NHS
Kent and Medway
Cancer Collaborative

Oncological Treatment of Colorectal & Anal Cancer

Pathway of Care

Kent & Medway Cancer Collaborative

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CONTENTS

1.0 INTRODUCTION

- This document has been written to provide guidance on the treatment of colorectal cancer in the Kent & Medway Cancer Collaborative (KMCC)
- Radiotherapy schedules are as defined in the Kent Oncology Centre Quality System Clinical Protocols.
- See network chemotherapy protocols for details of chemotherapy / systemic anti-cancer regimens (SACT).
- All patients will be considered for entry into a clinical trial where appropriate (see appendix A).
- All patients should be discussed at a multidisciplinary team meeting (MDM) before commencing initial treatment.
- All chemotherapy regimens listed within this document may be delivered at either Maidstone and Tunbridge Wells NHS Trust, East Kent Hospitals University NHS Foundation Trust, Medway NHS Foundation Trust, or Darent Valley Foundation Trust.

  Please note, some of the drugs/doses recommended within this document are outside of the U.K. licensed marketing authorisation.

2.0 MOLECULAR AND PHARMACOGENOMIC TESTING

2.1 DYPD testing

- All patients, prior to commencing treatment with a fluoropyrimidine based therapy (5-fluorouracil, capecitabine or tegafur) should be screened for four DPYD gene variants which have been associated with fluoropyrimidine-associated toxicity.

  Patients only require this genomic test to be carried out once, at the start of their first fluoropyrimidine treatment, as the results remain applicable to subsequent fluoropyrimidine cycles and future treatment regimens containing a fluoropyrimidine.

  Within the clinical pathway, the genomic test should be ordered for eligible patients at the point of consent for fluoropyrimidine chemotherapy or earlier if appropriate.
  Clinicians should follow the UK Chemotherapy Board guidance on dosing adjustments for fluoropyrimidine therapy following detection of a DPYD variant.

2.2 Genomic testing

- The National Genomic Test Directory specifies which genomic tests are commissioned by the NHS in England, the technology by which they are available, and the patients who will be eligible to access a test. This is in development; molecular testing for colorectal cancer in Kent will evolve in line with this guidance.

- In keeping with NICE Guidance for colorectal cancer, all patients with colorectal cancer should have MMR testing.

- In keeping with NICE Guidance for colorectal cancer, all patients with metastatic colorectal cancer suitable for systemic anti-cancer treatment should have testing for RAS and BRAF V600E mutations using tissue from their surgical resection, or from tissue from a suitable biopsy (e.g. a metastasis).

3.0 URIDINE TRIACETATE

- Uridine triacetate (Vistoguard) is an antidote for management of early-onset severe or life-threatening toxicity, including diarrhoea, within 96 hours following 5FU or capecitabine administration. It is not licensed in the UK, but is available on an unlicensed basis via a 24/7 emergency ordering service, via tel 0207 8872235.

  The policy statement (link below) from NHSE contains information on inclusion / exclusion criteria and also dosing information.

  https://www.england.nhs.uk/wp-content/uploads/2020/03/1929_Policy_Statement_Final_v2.pdf

4.0 COLORECTAL CANCER

- **Localised colorectal cancer**
  The majority of cases of colon and rectal cancer present with localised disease. In colon cancer, surgical excision is almost always the initial treatment. Many patients benefit from adjuvant chemotherapy following surgery. Patients with localised rectal cancer should have surgical excision, but some benefit from neoadjuvant radiotherapy or chemoradiation. Adjuvant chemotherapy should also be considered in many cases.

- **Metastatic colorectal cancer**
  Some patients present with distant metastases, and many develop metastatic disease following primary treatment. The majority of these will be treated with chemotherapy. In the small number of patients with limited metastatic disease at presentation, resection of metastases should be considered as part of the primary treatment.

4.1 Adjuvant Systemic Anti-Cancer Treatment (SACT) for colorectal cancer

- Following surgical resection of the primary colorectal cancer, many patients are offered adjuvant chemotherapy to reduce the risk of recurrence and improve overall survival. There is good evidence for its use in stage III (Dukes C, node positive) cancers. In stage II (Dukes B, node negative) disease the evidence is more equivocal, but patients with high risk features may well benefit from adjuvant chemotherapy.
- Stage III colorectal cancer can be considered as low or high risk based on the T stage and N stage. Age and co-morbidity should be taken into account before considering the type and duration of chemotherapy in the adjuvant setting. If a patient has received neoadjuvant chemotherapy before rectal surgery (usually for 3 months), then a further 3 months adjuvant chemotherapy is given, to make a total of 6 months treatment.
- It is recommended that CEA is measured before adjuvant chemotherapy, after 3 months of chemotherapy and after completion of adjuvant chemotherapy.

4.1.1 Indications for adjuvant chemotherapy

- Adjuvant Chemotherapy should be considered for:
  - PS 0 to 2 and adequate organ function
  - Stage III colorectal cancer
  - Stage II colorectal cancer in medically fit patients with risk factors:

    Major prognostic parameters:
    - Lymph node sampling <12
    - pT4 lesions including perforation

    Minor Prognostic parameters:
    - High grade tumour
    - Vascular invasion
    - Perineural invasion
    - Tumour presentation with obstruction
    - High preoperative CEA levels

Adjuvant chemotherapy should be given within 8-12 weeks of surgery (ideally 8 weeks).

4.1.2 Chemotherapy regimens

- **Stage II / III**
  - Modified De Gramont x 12 cycles
  - 5- fluorouracil and calcium folinate (folinic acid) weekly x 30 weeks
  - Capecitabine x 8 cycles

- **Stage III (for patients suitable for oxaliplatin) and high-risk stage II following discussion with the patient regarding risk / benefit ratio**
  - Capecitabine and Oxaliplatin every 3 weeks x 4 to 8 cycles
  - Oxaliplatin and Modified De Gramont x 6 to12 cycles

4.2 Neo-adjuvant chemotherapy for colon cancer

Based on the presented results of the FOXTROT trial, patients with operable, non-obstructed T3-4 N0-2 M0 colon cancer can be considered for neoadjuvant FOLFOX or CAPOX chemotherapy for up to 12 weeks prior to surgery. This has been shown to be well tolerated and safe with no increase in perioperative morbidity.

4.3 Neo-adjuvant treatment with curative intent for rectal cancer

Complete surgical excision of rectal cancers is extremely important to reduce the risk of local recurrence and increase overall survival. There is now evidence for many rectal cancers that neoadjuvant treatment with radiotherapy alone or chemoradiation can improve these outcomes. Following surgical excision, adjuvant chemotherapy is considered (as above: section 2.1).

In all patients who receive long course neoadjuvant chemoradiation, restaging imaging (MRI pelvis and CT thorax, abdomen and pelvis) must be done, and discussed in the colorectal MDM, 5-6 weeks after completion of the radiotherapy.

Pre-operative treatment should be considered for all rectal cancers which are T3/T4 or node positive. Consideration can be given to total neo-adjuvant treatment and organ preservation on a case by case basis.

4.3.1 Non-metastatic rectal cancer

4.3.1.1 Circumferential Resection Margin (CRM) Not Threatened

Following MRI staging, treatment is to be agreed at the MDM on an individual case basis.

Options include:

- Surgery alone
- Short course pre-operative radiotherapy with immediate or delayed surgery.
- Long course concurrent chemoradiation using
  - chemoradiation for 5 weeks with concurrent fluoropyrimidine with rectal surgery 8-12 weeks following completion of chemoradiation.
- Rectal preservation strategy.

4.3.1.2 CRM Threatened

Following MRI staging, treatment is to be agreed at the MDM on individual case basis. The aim is to maximise the potential for R0 resection at the time of surgery. The options are:

- chemoradiation for 5 weeks with concurrent fluoropyrimidine with rectal surgery 8-12 weeks following completion of chemoradiation.
- Raltitrexed + RT may be considered for patients who are unsuitable for fluoropyrimidines.
- Radiotherapy alone.
- For selected locally advanced tumours (T4, EMVI+, N2, CRM+) consideration should be given to total neoadjuvant therapy with either:
  - Short course radiotherapy followed by CAPOX chemotherapy (capecitabine and oxaliplatin) x 6 cycles followed by reassessment for surgery (RAPIDO trial)
  - Neoadjuvant chemotherapy (oxaliplatin doublet) followed by radiotherapy with or without chemotherapy for 5 weeks with concurrent fluoropyrimidine followed by consideration of rectal surgery.

For tumours involving the CRM, the decision for neoadjuvant treatment should be made following discussion in the MDT.

4.3.1.3 Post-operative completion chemotherapy for rectal cancer patients who have completed neo-adjuvant chemotherapy

Patients will be considered for a further 12 weeks of chemotherapy (fluoropyrimidine +/- oxaliplatin).

4.3.2 Rectal cancer with liver predominant metastases at presentation

Patients with rectal cancer with liver predominant metastases at presentation may be considered for combination treatments to include local treatment to the liver (usually surgery or radiofrequency ablation) if the metastases are operable or potentially operable following downstaging. All such patients should be discussed in the liver MDM (usually King's College Hospital, London). See also section 4.5.1.

The options include:

- 12 weeks neo-adjuvant chemotherapy (doublet with oxaliplatin or irinotecan + fluoropyrimidine) followed by chemoradiation for 5 weeks with concurrent fluoropyrimidine or short course radiotherapy. After completion of radiotherapy, rectal surgery is carried out, followed by 12 weeks of further chemotherapy (doublet with oxaliplatin or irinotecan + fluoropyrimidine). Local treatment to the liver is then considered (usually surgery or radiofrequency ablation).

- 12 weeks neo-adjuvant chemotherapy (doublet with oxaliplatin or irinotecan + fluoropyrimidine) followed by chemoradiation for 5 weeks with concurrent fluoropyrimidine. If the liver metastases are easily operable, then liver and rectal surgery is done (usually at King's College Hospital, London). This is followed by 12 weeks of completion chemotherapy (doublet with oxaliplatin or irinotecan + fluoropyrimidine).

- Primary rectal and liver surgery (in patients with small operable liver metastases, who do not require neoadjuvant treatment for the rectal cancer). This is followed by 6 months of adjuvant chemotherapy (doublet with oxaliplatin or irinotecan + fluoropyrimidine).

4.4 Post-operative chemo-radiotherapy for resected rectal cancer

Consider post-operative chemo-radiotherapy following resection of rectal cancer if there are positive margins or residual macroscopic disease, provided the patient has not received pre-operative radiotherapy. If being considered for adjuvant chemotherapy, post-operative chemo-radiotherapy should be scheduled after completion of chemotherapy.

4.5 Treatment of metastatic colorectal cancer

In patients with metastatic colorectal cancer (stage IV) advances in combination chemotherapy have extended survival. Access to a fluoropyrimidine, oxaliplatin and irinotecan during the treatment pathway is more important than the sequence in which they are given. Targeted agents may provide treatment options in circumstances where funding is available.

Patients with metastatic colorectal cancer should have tumour markers measured as per clinician's recommendation.

Some patients with unresected primary colorectal cancer and metastatic disease are referred for initial chemotherapy. This may be followed by resection of the primary cancer in some cases.

Patients with liver predominant disease may also be considered for liver directed intervention after discussions with the specialist liver MDM (King's).

Selected patients with low volume lung disease should also be discussed in a specialist lung MDM and considered for definitive surgical lung intervention (or radiofrequency ablation) or SABR.

Patients with liver metastases which are resected should be followed up with 6 monthly CEA measurements and CT and alternating MRI liver every 6 months for 2 years and annually for a further 3 years.

4.5.1 Colorectal cancer with liver predominant metastases at presentation

In patients with liver predominant metastases from colorectal cancer, there are a number of treatment options available. All patients with liver predominant disease are discussed at a specialist liver MDM (usually King's College Hospital, London).

- **Operable liver metastases at presentation;** peri-operative oxaliplatin based chemotherapy can be considered.
- **Inoperable liver metastases at presentation;** should be considered for systemic treatment with palliative intent.
- **Borderline resectable liver metastases at presentation;** should be considered for systemic treatment with neoadjuvant intent with the aim to achieve resection.
  RAS-wild type patients should be considered for treatment with combination chemotherapy including anti-EGFR antibody.

Assessment for response to chemotherapy should be undertaken at 8-12 weeks. Chemotherapy should not be given for extended periods because of the risk of Chemotherapy Associated Steatohepatitis (CASH).

Following liver resection, further chemotherapy may be considered.

4.5.1.1 Recurrence with liver predominant metastases

Patients who relapse with liver predominant metastases may benefit from liver resection, with peri-operative chemotherapy where appropriate.

For treatment guidance see section 4.5.1

4.5.2 Metastatic colorectal cancer (not resectable)

Most patients with metastatic colorectal cancer will not be suitable for resection of metastases. Chemotherapy is given with palliative intent, to improve quality of life and increase overall survival. Patients should be regularly assessed for response to chemotherapy and toxicity.

4.5.2.1 Chemotherapy regimens for metastatic colorectal cancer

Systemic anti-cancer therapy may be considered for patients with performance status 0, 1 or 2.
All patients newly diagnosed with metastatic colorectal cancer should have tumour molecular analysis including MMR, RAS/ RAF.

RAS Wild Type tumours

- Cetuximab or panitumumab (given in conjunction with 5-fluorouracil, folinic acid and either oxaliplatin or irinotecan regimens listed below see regimens below) are indicated as first line treatment given in conjunction with fluoropyrimidines and either oxaliplatin or irinotecan regimens listed below only for patients whose tumour is RAS wild-type.

BRAF mutation

- 1st line – chemotherapy as per clinical choice
- 2nd line- encorafenib* and cetuximab
- 3rd line – clinician's choice or encorafenib* and cetuximab

*****Patients must not have received previous treatment with any BRAF inhibitor, MEK inhibitor, cetuximab, panitumumab and any other EGFR inhibitors.

Deficient MMR

- 1st line- pembrolizumab or clinician choice chemotherapy
- 2nd line – chemotherapy clinician's choice or ipilimumab/nivolumab if has not received immunotherapy in first line setting.
- 3rd line- clinician choice

Regimens for metastatic colorectal cancer

- Capecitabine
- Capecitabine and Mitomycin-C
- Capecitabine and Oxaliplatin every 2 weeks
- Capecitabine and Oxaliplatin every 3 weeks
- 5-fluorouracil and Mitomycin-C
- 5-fluorouracil weekly bolus
- Irinotecan weekly
- Irinotecan every 3 weeks
- Irinotecan and Capecitabine
- Irinotecan and Modified De Gramont
- Modified De Gramont
- Oxaliplatin and Modified De Gramont
- Folfoxiri
- Trifluridine & Tipiracil

Patients who are intolerant to 5-fluorouracil and folinic acid, or for whom these drugs are not suitable (for example, patients who develop cardiotoxicity), may be considered for:

- Raltitrexed
- Raltitrexed and Oxaliplatin

N.B. Bevacizumab, aflibercept, panitumumab (subsequent line) and cetuximab (subsequent line), may be given in combination with cytotoxic chemotherapy, or where appropriate as a single agent, however these are currently not funded, so funding approval is required.

Patients who have previously had treatment with fluoropyridimine, oxaliplatin or irinotecan-based chemotherapy, anti-VEGF agents, anti-EGFR agents OR when these therapies are not suitable. May be considered for:

- Trifluridine & Tipiracil

4.6 PALLIATIVE RADIOTHERAPY FOR RECTAL CANCER

Consider for control of local symptoms in the following patients:

- Primary rectal cancer unsuitable for surgery due to either medical comorbidity or locally advanced tumour (and not fit for chemoradiation).
- Local recurrence of rectal cancer unsuitable for surgery.

4.7 Oxaliplatin Neuropathy Guidelines

Oxaliplatin-induced neuropathy is common. Please refer to Appendix B for assessment and management of this.

For patients who develop acute laryngopharyngeal dysaesthesia during or within the hours following the 2-hour infusion, the next oxaliplatin infusion should be administered over 6 hours (SmPC).

5.0 ANAL CANCER

All patients with a diagnosis of anal cancer should all be discussed in the specialist network anal cancer MDM at Maidstone. Patients with completely excised T1 N0 anal margin disease only may be managed by the local surgical team and do not require further treatment. The remaining large majority of patients are considered for radical chemoradiation.
Patients should be considered for a defunctioning colostomy if necessary before commencing this treatment

Indications for a defunctioning stoma.

- Tumours infiltrating into the posterior vagina.
- Patients with significant faecal incontinence due to sphincter dysfunction, secondary to tumour infiltration.
- Patients with significant pain or minor incontinence and tumours at risk of mechanical obstruction can be managed conservatively or with a defunctioning colostomy.

Patients who have residual viable disease at 6 months post chemoradiotherapy or who develop local or regional recurrence will be considered for a salvage AP resection.

5.1 Primary treatment

5.1.1 Radical treatment

- Concurrent chemoradiation with Mitomycin C + 5-Fluorouracil (5 weeks treatment)
- Capecitabine and Mitomycin C with radiotherapy.

See radiotherapy protocol RWF-QRTC51 IMRT Anal Protocol.

5.1.2 Palliative treatment

For frail patients and patients unsuitable for above radical treatment

- 5-Fluorouracil and Mitomycin C in combination with radiotherapy (palliative treatment)
- Radiotherapy alone

5.2 Systemic treatment for advanced disease

Consider clinical trial or other palliative regimens, options include:

First line

- Carboplatin AUC 5 and paclitaxel (days 1,8 &15 every 28 days)

Second Line

- Cisplatin & 5-Fluorouracil without radiotherapy
- Carboplatin & 5-Fluorouracil without radiotherapy
- Capecitabine and Cisplatin
- Capecitabine and Carboplatin
- Single agent paclitaxel
- Irinotecan

6.0 APPENDIX A: CLINICAL TRIALS

Refer to the local research team who will provide on request an orientation handbook, list of current trials and associated trial protocols and summaries.

Contact numbers

MTW – Clinical Trials Office	01622 225 033
Darent Valley Hospital – Clinical Trials Office	01322 428 100 ext 4810
Medway Hospital – Clinical Trials Office	01634 825 094
East Kent Hospitals – Clinical Trials Office:	
Solid Tumours	01227 866 393

7.0 APPENDIX B: GUIDANCE ON THE ASSESSMENT AND MANAGEMENT OF OXALIPLATIN INDUCED NEUROPATHY

Guidance on the assessment and management of oxaliplatin induced neuropathy

Introduction

- Use the neuropathy assessment tool on KOMS at each pre-chemo review.
- Symptoms of sensory or functional neuropathy may include tingling or numbness which may persist to the next pre-chemotherapy assessment.
- This guidance is for patients receiving treatment outside the context of a clinical trial. For patients being treated within a clinical trial setting, follow trial protocol (using assessment below as far as possible).
- Do not assess oxaliplatin induced neuropathy using CTC toxicity criteria.
- Dysaesthesia in the jaw is an unpleasant sensation and/or pain in the jaw.
- Laryngopharyngeal spasm is a sensation of difficulty in swallowing / breathing.

Assessment and action

Normal occurrence / Caution	Symptoms	Action at nurse assessment	Consultant review required / Action by consultant
Normal occurrence with oxaliplatin	Dysaesthesia (tingling in hands and feet) occurring with and up to 72 hours after infusion	No action required.	
	Dysaesthesia in the jaw (during infusion) and cold induced laryngopharyngeal spasm up to 48 hrs after infusion.	Advise patients to avoid cold drinks / cold weather. Consider administering next oxaliplatin infusion over 6 hours (SmPC).	
First caution / warning sign	Tingling persisting beyond 72 hours or painful cold-induced neuropathy	d/w consultant or clinicians authorised to prescribe chemotherapy Close monitoring at each subsequent cycle. Ask the following specific questions at each nursing assessment: 1. Is the dysaesthesia (during the infusion) and / or cold induced laryngopharyngeal spasm more severe? 2. Has the tingling continued for longer than during the previous cycle and / or is tingling still present when next cycle is due?	1. If yes, consultant review required. For consideration of DR at next cycle or omission of oxaliplatin. 2. If yes, consultant review required, for consideration of DR at next cycle or omission of oxaliplatin
Serious caution	Numbness in hands or feet Severe excitability channel neuropathy during infusion (very rare) seen as severe pain and numbness on infusion Painful neuropathy	Must be reviewed by a consultant Must be reviewed by a consultant Must be reviewed by a consultant	Consider DR or omission of oxaliplatin. Repeat consultant review before next cycle Consider DR or omission of oxaliplatin. Repeat consultant review before next cycle Consider Duloxetine. Starting at 30mg-60mg OD where available on Trust formulary. Alternatively, d/w pain management specialist.
Other cautions	A cumulative dose of 700-800mg/m^2 oxaliplatin has been reached	Must be reviewed by a consultant	
	All patients restarting oxaliplatin based chemotherapy after a break in treatment (this may be due to an intervention such as rectal cancer patients having surgery)	Must be reviewed by a consultant to assess for delayed onset neuropathy	

Notes

- Neurology referral should be considered in severe cases.
- Initial dose reductions should be at a 25% level. If there is no improvement or worsening symptoms, based on an assessment of risk and benefit, consider further dose reduction. Once reduced, doses should not be re-escalated.
- Disclaimer: This document is for use only within Kent and Medway. No responsibility will be accepted for the accuracy of this information when used elsewhere.

8.0 PERSONNEL AND CONTACT INFORMATION

A comprehensive, up to date list of MDM contact details can be found on the KMCC website via the following link: http://kmcc.nhs.uk/tumour-sites/terms-of-reference/

9.0 GLOSSARY

Acronyms in common usage throughout KMCC documentation

BNF	British National Formulary
BOPA	British Oncology Pharmacist Association
CNB	Cancer Network Board
COSHH	Control of substances hazardous to health regulations.
CYP	Children & Young People (in relation to the IOG)
DCCAG	Diagnostic Cross Cutting Advisory Group
DOG	Disease Orientated Group (NSSG/TSSG/TWG)
DVH	Darent Valley Hospital
DGT	Dartford and Gravesham NHS Trust
EK	East Kent
EKHUFT	East Kent Hospitals University Foundation Trust
EPS	Electronic Prescribing System
FP10(HNC)	Prescriptions issued by hospital doctors for dispensing in the community
GP	General Practitioner
HoP	High Level Operational Policy
IOSC	Improving Outcomes: A Strategy for Cancer
IV	Intravenous
K&C	Kent & Canterbury Hospital, Canterbury, (EKHUFT)
KMCC	Kent & Medway Cancer Collaborative
KMCRN	Kent & Medway Cancer Research Network
KOMS	Kent Oncology Management System
LSESN	London & South East Sarcoma Network
MFT	Medway Foundation Trust
MTW	Maidstone & Tunbridge Wells NHS Trust
NHS	National Health Service
NMP	Non-medical prescriber
NPSA	National Patient Safety agency
NOG	Non Surgical Oncology Group *(Permanent oncologist sub group of the DOGs with a specific responsibility for chemo/rad pathways and advice to the DOG, Network and GEOGRAPHICAL LOCATIONs on new drugs)*
PoC	Pathway of Care *(Network agreed disease site specific clinical guidelines)*
QEQM	Queen Elizabeth the Queen Mother Hospital, Margate (EKHUFT)
QoL	Quality of life
QSIS	Quality service information system
QST	Quality Surveillance Team

RAT	Research and Trial Group *(Permanent sub-group of the DOGs with a specific responsibility for taking forward the clinical trials agenda)*
RMH	Royal Marsden Hospital
RNOH	Royal National Orthopaedic Hospital
SACT	Systemic Anti-Cancer therapy
SACT regimen	Systemic Anti-cancer prescription on the electronic prescribing system
SACT protocol	Systemic Anti-cancer protocol on KMCC website
TTO	Treatment to take home
QVH	Queen Victoria Foundation Trust Hospital East Grinstead
UCLH	University College Hospital London
WHH	William Harvey Hospital, Ashford (EKHUFT)
WK	West Kent

10.0 DOCUMENT ADMINISTRATION

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