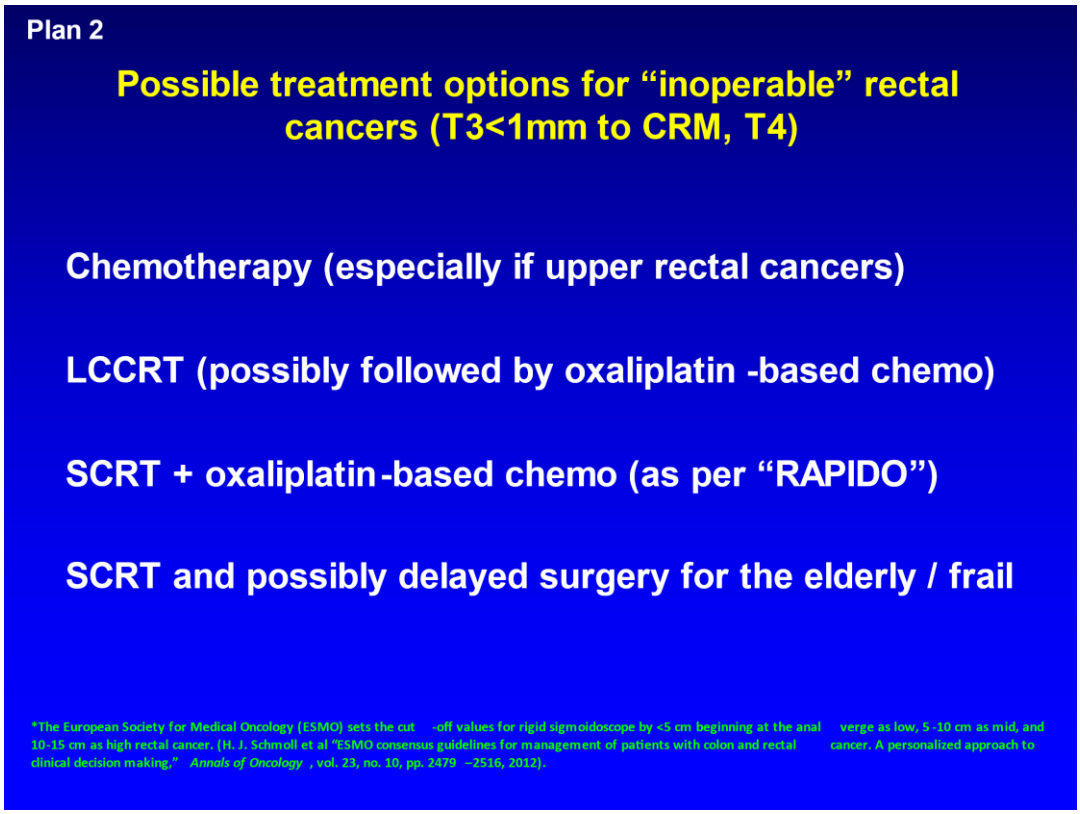
LCCRT / neoadjuvant chemotherapy:

Tables 2-3 demonstrate that Oxaliplatin based chemotherapy was used for between 6-16 weeks. A pragmatic solution until more evidence is available (some studies are only available in abstract form), is to use **12 weeks** of chemotherapy (FOLFOX x 6 or XELOX x 4). This would mean that the duration of treatment for both SCRT / chemo and LCCRT / chemo is about the same (20 weeks)

SCRT / neoadjuvant chemotherapy:

The largest positive study associated with SCRT is the RAPIDO study. This used **18 weeks** of post-RT chemotherapy (FOLFOX x 9 or XELOX x 6). This is therefore the recommended duration of chemotherapy in this situation. As stated earlier, the treatment related morbidity was greater than using pre-operative LCCRT alone. In this study, adjuvant chemotherapy after surgery did not improve

the trial end-points. A CT scan 8-10 weeks following SCRT could be considered due to the long gap between the end of RT and surgical assessment.



Low energy contact brachytherapy (Papillon)

Low energy contact brachytherapy (Papillon) may be offered alongside external beam radiotherapy to selected patients. It is indicated for patients with early-stage rectal cancers who are deemed unfit for surgery and aims to maximise the likelihood of achieving local control. This treatment approach should be discussed at the MDT and the patient referred to Clatterbridge Cancer Centre. Clinicians should refer to the GM Papillon Guideline for referral guidance.

Adjuvant chemotherapy following pre-operative treatment

The benefit of adjuvant chemotherapy following pre-operative chemotherapy and radiotherapy 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 pre-operative chemotherapy, then further post-operative adjuvant chemotherapy is unlikely to provide any further benefit. However, the benefits of further adjuvant chemotherapy can be debated in the MDT when the pathology from the resection specimen is available. If the histology indicates a high risk of systemic relapse, then a further 3 months of chemotherapy could be considered. If a patient has had a cCR and has not had surgery, then no further adjuvant chemotherapy is recommended since there is no significant evidence to support this.

Patients who achieve a Clinical Complete Response (cCR)

Patients should be informed that surgery is still the "gold-standard" but if they do choose close surveillance instead, they must be willing to comply with the follow-up guidelines (Please refer to OnCoRe database and ensure patients are managed using the latest surveillance recommendations - www.complete-response.com)

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 minimizing 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.

PRE-OPERATIVE CHEMOTHERAPY FOR OPERABLE LOCALLY ADVANCED COLONIC CANCER - cT3-4 cN1-2 cM0

Historically neo-adjuvant chemotherapy for operable colon cancer has not been a standard treatment option. Based on an analysis of non-randomised publications NICE guidance recommends neo-adjuvant chemotherapy can be considered for locally advanced T4 N0-2 M0 colon cancer.[8]

The FOXTROT trial is the largest randomised trial to have formally assessed the use of neo-adjuvant chemotherapy in patients with radiologically staged T3/T4 cancers. The study has been presented at international meetings and has been submitted for publication. The study randomized patients between:

1. Standard surgical resection followed by 24 weeks of adjuvant chemotherapy
2. 6 weeks of neo-adjuvant Oxaliplatin based chemotherapy followed by surgical resection, and then 18 weeks of post-operative adjuvant chemotherapy.

The FOXTROT data demonstrate that neo-adjuvant chemotherapy is safe; is associated with higher rates of administration of >1 cycle of chemotherapy; and a reduced rate of R1 or R2 resection compared with a standard approach. [9,10] An updated analysis for the primary endpoint of two year relapse free survival confirmed improved outcomes with pre-operative chemotherapy (HR 0.74 (0.55-0.99), p=0.042).

RAS wild-type patients who received Panitumumab in addition of standard chemotherapy did not appear to gain any benefit beyond that seen with chemotherapy alone. Left colon cancers and T4 cancers appeared most likely to benefit from neo-adjuvant chemotherapy compared to right colon and T3a tumours. In an exploratory analysis MMR deficient tumours did not appear to gain any benefit from a neo-adjuvant treatment strategy.

Neo-adjuvant chemotherapy can be considered as an option for patients with locally advanced T3/ T4 colon cancer who are fit for full dose Oxaliplatin based chemotherapy. MMR status should be assessed in all patients considered for neo-adjuvant chemotherapy. Based on the FOXTROT trial data presented so far patients with left colon MSS cancers are most likely to benefit from neo-adjuvant Oxaliplatin based combination chemotherapy. For this group neo-adjuvant chemotherapy should be considered after careful discussion at MDT with surgical colleagues regarding treatment options.

Recruitment of patients to clinical trials in this context should be encouraged where available.

[8] https://www.nice.org.uk/guidance/NG151

[9] FOxTROT: an international randomised controlled trial in 1052 patients evaluating neoadjuvant chemotherapy (NAC) for colon cancer. MT Seymour, et al. J Clin Oncol; 37(15): Abs 3504

[10] FOxTROT: neoadjuvant FOLFOX chemotherapy with or without panitumumab (Pan) for patients with locally advanced colon cancer. Virtual ASCO, 2020; Abstract 4013

PRE-OPERATIVE CHEMOTHERAPY FOR INOPERABLE LOCALLY ADVANCED COLONIC CANCER - CT3-4 CN1-2 CM0

The optimal treatment of patients with inoperable primary colonic tumours who do not have evidence of metastatic disease is uncertain. Practically these patients will be considered for doublet or triplet chemotherapy dependent on patient fitness and individual circumstances. Given the lack of benefit of EGFRi treatment in the neo-adjuvant setting (for both operable primary tumours e.g. FOXTROT, and operable liver metastases e.g. NewEPOC), there is significant uncertainty whether using these agents is beneficial and therefore for most patients EGFRi treatment would not be considered.

POST-OPERATIVE ADJUVANT CHEMOTHERAPY FOR COLON AND RECTAL CANCERS

TNM stage 2 (pT3-4 pN0 M0)/ Dukes' B

Data from the QUASAR trial[11] and a meta-analysis suggest that adjuvant chemotherapy provides a small improvement in survival of 3-5% in absolute terms compared with observation. Given the excellent prognosis of many patients treated with surgery alone and the small benefit of adjuvant chemotherapy only patients with "high-risk" features should be selected and the risks and benefits of treatment discussed on an individual case basis.

Clinical and pathological high-risk features include:

- pT4 tumour
- low lymph node yield (<12 nodes)
- presence of extramural lymphovascular or perineural invasion
- high grade/ poorly differentiated tumours
- mucinous histopathology
- obstructing or perforated primary tumours

Data from the QUASAR study also suggests that patients over 70years of age may gain no benefit from adjuvant 5FU chemotherapy.

Standard treatment options:

1. Observation
2. Oral Capecitabine chemotherapy for 6 months
3. Oxaliplatin/ Capecitabine for 3 months (e.g. fit, high-risk MSI-high patients)

MMR deficient/ MSI-high stage 2 cancers:

MMR deficiency has been identified as a biomarker associated with an improved prognosis compared to tumours which are MMR proficient. Clinical trial data shows that 22% of stage 2 and 12% of stage 3 cancers are mismatch repair (MMR) deficient.[12] The benefit of adjuvant chemotherapy, particularly single agent 5FU/ Capecitabine, is uncertain for MMR deficient tumours. MMR IHC status should be assessed, after discussion with the treating Oncologist, for patients with stage 2 or 3 colorectal tumours where the MMR status would influence decisions regarding adjuvant treatment.

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[11] Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomized study. QUASAR Collaborative Group, Lancet 2007; 370: 2020-29.

[12] Roth AD, et al. Integrated Analysis of Molecular and Clinical Prognostic Factors in Stage 2/ 3 colon cancer. JNCI 2012; 104(21): 1635-1646

High quality clinical data is lacking to inform the choice of chemotherapy for high-risk MMR deficient/ MSI-high tumours. Given the good prognosis associated with MMR deficient stage 2 tumours surveillance rather than chemotherapy will be recommended for most patients. For selected patients with a number of high-risk features Oxaliplatin containing chemotherapy could be considered.

TNM stage 3 (pT1-4 pN1-2 M0)/ Dukes' C

All patients fit enough to tolerate adjuvant post-operative chemotherapy should discuss the treatment options including their benefits and side-effects with an oncologist.

Standard treatment options include:

1. Oxaliplatin and Capecitabine (CapOx) (3 weekly regimen) for 3 months
2. Oxaliplatin and 5FU (FOLFOX) for 3-6 months
3. Single agent Capecitabine for 6 months

Decisions regarding which treatment option is selected should be made after considering relevant factors such as performance status, co-morbidity, age (<70yrs or >70yrs), and histopathological features of the cancer e.g. T3/N1 or T4/ N2 "risk groups", and (if available) MMR status. The final treatment decision will be determined after a discussion between the treating oncologist and the patient.

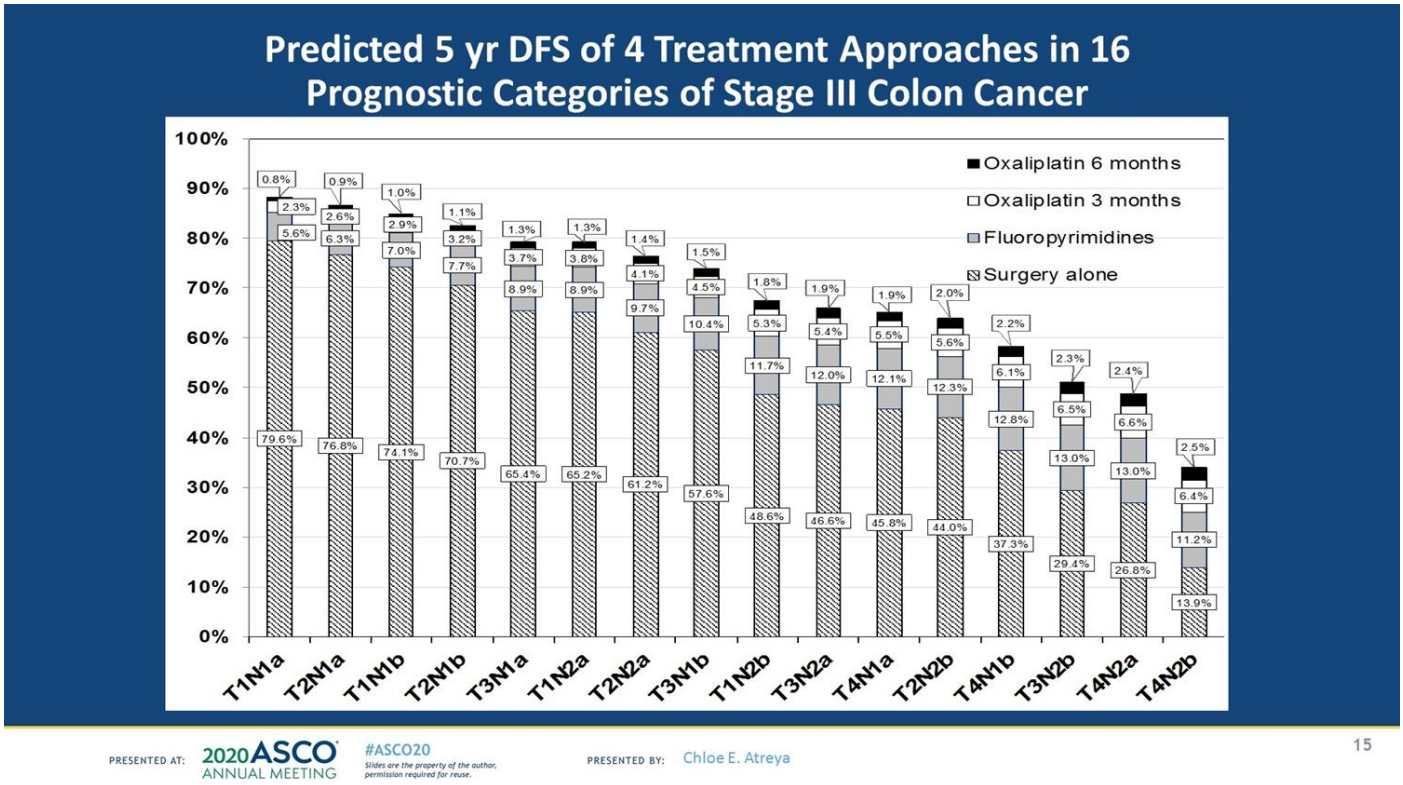
If combination chemotherapy is considered the duration of a selected chemotherapy is defined by data from the IDEA collaborative[13] and NICE guidance.[14,15] Analysis from the IDEA collaborative suggests that 3 months of Capecitabine and Oxaliplatin is associated with the same DFS and OS as a 6 month course but has lower rates of peripheral neuropathy. For FOLFOX, 3 months of chemotherapy is inferior to 6 months of FOLFOX chemotherapy, particularly in patients who have high-risk T4 N2 disease. NICE guidance recommends 3-6 months of FOLFOX treatment but local preference would be for patients to receive 6 months of FOLFOX. For most patients fit for combination chemotherapy 3 months of Capecitabine and Oxaliplatin will be preferred after considering the risks and benefits.

This guidance is relevant to patients who have not had pre-operative chemo-radiotherapy for rectal cancer. In this patient group the benefit of adjuvant chemotherapy following pre-operative chemo-radiotherapy is uncertain and these patients should be considered on a case by case basis. See section regarding pre-operative management of rectal cancer.

[13] Duration of Adjuvant Chemotherapy for Stage 3 colon cancer. A Grothey et al; N Engl J Med 2018; 378: 1177-1188

[14] Capecitabine and oxaliplatin in the adjuvant treatment of stage 3 (Dukes' C) colon cancer. NICE guidance: TA100. April 2006.

[15] https://www.nice.org.uk/guidance/NG151



This figure, based on data from the IDEA collaborative, demonstrates the predicted incremental benefits of chemotherapy treatment(s) in patients grouped by T and N stage and is a useful clinical aid for decision making.

	< 70 years	>70 years (approximate) *(Oxaliplatin likely to be of less benefit in patients > 70 years)*
Stage II (good risk)	-	-
Stage II (poor risk) 2-6% OS advantage	**Capecitabine 6/12** or CapOx 3/12 (ie: MSI-H, extensive T4 with other risk factors)	**No treat esp > 75 years/frail** or Capecitabine 6/12
Stage III (good risk i.e. T1-3 N1) 8-12% OS advantage	**CapOx 3/12** or FOLFOX 6/12 or Capecitabine 6/12 (if not fit for oxaliplatin based chemotherapy)	**Capecitabine 6/12** or No treat esp > 75 years/frail Or Fit patients < 75 years, *consider* CapOx 3/12
Stage III (poor risk i.e. T4 and/or N2) 10-15% OS advantage The small benefits of 6/12 vs 3/12 of FOLFOX will have to be discussed with patient and the pros/cons highlighted	**CapOx 3/12** or FOLFOX 6/12 or Capecitabine 6/12 (if not fit for oxaliplatin based chemotherapy)	**Capecitabine 6/12** or Fit patients < 75 years, *consider* CapOx 3/12

Bold type indicates preferred treatment option

SURGERY AND ABLATION IN THE MANAGEMENT OF METASTATIC DISEASE

Operable liver only metastases

Separate surgical guidelines for the assessment and management of potentially operable liver metastases have been produced by the HPB surgical team at Manchester Royal Infirmary.[16] All patients considered to have operable liver metastases and be fit for liver surgery should be discussed at the regional Liver metastases MDT with a liver surgeon and oncologist to plan management.

ADJUVANT CHEMOTHERAPY FOLLOWING LIVER RESECTION

The benefit of post-operative adjuvant chemotherapy is uncertain and likely to be small. Individual cases should be discussed with an oncologist.

PERI-OPERATIVE CHEMOTHERAPY

The EORTC 40983[17] trial demonstrated a small improvement in disease-free survival of borderline statistical significance. This strategy is considered a standard in clinical practice for patients with operable metastatic liver disease. A combination of factors including prior chemotherapy; size and number of liver metastases; synchronous vs. metachronous primary tumour; rectal vs. colon primary if synchronous; and technical surgical considerations will be considered at MDT prior to deciding whether to pursue a neo-adjuvant chemotherapy or a straight to surgery approach. Combination chemotherapy with Oxaliplatin/ Fp chemotherapy will be considered in most patients unless there is a relative or absolute contraindication (allergy, previous oxaliplatin chemotherapy, established peripheral neuropathy). Irinotecan/ 5FU chemotherapy is an alternative in these circumstances.

Cetuximab and Panitumumab should not be used in patients with operable liver limited metastatic disease based on the results of the NewEPOC trial.[18]

INOPERABLE LIVER ONLY METASTASES

Some patients initially deemed to have unresectable liver metastases may achieve a significant radiological response to palliative chemotherapy. Patients potentially fit enough to consider extensive surgery can be discussed at the regional Liver metastases MDT and may be considered for triplet first-line chemotherapy e.g. FOLFOXIRI. The use of EGFRi treatments in patients with inoperable disease but where surgery may be considered if there is a response to treatment is uncertain given the results of the NewEPOC trial.

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[16] https://manchestercancer.files.wordpress.com/2014/09/guidelines-for-management-of-colorectal-hepatic-metastases.pdf

[17] Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Nordlinger B et al, Lancet Oncol; 2013, 14 (12), p1208-1215

[18] Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis (New EPOC): long-term results of a multicentre, randomised, controlled, phase 3 trial. Bridgewater J et al, Lancet Oncol; 2020, 21: p398-411

Peritoneal only metastatic disease

NICE NG151 recommends that patients with peritoneal only metastatic disease be offered chemotherapy, and referral to consider cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) by a nationally commissioned specialist team. The Christie Colorectal and Peritoneal surgical team have developed referral guidelines for this procedure which should be referred to.[19]

Lung only metastatic disease

NICE NG151 recommends that patients with metastases in the lung be considered for metastasectomy, ablation or stereotactic body radiation (SABR) by a specialist MDT. Patients should be referred to the regional Thoracic team at Wythenshawe Hospital who can review the case at the specialist MDT and consider relevant treatment options.

The benefits of resection and ablation are relatively uncertain and this can be discussed with patients. The PULMICC trial was a feasibility study which randomized patients between surgery and surveillance but closed without reaching its recruitment target. The hazard ratio for death comparing metastasectomy with control was 0.82 (95%CI 0.43, 1.56). [20] The study authors have noted that survival rates were higher than expected in the control arm, who did not have a lung resection.[21] However, the study recruited 93 of a planned 300 patients and is underpowered to demonstrate a difference in outcome.

Stereotactic Ablative radiotherapy (SABR) for oligometastatic disease

SABR can be considered for patients with 1-3 sites of metastatic disease where the largest lesion is <6cm. Patients must have had a disease free interval of >6months from primary treatment to manifestation of metastatic disease. SABR is delivered as 30-50Gy in 3-5 fractions on alternate days. Patients must be able to lie flat for up to an hour. The following sites are commissioned for treatment. Please refer to the relevant clinician:

Liver – Dr Radhakrishna/ Dr Lubna Bhatt

Lung – Dr Bayman/ Dr Woolf

Spine/ Bone – Dr Colaco/ Dr Wylie

Lymph node – Dr Lavin/ Dr Radhakrishna/ Dr Woolf

Adrenal – Dr Bayman/ Dr Radhakrishna/ Dr Woolf

[19] https://hive.xchristie.nhs.uk/Interact/Pages/Content/Document.aspx?id=1481&SearchId=

[20] Pulmonary Metastasectomy versus Continued Active Monitoring in Colorectal Cancer (PulMiCC): a multicentre randomised clinical trial. Treasure T, et al., Trials (2019) 20:718

[21] Pulmonary Metastasectomy in Colorectal Cancer: updated analysis of 93 randomized patients - control survival is much better than previously assumed. Milosevic M, et al., Colorectal Disease. https://onlinelibrary.wiley.com/doi/full/10.1111/codi.15113

MANAGEMENT OF ADVANCED DISEASE

Palliative radiotherapy

MANAGEMENT OF PELVIC SYMPTOMS

A palliative radiotherapy approach may be appropriate, either due to advanced tumour staging or a patient's fitness/comorbidities. The term 'palliative' encompasses 2 treatment indications: 1) palliation of pelvic symptoms or 2) aiming for long term control. The treatment indication, patient's symptoms, ECOG Performance Status and anticipated toxicity will influence the radiotherapy prescription. Common schedules include:

- 20Gy in 5#
- 25Gy in 5# (this regimen may also be used alongside Papillon for patients with early rectal cancers, aiming for long term control)
- 30Gy in 10#

MANAGEMENT OF SYMPTOMATIC DISTANT METASTASES

In patients with symptomatic distant metastases to bone, brain, lymph nodes or lungs palliative radiotherapy may be considered in individual cases. The exact details of treatment will be decided based upon clinical oncology review.

SELECTIVE INTERNAL RADIOTHERAPY (SIRT)

SIRT can be considered in patients with liver limited metastatic disease who have a maximum of 5 liver lesions, and have previously received Oxaliplatin and Irinotecan chemotherapy. The full criteria to consider SIRT are described in an NHSE Clinical Commissioning document[22] which should be referred to. All patients should be reviewed at the Friday AM Christie SIRT radiology meeting to discuss suitability. SIRT should not be considered in the first-line treatment of patients.[23,24]

Palliative chemotherapy

There is extensive evidence from randomized trials to support the use of 5FU, Irinotecan and Oxaliplatin as palliative chemotherapy in advanced colorectal cancer patients who are fit for chemotherapy in a first and second line setting. All patients with locally advanced or metastatic colorectal cancer should be discussed at an MDT with an oncologist. Decisions regarding the precise treatment a patient receives will be taken by the treating oncologist following assessment of the patient and discussion of the risks and benefits of treatment.

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[22] https://www.england.nhs.uk/publication/independent-evaluation-of-the-selective-internal-radiation-therapy-commissioning-through-evaluation-scheme/

[23] First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. Wasan H, et al., Lancet Oncol, 2017, 18(9), p1159-1171

[24] https://www.nice.org.uk/guidance/NG151

Histological confirmation of diagnosis should be sought in all patients. Assessment of molecular biomarkers, as described earlier, should be performed in all patients where this would be clinically relevant e.g. patients are fit for anti-EGFR mAb and combination chemotherapy.

Guide to molecular stratification and treatment of advanced colorectal cancer

Biomarker Group	Standard treatment		
	1st line	2nd line	3rd line
General considerations		Early phase trials/ pre-screening if relevant	SIRT if fulfills commissioning criteria Early phase trials/ pre-screening if relevant
RAS wild-type (~40%)	EGFRi treatment e.g. Cetuximab or Panitumumab, in combination with either Oxaliplatin/ 5FU or Irinotecan/ 5FU[25]	Oxaliplatin or Irinotecan based chemotherapy dependent upon first line treatment	Trifluridine[26] and/ or Consider testing for NTRK fusion re Larotrectinib
RAS mutant (~50%)	Oxaliplatin/ 5FU or Irinotecan/ 5FU or FOLFOXIRI	Oxaliplatin or Irinotecan based chemotherapy dependent upon first line treatment	Trifluridine
BRAF V600E mutation (~ 8%)	Oxaliplatin/ 5FU or Irinotecan/ 5FU or FOLOXIRI[27,28]	Encorafenib and Cetuximab[29]	Trifluridine or Cetuximab and Encorafenib (if not previously given)

[25] Cetuximab and Panitumumab for previously untreated metastatic colorectal cancer (TA439), March 2017

[26] Trifluridine-tipiracil for previously treated metastatic colorectal cancer (TA405), August 2016

[27] Phase 3 trial of FOLFOXIRI compared to FOLFIRI, Falcone A et al, J Clin Oncol; 25(13): 1670-1676

[28] Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer, Loupakis F et al, N Engl J Med; 2014; 371:1609-1618

[29] Encorafenib, Binimetinib and Cetuximab in BRAF V600E – mutated colorectal cancer, N Engl J Med 2019; 381: 1632-1643

MMR deficient/ MSI-high (approximately 4% of patients)	Immunotherapy e.g. Pembrolizumab[30] or Oxaliplatin/ 5FU or Irinotecan/ 5FU	If no prior immunotherapy then. Nivolumab/ Ipilimumab Or If prior immunotherapy and 1. RAS/ BRAF wt – Doublet chemo + EGFRi 2. RASwt/ BRAF V600mt – Encorafenib/ Cetuximab 3. RASmt/ BRAF wt – standard chemotherapy	If no prior immunotherapy then. Nivolumab/ Ipilimumab Or Trifluridine

Notes:

- General
  - Patients who are unfit for combination chemotherapy due to performance status or co-morbidity in any of the molecular groups may be considered for single agent capecitabine first-line chemotherapy
  - Recruitment to on-going clinical trials should be considered where possible. Discussion with early phase trial team should be considered in 2nd/ 3rd line setting for molecular pre-screening if relevant.
  - Drugs funded by NHS England via the Blueteq system:
    - Include Cetuximab and Panitumumab in combination with chemotherapy, Cetuximab and Encorafenib 2nd line (BRAF V600E), Trifluridine 3rd line, Pembrolizumab and Nivolumab/ Ipilimumab.
    - The relevant request form should be completed and emailed to the-christie.drug.requests@nhs.net
- First-line EGFRi targeted treatment in combination with doublet chemotherapy:
  - Patients need to have confirmed RAS and BRAF V600 wild-type status
  - The benefits of EGFRi treatment in RAS wild-type patients is uncertain in patients with right colon cancer (proximal to splenic flexure) and clinicians may take this into consideration when making treatment decisions
  - MSI-H patients who are RAS/ BRAF wild-type, and therefore candidates for EGFRi treatment, should receive first line immunotherapy with Pembrolizumab and are then candidates for 2nd line chemotherapy plus EGFRi.
- FOLFOXIRI (5FU, Oxaliplatin and Irinotecan chemotherapy)
  - This can be considered in two main scenarios:

[30] https://www.nice.org.uk/guidance/ng161/resources/

- Patients with BRAF V600E mutant disease as first-line therapy
- Patients with RAS mutant disease who have inoperable metastatic liver disease but who may become operable if they have a significant response to treatment

  - Patients should be PS 0-1 with no significant co-morbidity

- Trifluridine

  - Patients need to have received prior Oxaliplatin and Irinotecan chemotherapy and be PS 0-1
  - Additional prognostic factors can be taken into consideration when making decisions regarding treatment decisions[31] e.g. number of sites of disease (1-2 vs 3 or more); time since metastatic diagnosis (>18 months vs. <18 months); presence of liver metastases (no vs. yes)

- Re-challenge chemotherapy

  - Re-challenge with either irinotecan or oxaliplatin based chemotherapy may be considered in selected patients where there is no contra-indication e.g. allergy/ intolerance, peripheral neuropathy, and where there is evidence of previous response to the specific drug considered. No randomized trials have been performed of this approach but non-randomised case series show evidence of response in a 3rd or 4th line setting.

- BRAF mutations

  - Patients with BRAF V600E mutation can be considered for use of Encorafenib and Cetuximab dependent on funding situation.
    - Eligible patients must be PS 0-1 and have a confirmed BRAF V600E metastatic colorectal cancer
    - NICE approved the use of Encorafenib and Cetuximab in November 2020.[32]
  - In patients with a BRAF V600E mutation who are also MSI-high it is likely that immunotherapy is the more effective treatment option and should be considered prior to BRAF targeted treatment.
  - Patients with non-V600E mutations are not eligible for Encorafenib and Cetuximab treatment. These patients represent a rare subgroup who do not appear to have the poor prognosis associated with the V600E mutation. Currently these patients can be considered for standard chemotherapy options including an EGFRi if they are RAS wild-type.

- Immunotherapy

  - The benefit of immunotherapy drugs is currently limited to MSI-high metastatic colorectal cancer and shouldn't be considered in MSS/ MSI-low, or patients with unknown status, outside of a clinical trial
  - Data from the Keynote-177 trial[33] show a significant benefit for Pembrolizumab in MSI-high metastatic colorectal cancer compared with standard chemotherapy. NICE have approved the use of Pembrolizumab for MSI-high/ MMR

[31] Tabernero J et al. Abstract 677. Presented at the 2019 Gastrointestinal Cancers Symposium

[32] https://www.nice.org.uk/guidance/indevelopment/gid-ta10496

deficient colorectal cancer.[34] Importantly patients cannot switch from standard chemotherapy to immunotherapy in a first-line palliative scenario. It is therefore of paramount importance that MSI or MMR testing is requested at the earliest opportunity to avoid delays in commencing treatment for patients.

- Pembrolizumab first-line and Nivolumab/ Ipilimumab[35] second- and subsequent lines is NICE approved and available by Blueteq request

- NTRK gene fusions

  - Larotrectinib is NICE approved for tumours with NTRK gene fusions. NICE guidance[36] and Blueteq referral guidelines should be referred to.

  - NTRK gene fusions occur in RAS and BRAF wild-type tumours. Patients who fulfill thiscriteria, are PS 0/1, and wish to consider further treatment could have NTRK gene fusion testing performed.

- Additional biomarker defined sub-groups of patients with metastatic colorectal cancer may be candidates for compassionate use applications for drugs currently unlicensed for this indication e.g. Her2 amplification and Her2 targeted treatment

[33] Pembrolizumab versus Chemotherapy for MSI-high/ MMR deficient Metastatic Colorectal Cancer: The Phase 3 Keynote-177 Study. Andre T, et al. ASCO 2020 Virtual meeting. LBA4. J Clin Oncol 38(18s)

[34] https://www.nice.org.uk/guidance/gid-ta10420/documents/final-appraisal-determination-document

[35] https://www.nice.org.uk/guidance/ta716

[36] Larotrectinib for treating NTRK fusion-positive solid tumours https://www.nice.org.uk/guidance/ta630