Kent and Medway Cancer Collaborative

Oncological Treatment of Colorectal & Anal Cancer

Pathway of Care

Kent & Medway Cancer Collaborative

Publication date	July 2018
Expected review date	July 2019
Version number	10.0
Version status	Final

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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 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 a small number of patients with limited metastatic disease (usually liver predominant) at presentation, resection of metastases may be part of the primary treatment.

All patients with colorectal cancer should have RAS testing carried out either from the tissue from their surgical resection, or from tissue from a suitable biopsy (e.g. of a liver metastasis).

NICE guidelines recommend testing for microsatellite instability (MSI) and the result reviewed, before treatment decisions are made. This is essential for patients with stage II disease who are being considered for chemotherapy.

2.1 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.

In general, adjuvant chemotherapy is given for six months. 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 completeion of adjuvant chemotherapy.

2.1.1 Indications for adjuvant chemotherapy

- Adjuvant Chemotherapy should be considered for:
  - Stage III colorectal cancer (node positive)
  - Stage II colorectal cancer (node negative) in medically fit patients with high risk features such as:
    - Poorly differentiated or mucinous histology
    - T4 lesions
    - Low lymph node yield
    - Presentation with bowel obstruction
    - Perineural invasion
    - Extramural vascular invasion

Individual MDMs should decide which lower risk patients should receive chemotherapy.

2.1.2 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 (see NICE TA100 section 2.1.3)

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 8 cycles (see NICE TA100 section 2.1.3)
- Oxaliplatin and Modified De Gramont x 12 cycles (see NICE TA100 section 2.1.3)

For low risk stage III patients, ie T3N1, 3 months of combination treatment may be an appropriate option. High risk patients, ie T4N2, should receive 6 months of adjuvant treatment. Consideration can be given to continuing the fluoropyrimidine alone after 3 months of combination treatment.

2.1.3 NICE guidance for adjuvant treatment with capecitabine and oxaliplatin (TA100)

NICE guideline TA100 states that **Capecitabine** and **Oxaliplatin** are recommended as possible adjuvant treatments after surgery for stage III colon cancer, when used in the following ways:

- Capecitabine on its own
- Oxaliplatin together with 5-fluorouracil and folinic acid

2.2 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.

2.2.1 Non-metastatic rectal cancer

2.2.1.1 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 (over 1 week) with surgery within 1 week following completion of radiotherapy
- Long course concurrent chemoradiation using
    - chemoradiation for 5 weeks with concurrent fluoropyrimidine with rectal surgery 8-12 weeks following completion of chemoradiation.

2.2.1.2 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.
- 12 weeks neo-adjuvant chemotherapy (oxaliplatin + fluoropyrimidine) followed by chemoradiation for 5 weeks with concurrent fluoropyrimidine. Rectal surgery should be carried out 8-12 weeks following completion of chemoradiation.

For tumours beyond the CRM, then neoadjuvant chemotherapy followed by chemoradiation and surgery is the preferred option. For tumours involving the CRM, the decision for neoadjuvant treatment should be made following discussion in the MDT.

2.2.1.3 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).

2.2.2 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 2.4.1

The options include:

- 12 weeks neo-adjuvant chemotherapy (doublet with oxaliplatin or irinotecan + fluoropyrimidine) followed by chemoradiation for 5 weeks with concurrent fluoropyrimidine. After completion of chemoradiation, 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).

2.3 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.

2.4 Treatment of metastatic colorectal cancer

In patients with metastatic colorectal cancer (stage IV) ~~recent~~ 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 such as cetuximab, bevacizumab, aflibercept and panitumumab provide ~~additional~~ treatment options in circumstances where funding is available. All patients with metastatic colorectal cancer being considered for systemic treatment should have RAS and RAF testing.

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 other ~~new~~ technologies after discussions with the specialist liver MDM (King's).

Patients with liver predominant metastases are discussed below (section 2.4.1) as liver resection can lead to potential cure or long term control in some cases.

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).

Patients with liver metastases which are resected should be followed up with CT scanning every 6 months.

2.4.1 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 should be considered.

Inoperable liver metastases at presentation; RAS-wild type patients should be treated with combination chemotherapy with anti-EGFR antibody in appropriately selected patients.

Borderline resectable liver metastases at presentation; aim to achieve resection in RAS-wild type patients with combination chemotherapy using 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.

2.4.1.1 Recurrence with liver predominant metastases

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

2.4.2 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. Fluoropyrimidines (5FU and capecitabine), oxaliplatin and irinotecan are the most effective chemotherapy drugs. Patients should be regularly assessed for response to chemotherapy and toxicity. Cetuximab or panitumumab may be added to irinotecan or oxaliplatin based chemotherapy as first line treatment in RAS wild type metastatic colorectal cancer.
Bevacizumab in combination with fluoropyrimidine based chemotherapy may be considered (funding approval required).

2.4.2.1 Chemotherapy regimens for metastatic colorectal cancer

- Systemic anti-cancer therapy may be considered for patients with performance status 0, 1 or 2.

- 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 only for patients whose tumour is RAS wild-type.

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

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 by commissioners within KMCC, 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 (NICE TA 405)

2.4.3 NICE guidance

There are four NICE technology appraisals currently published for advanced colorectal cancer. Recommendations are as follows:

2.4.3.1 Irinotecan, oxaliplatin and raltitrexed for advanced colorectal cancer (TA33)

Irinotecan and oxaliplatin, within their licensed indications, are recommended as treatment options for people with advanced colorectal cancer as follows:

- Irinotecan in combination with 5-fluorouracil and folinic acid as first-line therapy, or irinotecan alone in subsequent therapy
- Oxaliplatin in combination with 5-fluorouracil and folinic acid as first-line or subsequent therapy.

Raltitrexed is not recommended for the treatment of patients with advanced colorectal cancer. Its use for this patient group should be confined to appropriately designed clinical studies.

2.4.3.2 Capecitabine for metastatic colorectal cancer (TA61)

Oral therapy, with either **capecitabine**, is recommended as an option for the first-line treatment of metastatic colorectal cancer.

2.4.3.3 Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (TA118)

NICE guidance TA118 states that **Bevacizumab** in combination with 5-fluorouracil plus folinic acid, with or without irinotecan**, is not recommended** for the first-line treatment of metastatic colorectal cancer.

It also states that **Cetuximab** in combination with irinotecan **is not recommended** for the second-line or subsequent treatment of metastatic colorectal cancer after the failure of an irinotecan containing chemotherapy regimen.

However, these drugs are potentially available following an application to the Cancer Drug Fund on a named patient basis for the treatment of appropriate patients with metastatic colorectal cancer.

2.4.3.4 Cetuximab and panitumumab for previously untreated metastatic colorectal cancer (TA439)

Cetuximab is recommended, within its marketing authorisation, as an option for previously untreated epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer in adults in combination with:

- 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX) or
- 5-fluorouracil, folinic acid and irinotecan (FOLFIRI).

1.2 Panitumumab is recommended, within its marketing authorisation, as an option for previously untreated RAS wild-type metastatic colorectal cancer in adults in combination with:

- FOLFOX or
- FOLFIRI.

1.3 The drugs are recommended only when the companies provide them with the discounts agreed in their patient access schemes.

2.5 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.

2.6 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).

3.0 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 locally 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.

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

3.1 Primary treatment

3.1.1 Radical treatment

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

3.1.2 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

3.2 Systemic treatment for advanced disease

Consider clinical trial or other palliative regimens, options include:

- Cisplatin & 5-Fluorouracil without radiotherapy
- Carboplatin & 5-Fluorouracil without radiotherapy
- Capecitabine and Cisplatin
- Capecitabine and Carboplatin
- Paclitaxel (Days 1,8 &15 every 28 days)

N.B. Carboplatin should be used only if the patient is unsuitable for Cisplatin.

4.0 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

5.0 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/

6.0 Appendix B: Oxaliplatin Neuropathy Guidelines

Guidance on the assessment and management of oxaliplatin induced neuropathy

Introduction

- 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?	1. If yes, consultant review required. For consideration of DR at next cycle or omission of oxaliplatin.
		2. Has the tingling continued for longer than during the previous cycle and / or is tingling still present when next cycle is due?	2. If yes, consultant review required, for consideration of DR at next cycle or omission of oxaliplatin.
Serious caution	Numbness in hands or feet	Must be reviewed by a consultant	Consider DR or omission of oxaliplatin. Repeat consultant review before next cycle
	Severe excitability channel neuropathy during infusion (very rare), seen as severe pain and numbness on infusion	Must be reviewed by a consultant	Consider adding calcium and magnesium infusion. Consider DR or omission of oxaliplatin. Repeat consultant review before next cycle
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.
- Dose reductions should be at a 25% level and if there is no improvement or worsening, omit further doses, (i.e there should be no subsequent dose reductions for neuropathy). Improvement should be seen within one cycle (there should be only one cycle chance for neuropathy improve).

7.0 Glossary

Acronyms in common usage throughout KMCC documentation

CNB	Cancer Network Board
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
EK	East Kent
EKHUFT	East Kent Hospitals University Foundation Trust
HoP	High Level Operational Policy
IOSC	Improving Outcomes: A Strategy for Cancer
K&C	Kent & Canterbury Hospital, Canterbury, (EKHUFT)
KMCC	Kent & Medway Cancer Collaborative
KMCRN	Kent & Medway Cancer Research Network
LSESN	London & South East Sarcoma Network
MFT	Medway Foundation Trust
MTW	Maidstone & Tunbridge Wells NHS Trust
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
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
QVH	Queen Victoria Foundation Trust Hospital East Grinstead
UCLH	University College Hospital London
WHH	William Harvey Hospital, Ashford (EKHUFT)
WK	West Kent

8.0 Document Administration

Document Title	Oncological Treatment of Colorectal & Anal Cancer
Principle author	Colorectal NOG/ Caroline Waters
Co-author(s)	Colorectal NOG
Current version number	10
Current status	Final
Agreed as "Fit for Publication" by	
Original publication date	2018
Expected review date by	2019

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Revision History			
Date of revision	New Version Number	Nature of Revision	Confirmation of Accuracy by
June 2009	V0.3		C Waters
October	V0.4		C Waters/ J Hall
December 2009	V0.6		C Waters and colorectal NOG
April 2010	V0.7		C Waters and colorectal NOG
April 2010	V1	Published	
June 2010	V2	Additional information added to oxaliplatin neuropathy guidelines	Colorectal NOG
January 2011	V2.1	Changes to **Section 2.3** on post-operative radiotherapy for resected rectal cancer. **Section 2.4.1.1** on colon cancer with liver predominant metastases on presentation	Colorectal NOG
April 2011	V3	Published	Colorectal NOG
October 2011	V3.1-3.2	Changes to sections 2.2.1.1, 2.4 and 2.4.2	Colorectal NOG
October 2011 November 2011 December 2011	V4 V4.1 V5	Published Changes to sections Addition to section 2 of sentence regarding k-ras testing for all patients.	Colorectal NOG Colorectal NOG Colorectal NOG
June 12	v5.1	Addition of SEC CDF short form specified chemotherapy regimens that can be given with cetuximab or bevacizumab.(section 2.4.2.1) Removal of Cape/MMC with RT as an option for palliative treatment of anal cancer (section 3.1.2)	Colorectal NOG
July 2012	v6	Published	Colorectal NOG
March 2013	v6.1	draft	Colorectal NOG
April 2013	v7	Final	Colorectal NOG
May -June 2013	V7.1 -7.2	Draft - Aflibercept added and document	CRC NOG

		updated in line with NCDF list. UFToral removed and oxaliplatin neuropathy guidelines updated	
August 2013	v8	Published	CRC NOG / Julia Hall
November 2013- May 2014	v8.1- 8.2	Updated oxaliplatin neuropathy guidelines. Re-wording of section 2.4.2.1	
June 2014	V9	Published	
Dec 2016 onwards	V9.1 – 9.5	Updated in line with NICE TA 405 Re-wording of indication for Raltitrexed protocols. Revision of treatment options for Anal Cancer Review of NICE TA 176 Extensive review of all sections with updates.	CRC NOG
July 2018	V10	Final	CRC NOG