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Non-Surgical Oncology Guidelines – excluding Neoadjuvant and Non-Operative Management of Rectal Cancer

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Molecular Assessments in Colorectal Cancer

General considerations

Molecular testing in oncology patients has a number of facets including screening for Lynch Syndrome and providing prognostic and predictive information regarding treatments. As molecular test results impact on treatment choices it is key that results are available in a timely manner to optimize clinical decision making and patient experience and outcomes. To deliver this each MDT should work to ensure that relevant molecular testing is requested at the earliest opportunity to avoid treatment delays.

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 whether there is loss of expression of any of the MMR proteins and can direct additional testing to exclude or confirm Lynch Syndrome.
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% of tumours may have discordant results. IHC testing has been favoured as the initial diagnostic test, particularly in stage 2- 3 cancers, due to the rapid turnaround times for test results. For stage 4 patients, in whom MMR testing has not previously been performed, and who will be having additional mutation testing performed then MSI testing is sometimes preferred.

Lynch Syndrome Genetic Testing Pathway: North West Genomics Medicine Service Alliance /

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. In Greater Manchester MMR testing for all patients is offered at diagnosis with the histopathology departments at Manchester Royal and Salford Royal providing testing and clinical leadership.

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.[2]

MMR deficiency is noted in 3-4% of Stage 4 Colorectal Cancer patients and their survival, compared to patients with MMR proficient cancers receiving standard chemotherapy, is shorter. Pre-clinical data also suggests that MMR deficiency can result in a reduced benefit from 5FU chemotherapy. Recent trials have confirmed that immunotherapy treatment is superior to chemotherapy in patients with Stage 4 or locally advanced and inoperable MMR deficient/ MSI-H tumours.[3,4,5,6]

Currently MMR/ MSI status affects treatment decisions in the following clinical scenarios:

1. Resected Stage 2 colorectal cancer - MMR deficient patients have an improved prognosis and the benefit of standard adjuvant capecitabine is uncertain. Standard treatment would be surveillance.

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

[2] 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.

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

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

[5] Andre T, et al., Nivolumab plus ipilimumab versus nivolumab in microsatellite instability-high metastatic colorectal cancer (CheckMate 8HW): a randomised, open-label, phase 3 trial. Lancet Oncology, 2025; V405, p383-395

[6] Andre T, et al., Nivolumab plus Ipilimumab in Microsatellite-Instability–High Metastatic Colorectal Cancer. N Engl J Med 2024;391:2014-2026

2. Stage 4 colorectal cancer or inoperable locally advanced tumours - MMR deficient/ MSI-high patients should be considered for immunotherapy.

3. Operable locally advanced, non-metastatic colon or rectal cancers - MMR deficient/ MSI-high patients should be considered for trials examining the benefits of neo-adjuvant immunotherapy.

Sporadic tumour testing

Sporadic alterations occurring in RAS (KRAS and NRAS), BRAF, Her2 and NTRK are routinely tested in all patients with stage 4 colorectal cancer as recommended by NHS England and NICE.[7] Additional molecular alterations are sometimes also reported in screening for clinical trials. Mutations in the RAS genes are associated with shorter survival and a lack of benefit from EGFR targeted treatment. The BRAF V600E mutation is associated with significantly shorter survival and a 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.[8] It is likely that additional sporadic tumour abnormalities, beyond those currently recommended for testing, will be added to the test directory over time.

Currently assessment of these alterations is limited to patients with Stage 4 or locally advanced inoperable tumours. In operable Stage 2 or 3 colorectal cancer there isn't currently evidence to support routine testing of these targets. 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 due to Lynch Syndrome.

All Stage 4 patients being considered for systemic treatment should have an assessment of the NHS England M1.1 panel (includes RAS, BRAF and Her2 testing) as part of their initial assessment. NTRK fusions can be assessed in patients who do not have mutations in RAS or BRAF, are PS 0/1 and are candidates for further treatment in a 3rd/ 4th line setting.

Histopathological material from either the primary tumour or a metastasis can 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

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

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

following link: https://mft.nhs.uk/nwglh/test-information/cancer/solid-tumour/sample-requirements/referral-form/

Currently mutation testing influences decision making in the following scenarios:

1. RAS wild-type tumours
    a. Stage 4/ locally advanced left colon or rectal cancers - candidates for chemotherapy plus EGFR inhibitor treatment
    b. Stage 4/ locally advanced right colon cancer (proximal to splenic flexure) - The benefits of EGFRi treatment in RAS wild-type patients is uncertain. Consideration of recruitment to clinical trials should be considered where available.
2. BRAF V600E mutation present – Patients are candidates for Encorafenib/ Cetuximab targeted treatment

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 7% 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 result in a build-up of active metabolites resulting in 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 national guidance,[9] and the Christie Hospital SOP. Alternative chemotherapy agents such as raltitrexed, lonsurf, oxaliplatin and irinotecan are not metabolized by DPD and can be safely used at standard doses in patients with DPYD mutations.

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 the four commonest mutations in Caucasian populations which have been associated with fluoropyrimidine toxicity. Severe

[9] https://www.uksactboard.org/_files/ugd/638ee8_4d24d37a598c485d9ef4d1ba90abccd5.pdf

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. In patients who experience severe toxicity despite a normal DPYD test result additional germline testing through the MOLGEN clinical trial can be considered.

LOCALLY ADVANCED RECTAL CANCER

Refer to Network Guideline document "Neo-adjuvant and non-operative management of Rectal Cancer"[10]

LOCALLY ADVANCED COLON CANCER

PRE-operative SACT for OPERABLE locally advanced colonic cancer - cT3-4 cN1-2 cM0

MMR deficient/ MSI-High Tumours

Evidence is rapidly accumulating to support the use of immunotherapy as neo-adjuvant treatment for MMR deficient colon and rectal cancers. This treatment appears to be associated with a high chance of complete pathological response and a manageable side-effect profile[11]. In rectal cancer, immunotherapy may replace surgery, radiotherapy and chemotherapy.[12] MMR deficient patients should be considered for clinical trials investigating neo-adjuvant immunotherapy where available.

Data from the FOXTROT study has demonstrated that neo-adjuvant Oxaliplatin/ Fluoropyrimidine chemotherapy in MMR deficient tumours is associated with poor histological response and no improvement in 2 year recurrence rates.[13]

MMR proficient/ MSS Tumours

NICE guidance[14] recommends neo-adjuvant chemotherapy can be considered for locally advanced T4 N0-2 M0 colon cancer based on an analysis of non-randomised publications.

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[10] https://gmcancer.org.uk/wp-content/uploads/2024/05/Neoadjuvant-and-Non-operative-Management-of-Rectal-Cancer-Guidelines-v4.pdf

[11] Neo-adjuvant Immunotherapy in Locally Advanced Mismatch Repair-Deficient Colon Cancer. M Chalabi et al. NEJM, 2024; 390: 1949-1958

[12] PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. A Cercek et al. NEJM, 2022; 386:2363-2376

[13] Morton D, et al., Preoperative Chemotherapy for Operable Colon Cancer: Mature Results of an International Randomized Controlled Trial. J Clin Oncol. 2023 Jan 19;41(8):1541–1552

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

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 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 chemotherapy overall; and a reduced rate of R1 or R2 resection compared with a standard approach. Neo-adjuvant chemotherapy improved the primary endpoint of 2-year relapse free survival by 4.6% (21.5% vs 16.9% (HR 0.72 (0.54-0.98), p=0.037)). In the MMR proficient subgroup of patients a larger improvement in 2-year relapse free survival was noted (30% vs 23%, HR 0.69, p=0.032).

Left colon cancers and T4 cancers appeared most likely to benefit from neo-adjuvant chemotherapy compared to right colon and T3a tumours. As noted previously in an exploratory analysis MMR deficient tumours did not appear to gain any benefit from a neo-adjuvant chemotherapy treatment strategy.

Based on the FOXTROT trial data patients with left colon MMR proficient/ 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. Patients will be considered for 2 cycles of OxCap or 3 cycles of Oxaliplatin/ 5FU chemotherapy. As is discussed in the adjuvant chemotherapy section OxCap will be preferred in most patients and the duration of adjuvant chemotherapy will be shorter than used in FOXTROT.

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

PRE-operative treatment for INOPERABLE locally advanced colon cancer - cT3-4 cN1-2 cM0

MMR deficient/ MSI-High Tumours

Immunotherapy treatment should be considered for fit patients with no contra-indication as this is likely to be more effective than chemotherapy. Both single agent and doublet immunotherapy could be considered dependent upon a patients fitness, co-morbidities, age and preferences. Treatment is on a palliative basis with either 2 years of Ipilimumab/ Nivolumab or Pembrolizumab. In patients who achieve a good response to immunotherapy

further MDT discussion to assess surgical options can be considered. There is limited data regarding the optimal duration of treatment prior to consideration of surgery.

Large bowel obstruction because of rapid response to treatment is a recognised risk of immunotherapy treatment.[15] Patients felt to be at high-risk of bowel obstruction should be considered for a defunctioning surgical procedure (rather than stent) prior to commencing immunotherapy.

MMR proficient/ MSS Tumours

The optimal treatment of patients with inoperable primary colonic tumours who do not have evidence of metastatic disease is uncertain. The treatment options considered will reflect the first-line treatment options available for patients with Stage 4 colorectal cancer.

[15] Platt J, et al., Risk of bowel obstruction in patients with colon cancer responding to immunotherapy: an international case series. ESMO Open. 2024 Sep;9(9):103698

POST-operative adjuvant chemotherapy for colon and rectal cancers
TNM Stage 2 (pT3-4 pN0 M0)

Data from the QUASAR trial[16] 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 tumour
- mucinous histopathology
- obstructing or perforated primary tumour

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

Clinical trial data shows that 22% of stage 2 and 12% of stage 3 cancers are mismatch repair (MMR) deficient.[17] MMR deficiency has been identified as a biomarker associated with an improved prognosis compared to tumours which are MMR proficient.[18] Analysis of the QUASAR study has shown for Stage 2 tumours the risk of recurrence is significantly reduced (MMRd 10% recurrence vs. MMR proficient 27%, p<0.00001).

The benefit of Oxaliplatin in all Stage 2 tumours is uncertain and a pooled analysis has suggested that the addition of oxaliplatin is not associated with improved Overall

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

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

[18] Value of mismatch repair, KRAS, and BRAF mutations in predicting recurrence and benefits from chemotherapy in colorectal cancer. Hutchins G, et al. 2011 Apr 1;29(10):1261-70.

Survival.[19] Only 13-14% of patients in this analysis had T4 primary tumours and data from the IDEA collaborative for Stage 3 cancers suggests that T4 status confers a significantly worse prognosis. Whether Oxaliplatin based chemotherapy provides a benefit in this specific Stage 2 subgroup is uncertain and should still be considered an option in selected patients.

Given their excellent prognosis most Stage 2 MMR deficient tumours will be considered for surveillance rather than adjuvant chemotherapy. There is uncertainty regarding the benefit single agent 5FU/ Capecitabine in MMR deficient tumours. High quality clinical data is lacking to define the benefit of Oxaliplatin based chemotherapy. In selected MMR deficient cases, where no pre-operative immunotherapy has been given, Oxaliplatin adjuvant chemotherapy can be considered e.g. T4 tumours.

Standard treatment options:

1. Observation
2. Oral Capecitabine chemotherapy for 6 months
3. Oxaliplatin/ Capecitabine for 3 months – option for T4 and/ or MMR deficient/ MSI-high tumours

TNM Stage 3 (pT1-4 pN1-2 M0)

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

Standard treatment options include:

1. Oxaliplatin and Capecitabine (CapOx) (3 weekly regimen) for 3 months
2. Oxaliplatin and 5FU (FOLFOX) for 3-6 months – with 6 months treatment preferred
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

[19] Assessment of the Addition of Oxaliplatin to Fluoropyrimidine-Based Adjuvant Chemotherapy in Patients with High-Risk Stage II Colon Cancer: An ACCENT Pooled Analysis. Chibaudel B, et al. JCO, 2024

groups", and 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 chemotherapy is defined by data from the IDEA collaborative[20] and NICE guidance.[21,22] 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 has inferior disease-free survival compared to 6 months of FOLFOX chemotherapy, particularly in patients who have high-risk T4 N2 disease. For most patients fit for combination chemotherapy 3 months of Capecitabine and Oxaliplatin will be preferred after considering the risks and benefits. NICE guidance recommends 3-6 months of FOLFOX treatment, based on a cost-effectiveness analysis, but local preference would be for patients to receive 6 months of FOLFOX if OxCap chemotherapy is not an option. For high-risk patients 3 months of OxCap followed by a further 3 months of capecitabine may be considered although the benefits of this are uncertain.

Immunotherapy is not currently licensed or approved for the adjuvant treatment of MMR deficient/ MSI-H Stage 3 colorectal cancer. Results of the ATOMIC trial have shown an improvement in disease free survival for patients receiving chemotherapy plus immunotherapy compared to chemotherapy alone.[23] This treatment is not an option pending drug licensing and NICE Technology appraisal.

Adjuvant chemotherapy following neo-adjuvant treatment

There are uncertainties regarding the benefits of post-operative chemotherapy in patients who have received pre-operative long course chemo-radiotherapy, TNT or neo-adjuvant SACT for colon cancer. Treatment decisions will need to be made based on the specific pre-operative treatment and its duration e.g. OxCap vs FOLFOX, tolerance and response to pre-operative treatment, and fitness post-operatively.

Significant residual tumour histologically following pre-operative treatment would indicate a poor prognosis but doesn't indicate that further chemotherapy would be beneficial. Based on data from the SCOT study and IDEA collaborative it appears

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

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

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

[23] Sinicrope F, et al., Randomized trial of standard chemotherapy alone or combined with atezolizumab as adjuvant therapy for patients with stage III deficient DNA mismatch repair (dMMR) colon cancer (Alliance A021502; ATOMIC). J Clin Oncol 43, 2025 (suppl 17; abstr LBA1)

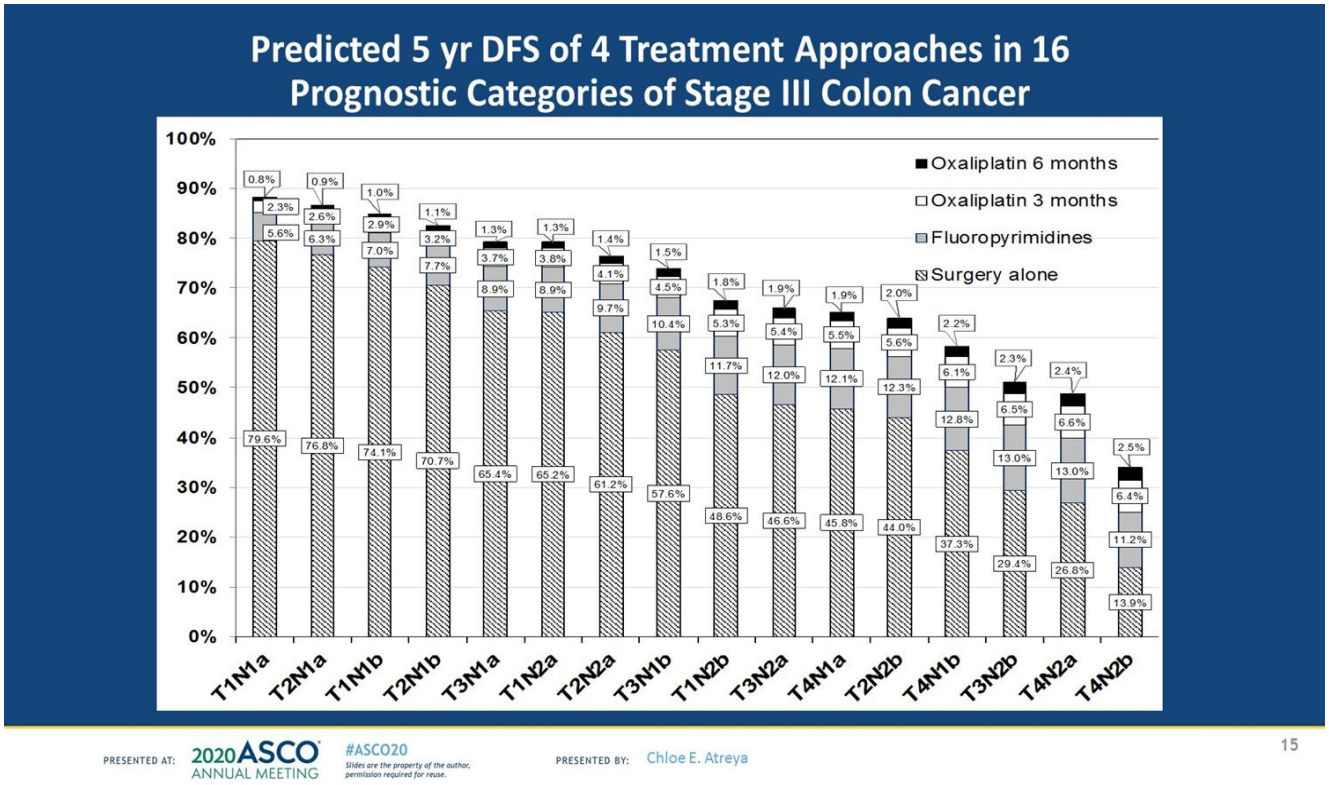
unlikely that extending the duration of Oxaliplatin/ Capecitabine chemotherapy beyond 12 weeks will significantly improve Disease Free or Overall Survival in this high-risk patient group. Therefore, if the patient has received 12 weeks of pre-operative Oxaliplatin based chemotherapy, then further post-operative adjuvant chemotherapy is unlikely to provide any further benefit.

For colon cancer patients treated with neo-adjuvant chemotherapy as per the FOxTROT trial the patient would be expected to have a further period of post-operative chemotherapy regardless of post-op histology as long as they are fit and have tolerated pre-operative treatment. The FOxTROT study gave 18 weeks of adjuvant combination chemotherapy following neo-adjuvant chemotherapy. In the context of the IDEA collaborative results a minimum of 6 weeks post-operative OxCap/ Oxaliplatin based chemotherapy could be given in fit patients, to provide a total duration of 12 weeks treatment, but upto 18 weeks of post-op chemo could be considered dependent on patient circumstances.

For rectal cancer patients who have received chemo-radiotherapy, but not TNT, the benefit of adjuvant chemotherapy following pre-operative chemo-radiotherapy is uncertain and these patients should be considered on a case by case basis.

For rectal cancer patients who have received a form of TNT including 12 weeks of Oxaliplatin based treatment the benefits of further adjuvant chemotherapy are uncertain. If a patient received OxCap for 12 weeks based on the IDEA collaborative data it is unlikely that further chemotherapy would be advised. If the patient received FOLFOX or FOLFOXIRI for 12 weeks pre-operatively the pro's and con's of a further 12 weeks of chemotherapy could be considered.

Adjuvant chemotherapy is not recommended in patients who have had a clinical complete response to pre-operative Long course Chemoradiotherapy and have not proceeded to surgery. There is no evidence to support this practice.



The above 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)	**Surveillance**	**Surveillance**
Stage II (poor risk) 2-6% OS advantage	**<u>Capecitabine 6/12</u>** or CapOx 3/12 (i.e.: MSI-H, T4 with other risk factors)	**<u>No treatment esp > 75 years/frail</u>** or Capecitabine 6/12
Stage III (good risk i.e. T1-3 N1) 8-12% OS advantage	**<u>CapOx 3/12</u>** or FOLFOX 6/12 or Capecitabine 6/12 (if not fit for oxaliplatin based chemotherapy)	**<u>Capecitabine 6/12</u>** 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 Regional HPB surgical team at Manchester Royal Infirmary.[24] All patients considered to have operable liver metastases and who are fit for liver surgery should be discussed at the regional Liver metastases MDT.

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[25] 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.[26]

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 doublet or triplet first-line chemotherapy e.g. FOLFOXIRI. The use of EGFRi treatments in patients with inoperable disease

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[24] https://gmcancer.org.uk/cancer-pathway-boards/hepato-pancreatic-biliary/

[25] 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

[26] 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

but where surgery may be considered if there is a response to treatment is uncertain given the results of the NewEPOC trial.

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. Referral to the Christie Colorectal and Peritoneal surgical team should be considered in selected cases.

Lung only metastatic disease

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

The benefits of resection and ablation are relatively uncertain and this should 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 surgical resection with control was 0.82 (95%CI 0.43, 1.56). [27] The study authors have noted that survival rates were higher than expected in the control arm, who did not have a lung resection.[28] However, the study recruited only 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.

Liver – Dr Radhakrishna/ Dr Bhatt
Lung – Dr Bayman/ Dr Woolf/ Dr Coote/ Dr Chan/ Dr Harris/ Dr Pemberton/ Prof Faivre-Finn
Spine/ Bone – Dr Colaco/ Dr Wylie
Lymph node – Dr Lavin (Pelvis) / Dr Radhakrishna (abdominal) / Dr Woolf (abdominal)

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

[28] 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

Adrenal – Dr Bayman/ Dr Radhakrishna/ Dr Woolf

Management of advanced disease
Palliative radiotherapy

Management of pelvic symptoms

Palliative radiotherapy may be appropriate, either due to a patient's symptoms or 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.

Patients with brain metastases should be referred to the neuro-oncology MDT (via patient pass) for consideration of surgery or SRS if they are KPS >=70, have controlled or controllable extracranial disease and prognosis >6 months. However, if the performance status has only declined due to neurological symptoms, then surgery may be considered.

For those deemed unsuitable for surgery/SRS (i.e. multiple brain metastases) the role of whole brain radiotherapy is uncertain. If patients remain good performance status and have other systemic options then 20Gy/5# to the whole brain can be considered.

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[29] which should be referred to. All patients should be

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

reviewed at the Friday AM Christie radiology meeting to discuss suitability. SIRT should not be considered in the first-line treatment of patients.[30,31]

Palliative chemotherapy

All patients with locally advanced or metastatic colorectal cancer should be discussed at an MDT with an oncologist. 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 treatment. 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.

Histological confirmation of diagnosis should be sought in all patients. As described previously assessment of molecular biomarkers should be performed in all patients considered fit for treatment to inform treatment options.

Guide to molecular stratification and treatment of advanced colorectal cancer

Biomarker Group	Standard treatment			
	1st line	2nd line	3rd line	4th / 5th line
General considerations	Molecular Status Consideration of whether patient will ever be a surgical candidate	Early phase trials/ pre-screening if relevant	SIRT if fulfills commissioning criteria Early phase trial pre-screening if relevant NTRK testing	

[30] 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

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

RAS and BRAF wild-type (~40%)	Left colon/ rectal primary tumours - EGFRi treatment e.g. Cetuximab or Panitumumab, in combination with either Oxaliplatin/ 5FU or Irinotecan/ 5FU[32] Right colon primary tumours - EGFRi treatment is of uncertain benefit in patients with right colon primary tumour location. Ideally these patients should be considered for recruitment to a clinical trial examining	Oxaliplatin or Irinotecan based chemotherapy dependent upon first line treatment	Trifluridine/ Bevacizumab [33] or if not suitable Trifluridine,[34] Regorafenib or Fruquintinib and Consider testing for NTRK fusion re Larotrectinib[35]	Regorafenib[36, 37] and Fruquintinib[38] are options.

[32] https://www.nice.org.uk/guidance/ta439

[33] https://www.nice.org.uk/guidance/ta1008

[34] https://www.nice.org.uk/guidance/ta405

[35] https://www.nice.org.uk/guidance/ta630

[36] Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo- controlled, phase 3 trial. Lancet 2013; 381: 303-12

[37] https://www.nice.org.uk/guidance/ta866

[38] https://www.nice.org.uk/guidance/ta1079

	benefits of EGFRi.			
RAS mutant (~50%)	Oxaliplatin/ 5FU or Irinotecan/ 5FU or FOLFOXIRI	Oxaliplatin or Irinotecan based chemotherapy dependent upon first line treatment	Trifluridine/ Bevacizumab or if not suitable Trifluridine, Regorafenib or Fruquintinib	Regorafenib and Fruquintinib are options
BRAF V600E mutation (~ 8%)	Doublet or Triplet chemotherapy e.g. Oxaliplatin/ 5FU or Irinotecan/ 5FU or FOLOXIRI[39,40]	Encorafenib and Cetuximab[41,42]	Triflurdine/ Bevacizumab or if not suitable Trifluridine, Regorafenib, or Fruquintinib or Encorafenib/ Cetuximab and (if not previously given)	Regorafenib and Fruquintinib are options

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

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

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

[42] https://www.nice.org.uk/guidance/ta668

MMR deficient/ MSI-high (approximately 4% of patients)	Immunotherapy e.g. Ipilimumab/ Nivolumab[43] or Pembrolizumab [44] Chemotherapy only an option if there is a contraindication to immunotherapy	If no prior immunotherapy received then consider immunotherapy as per 1st line[45,46] or If prior immunotherapy manage based on mutation profile 1. RAS/ BRAF wt – Doublet chemo + EGFRi 2. RASwt/ BRAF V600mt – Encorafenib/ Cetuximab 3. RASmt/ BRAF wt – standard chemo	Options depend on treatment given in first and 2nd line settings. Options may included: Doublet chemotherapy Or Encorafenib/ Cetuximab if BRAF V600E mutation present Trifluridine/ Bevacizumab or if not suitable Trifluridine, Regorafenib or Fruquintinib	Regorafenib and Fruquintinib are options

Notes:

[43] https://www.nice.org.uk/guidance/ta1065

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

[45] https://www.nice.org.uk/guidance/ta914

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

➢ **General**

- Patients who are unfit for combination chemotherapy due to poor performance status or co-morbidity in any of the molecular groups may be considered for single agent capecitabine or irinotecan first-line chemotherapy.
- Recruitment to on-going clinical trials should be considered where possible. Discussion with the early phase trials team should be considered in 2nd/ 3rd line setting for molecular pre-screening if relevant.
- Drugs funded by NHS England via the Blueteq system:
    - Cetuximab or Panitumumab in combination with first-line chemotherapy in RAS/ BRAF wild-type tumours
    - Cetuximab and Encorafenib 2nd line (BRAF V600E)
    - Trifluridine/ Bevacizumab, single agent Trifluridine, Fruquintinib and Regorafenib 3rd, 4th and 5th line
    - Immunotherapy – Pembrolizumab; Ipilimumab/ Nivolumab
    - 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.
- MMRd/ MSI-H patients who are RAS/ BRAF wild-type, and therefore candidates for EGFRi treatment, would be planned to receive first line immunotherapy and are then candidates for 2nd line chemotherapy plus EGFRi dependent upon primary tumour location.

➢ **FOLFOXIRI (5FU, Oxaliplatin and Irinotecan chemotherapy)**

- This is an option in fit patients with no significant co-morbidity. In particular patients with RAS mutant disease who have inoperable metastatic liver disease but who may become operable if they have a significant response to treatment.

➢ **Trifluridine/ Bevacizumab**

- Patients need to have received prior Oxaliplatin and Irinotecan chemotherapy and be PS 0-1.

- No contra-indication for Bevacizumab.
- Given data from the SUNLIGHT trial[47] this is the preferred 3rd line treatment option.

➢ **Single agent Trifluridine**

- This is an option in patients with a contraindication to Bevacizumab.
- Additional prognostic factors can be taken into consideration when making decisions regarding treatment decisions[48] 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).

➢ 4th line and 5th line treatment options

- Regorafenib, Fruquintinib and best supportive care are the main options considered for patients in the 4th line and beyond setting. The benefits and side-effects of each option should be discussed with patients to come to an individualized decision regarding their preferred treatment options.

➢ **Regorafenib**

- Patients need to have received prior 5FU, Oxaliplatin and Irinotecan chemotherapy and are PS 0-1.
- Given the relative benefits of Regorafenib it is normally considered an option following progression on 3rd line Lonsurf/ Bevacizumab. It can be given 4th line or 5th line following Fruquintinib.
- If Regorafenib is used the preferred regimen is to escalate the dose during cycle 1 to identify a tolerable dose for subsequent cycles.[49]

➢ **Fruquintinib**

- Patients need to have received prior 5FU, Oxaliplatin and irinotecan chemotherapy and are PS 0-1.
- Given the relative benefits of Fruquintinib it is considered an option following progression on 3rd line Lonsurf/ Bevacizumab or an alternative if patients are

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[47] Prager GW, et al., Trifluridine–Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer. N Engl J Med 2023;388:1657-1667

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

[49] Bekaii-Saab TS, et al., Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study. Lancet Oncology. Vol 20, Issue 8; p1070-1082August 2019

not suitable for Lonsurf/ Bevacizumab. It can be given 5th line following Regorafenib.

- **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.

➢ **BRAF mutations and targeted treatment**

- Patients with BRAF V600E mutation can be considered for use of Encorafenib and Cetuximab as 2nd or 3rd line treatment[50]
    - Eligible patients must be PS 0-1 and have a confirmed BRAF V600E metastatic colorectal cancer
- In BRAF V600E mutation positive tumours which are also MSI-high/ MMR deficient tumours immunotherapy is a more effective treatment option and would be preferred prior to giving BRAF V600E targeted treatment.
- Patients with non-V600E mutations are not eligible for Encorafenib and Cetuximab treatment. These patients represent a rare subgroup with uncertainty regarding the implications of the mutations. 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 MMR deficient/ MSI-high metastatic colorectal cancer and shouldn't be considered in MMR proficient/ MSS/ MSI-low, or patients with unknown status, outside a clinical trial.
- Data from the Keynote-177 trial[51] show a significant benefit for Pembrolizumab in MSI-high metastatic colorectal cancer compared with standard chemotherapy. NICE have approved the use of Pembrolizumab as first line

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

[51] 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)

treatment for MSI-high/ MMR deficient colorectal cancer.[52] It is also approved 2nd line for patients who have received no prior immunotherapy and are not considered candidates for Ipilimumab/ Nivolumab.[53]

- The CheckMate 8HW trial has demonstrated that Ipilimumab/ Nivolumab is superior to either standard chemotherapy, or single agent Nivolumab.[54,55] It is however associated with a higher risk of autoimmune toxicities. Ipilimumab/ Nivolumab is approved by NICE in a first-[56] and second-[57] line treatment setting for patients who have not received prior immunotherapy.

- 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.

- Oncologists and patients will need to weigh up the risks and benefits of Ipilimumab/ Nivolumab and Pembrolizumab in determining the treatment strategy. Given its superior Overall and Progression- free Survival data Ipilimumab/ Nivolumab will be the preferred treatment for many patients. In patients considered to have a higher risk of toxicities from Ipilimumab/ Nivolumab (e.g. underlying autoimmune disease; other co-morbidity; elderly; borderline performance status) then Pembrolizumab may be the preferred option.

➢ **NTRK gene fusions**

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

[53] https://www.nice.org.uk/guidance/ta914

[54] Andre T, et al., Nivolumab plus Ipilimumab in Microsatellite-Instability–High Metastatic Colorectal Cancer. N Engl J Med 2024;391:2014-2026

[55] Andre T, et al., Nivolumab plus ipilimumab versus nivolumab in microsatellite instability-high metastatic colorectal cancer (Check-Mate 8HW): a randomised, open-label, phase 3 trial. Lancet Oncology, 2025; V405, p383-395

[56] https://www.nice.org.uk/guidance/ta1065

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

- Larotrectinib is NICE approved for tumours with NTRK gene fusions. NICE guidance[58] and Blueteq referral guidelines should be referred to when considering this treatment.

- Less than 1% of metastatic colorectal cancers have an NTRK gene fusion and they occur in RAS and BRAF wild-type tumours. Patients who fulfill these criteria and are PS 0/1, and wish to consider further treatment could have NTRK gene fusion testing performed.

➢ **Additional considerations**

Sub-groups of patients with metastatic colorectal cancer may be candidates for clinical trials or compassionate use applications for drugs currently unlicensed for this indication. These options can be explored in ind

[58] https://www.nice.org.uk/guidance/ta630