# Somerset, Wiltshire, Avon and Gloucestershire (SWAG) Cancer Services

# Colorectal Cancer Clinical Advisory Group

# Clinical Guidelines

# June 2019

**Revision due: April 2021**

## VERSION CONTROL

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| Draft 0.2 | 9th April 2015 | Pathology guideline update | N Wong |
| Draft 0.2 | 22nd June 2015 | Addition of Chemotherapy for Liver Mets Guidelines | M Williams |
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This document has been edited by:

Michael Thomas, Chair of the SWAG Colorectal CAG, Consultant Colorectal Surgeon, University Hospitals Bristol NHS Foundation Trust

Mike Williamson, previous Chair of the SWAG Colorectal CAG, Consultant Colorectal Surgeon, Royal United Hospital Bath NHS Foundation Trust

Newton Wong, Consultant Histopathologist, North Bristol NHS Trust

Helen Dunderdale, SWAG Cancer Network CAG Support Manager

These clinical guidelines have been agreed by:

| Name | Position | Trust | Date agreed |
|---|---|---|---|
| Nader Francis | Consultant Colorectal Surgeon | Yeovil District Hospital NHS Foundation Trust | June 2019 |
| Louise Hunt | Consultant Colorectal Surgeon | Taunton and Somerset NHS Foundation Trust | June 2019 |
| Edward Courtney | Consultant Colorectal Surgeon | Royal United Hospital Bath NHS Foundation Trust | June 2019 |
| Krishna Kandaswamy | Consultant Colorectal Surgeon | Weston Area Health NHS Trust | June 2019 |
| Ann Lyons | Consultant Colorectal Surgeon | North Bristol NHS Trust | June 2019 |
| Neil Borley | Consultant Colorectal Surgeon | Gloucestershire Hospitals NHS Foundation Trust | June 2019 |

# Colorectal CAG Clinical Guidelines Contents

# 1. Introduction

The following guidelines pertain to the local management of colorectal malignancies for the Somerset, Wiltshire, Avon and Gloucestershire (SWAG) Network Colorectal Oncology Clinical Advisory Group (CAG).

The CAG refers to the National Institute for Health and Care Excellence (NICE) Colorectal Cancer clinical guidelines (December 2014):

https://www.nice.org.uk/guidance

Primary care clinicians should refer to the NICE guidelines *Suspected Cancer: recognition and management of suspected cancer in children, young people and adults* (2015) for the signs and symptoms relevant when referring to colorectal oncology services. Further details on the two week wait referral process can be found in the CAG constitution.

The CAG is committed to offering all eligible patients entry into clinical trials where available. Consent to provide tissue for research purposes will also be sought wherever appropriate.

All patients with colorectal cancer are recommended to take long term low dose aspirin (75mg) if tolerated.

# 2. The CAG Agreed Clinical Guidelines for Colorectal Cancer (NS/SCS/CC-16-008)

### 2.1 Investigations for patients suspected of having colorectal cancer

Patients with high-risk symptoms are fast tracked to an urgent 'two-week' clinic appointment or straight to a diagnostic test where appropriate.

Investigations for patients suspected of having colorectal cancer will vary according to the symptomatic presentation. The investigations should be performed as expediently as possible to allow treatment within recognised target times.

**Change of Bowel Habit**

- Colonoscopy is the recommended investigation and allows biopsy to better confirm the diagnosis, remove polyps and to extend the diagnostic yield for non-cancer diseases
- CT colonography is an alternative investigation, especially when colonoscopy has already failed or in elderly and comorbid patients using the minimal prep versions
- If colorectal cancer is confirmed, a CT of the chest, abdomen and pelvis will be requested.

**Bleeding**

Flexible sigmoidoscopy to splenic flexure; full colonoscopy if appropriate If colorectal cancer is confirmed, a full colonoscopy or CT colonogram will be requested to exclude disease in unseen colon. If colorectal cancer is confirmed a CT of the chest, abdomen and pelvis will be requested.

**Iron-deficiency Anaemia**

- Colonoscopy and gastroscopy with D2 duodenal biopsy
- Minimal prep CT colonography is an alternative in elderly and comorbid patients
- If colorectal cancer is confirmed a CT of the chest, abdomen and pelvis will be requested.

**Abdominal Mass**

- Two-week wait outpatient for clinical examination/confirmation
- Abdominal & pelvic (consider chest) CT scan
- Colonoscopy if the mass is likely to be related to the colon or after confirmation on CT.

**Rectal Mass**

- Two-week wait outpatient for clinical examination/confirmation
- If suspected rectal cancer, a colonoscopy and biopsy or CT colonography (after biopsy in clinic) will be requested to exclude synchronous disease
- If suspected rectal cancer, a CT of the Chest/Abdomen/Pelvis will be requested
- If suspected rectal cancer, an MR Pelvis will be requested.

### 2.2 Imaging Guidelines

**Colonoscopy:** The endoscopist should biopsy / remove lesions as appropriate. Patients will be informed about the possibility of discomfort, risks of perforation and bleeding. Doctors performing colonoscopies must audit their results and aim to have high completion (>90% caecal intubation) and low perforation (0.1%) rates.

**CT colonography**: Allows diagnosis of colon lesions with similar specificity and sensitivity to colonoscopy but does not allow biopsy. It is particularly useful in cases where colonoscopy cannot be completed. It is a useful and safer alternative to colonoscopy in patients who cannot tolerate full bowel prep and is best performed using long oral prep.

**CT Chest, abdomen & pelvis:** All non-allergenic patients should receive oral and intra venous contrast. Examinations should be performed to the highest specificity of the local machine. Images will be taken of the liver in the portal venous phase of contrast enhancement.

**Barium Enema:** This is no longer regarded as a good alternative to colonoscopy or even CT colonography due to the relative lack of sensitivity and specificity compared to alternatives. It may be used when there is no alternative because of local issues with supply and demand in the interests of meeting targets.

**MRI Rectum:** Scanning protocols should comprise sagittal T2 3mm and axial T2 5mm slices of the whole pelvis with additional axial-oblique T2 high resolution slices perpendicular to the plane of the rectal tumour.

### 2.3 Histopathology guidelines

The CAG guidelines for the examination and reporting of colorectal cancer specimens refer to the following publications:

- Dataset for colorectal cancer histopathology reports (3rd edition). The Royal College of Pathologists, 2014. http://www.rcpath.org/Resources/RCPath/Migrated%20Resources/Documents/G/G049_ColorectalDataset_July14.pdf
- TNM classification of malignant tumours (7th edition). UICC, 2009
- WHO Classification of Tumours of the Digestive System. IARC Press, 2010
- Reporting lesions in the NHS bowel cancer screening programme. Guidelines from the Bowel Cancer Screening Programme Pathology Group. NHS Cancer Screening Programmes, 2007.

**Specimen Types**

Colon: Endoscopic biopsies, Polypectomy specimens, Colectomy specimens.

Rectum: Endoscopic biopsies, Polypectomy specimens, TEM specimens, Anterior Resection specimens, Abdomino-perineal Resection specimens.

**Colorectal Cancer Specimen Examination**

Refer to: Dataset for colorectal cancer histopathology reports (3rd edition). The Royal College of Pathologists, 2014.
http://www.rcpath.org/Resources/RCPath/Migrated%20Resources/Documents/G/G049_ColorectalDataset_July14.pdf

**Grading and Staging of Colorectal Cancers**

Refer to: Dataset for colorectal cancer histopathology reports (3rd edition). The Royal College of Pathologists, 2014.
http://www.rcpath.org/Resources/RCPath/Migrated%20Resources/Documents/G/G049_ColorectalDataset_July14.pdf

In particular, the Colorectal Lead Pathologists should ensure that completed staging data is reported for all 'cancer polyps', i.e. invasive adenocarcinoma arising within a locally resected adenoma/polyp. This data (which includes minimum clearance from resection margins, and Kikuchi and/or Haggitt levels) are outlined in the Royal College of Pathologists dataset for colorectal cancer histopathology reports (3rd edition), 2014.

**Clinical Governance**

Pathologists reporting colorectal cancer resection specimens will undertake the following tasks:

- Participate in relevant EQA schemes
- Have access to and be familiar with the abovementioned publications 1)-3) and, if participating in the Bowel Cancer Screening Programme, publication 4).

**Bowel Cancer Screening Programme (BCSP)**

Pathologists examine, dissect and report specimens derived from BCSP patients according to the 'Guidelines from the Bowel Cancer Screening Programme Pathology Group', NHS Cancer Screening Programmes 2007.

BCSP pathologists should participate in the National BCSP EQA scheme.

**Proforma for Reporting of Colorectal Cancer Resections**

Refer to the Proforma for Colorectal Cancer Resections as published by the Royal College of Pathologists.
http://www.rcpath.org/Resources/RCPath/Migrated%20Resources/Documents/G/G049_ColorectalDataset_July14.pdf

**Proforma for Reporting of Colorectal Local Excision Specimens**

Refer to the Proforma for Local Excision Specimens as published by the Royal College of Pathologists.
http://www.rcpath.org/Resources/RCPath/Migrated%20Resources/Documents/G/G049_ColorectalDataset_July14.pdf

**Standard operating protocol for reflex mismatch repair immunohistochemistry of colorectal carcinoma**

This standard operating protocol addresses the guidance issued in the 2014 Royal College of Pathologists dataset for colorectal carcinoma (CRC): "In summary, MMR immunohistochemistry is currently considered a core dataset item for patients under 50 years at the time of diagnosis and for patients, in whom an assessment of prognosis is appropriate, with adenocarcinomas classified as poorly differentiated morphologically or tumours showing other morphological features of MMR deficiency".

1. Reflex mismatch repair (MMR) immunohistochemistry should be performed on CRCs resected from patients less than 50 years of age at time of diagnosis. By contrast, MMR immunohistochemistry for assessment of prognosis should be an 'on-demand' process; it is anticipated that these requests will come from oncologists.

2. The reflex MMR testing should be organised by the Histopathology Department that has received and reported the CRC resection specimen.

3. When the histopathology of the CRC resection specimen is presented at the local Lower GI MDT meeting, the MDT should be informed that MMR immunohistochemistry data is awaited for the patient's CRC.

4. The local Lower GI MDT should take responsibility for chasing up this data.

5. Once the completed MMR data is presented to the local Lower GI MDT and if there is evidence of MMR deficiency, the MDT should refer the patient to its local Clinical Genetics service.

6. This reflex testing does not include microsatellite instability (MSI), BRAF mutation or MLH1 hypermethylation analyses.

7. This reflex testing does not replace pre-existing local MDT protocols for identifying potential Lynch syndrome patients for referral to Clinical Genetics.

MMR CRC SOP v1.0 (Newton Wong, 6 May 2015)

**2.4 Management of Rectal Cancer**

Defined as tumours below the sacral promontory/within 18 cms of anal verge

**2.4.1 Investigation and staging:**

- Assessment of patient's general health and operative risk: ASA and PPOSSUM score if available. Record ASA and WHO Performance Status for NBOCAP database
- Digital examination (consider EUA in difficult cases)
- Bloods (FBC, U&E, LFT), baseline CEA
- Colonoscopy or CT colonography to visualise the colon (or within 6 months of potentially curative surgery performed as an emergency)
- CT chest, abdomen & pelvis to exclude metastatic disease
- MR rectum to assess operability / at risk CRM
- MR liver if liver metastases to assess suitability for hepatic resection. All patients with liver metastases will be referred to a regional hepatobiliary MDT for their opinion about optimal management
- All patients with potentially resectable lung metastases on CT will be referred to the regional lung MDT for their opinion about optimal management
- Early rectal cancer assessed by high quality MRI and EUS as stage T1 should be considered for local resection. Patients considered suitable for Transanal Endoscopic Microsurgery (TEMs) should be referred to UH Bristol or Cheltenham. All surgeons undertaking TEMS are accredited to perform this procedure
- PET will be considered when there is a high clinical or biochemical suspicion of systemic, metastatic or local recurrence in the context of negative or equivocal CT where there are further treatment options

- All investigations and histopathology results are discussed at the local MDT before treatment.

### 2.4.2 Treatment Options

Patients with rectal cancer are managed by surgeons with appropriate training who have completed the national TME, MDT Development Programme or equivalent, LOREC, and have fully audited outcome measures, and are working within a multidisciplinary team.

Preoperative long course chemo-radiotherapy is indicated if clinical examination (fixed, tethered) and/or MR indicate that circumferential margins are potentially at risk i.e. R1 or R2 resections.

Preoperative short course radiotherapy should be considered if MR indicates that margins are likely to be clear but there is a higher than usual risk of loco-regional recurrence i.e. major lymph node involvement.

Careful consideration should be given to the relative merits of palliative resection for rectal cancer, as should treatment with endoluminal stenting and palliative radiotherapy.

When a stoma is required or considered a possibility, all patients should see an accredited stoma nurse, ideally prior to admission, to allow adequate time for preparation.

The first definitive treatment is normally the first intervention intended to remove or shrink the tumour. Where there is no anti-cancer treatment, palliative intervention/best supportive care will be recorded.

### 2.4.3 Surgery

**Preparation for Surgery – refer to Appendix 1**

**Upper third rectal cancer:** Anterior Resection

- Excision outside mesorectum with pelvic autonomic nerve preservation aiming for minimum of 5cms clearance below the lower edge of the cancer
- Cytocidal washout of rectal stump & peritoneal cavity is recommended
- Covering stoma only when necessary.

**Middle & lower third rectal cancer:** Low Anterior resection

- Total Mesorectal Excision (TME) with pelvic autonomic nerve preservation
- Cytocidal washout of rectal stump & peritoneal cavity is recommended
- Consider a colonic pouch
- Temporary covering stoma should be considered in most cases.

**Low rectal cancer:** Where distal clearance <1cm, sphincter involvement, poor anal tone

The consensus of the SWAG Colorectal CAG is to offer Transanal Total Mesorectal Excision (TATME) for low rectal cancer in the following circumstances:

- The procedure is undertaken by two surgeons who have undergone formal training
- An appropriate AirSeal device is utilised
- Mentorship is to continue for as long as the surgeon/s deem it to be necessary
- Details of each procedure will be uploaded on to the LOREC registry here, to facilitate audit.

Intersphincteric Abdomino-Perineal Excision (APERi):

For low but early rectal cancer where the anal sphincter cannot be preserved (consider entering patients into a trial of local excision). For rectal cancer in patients with poor anal tone as an alternative to TME Hartmann's (see below).

Standard abdomino-perineal Excision (APERs):

For low rectal cancer within or just beyond the rectal wall in whom intersphincteric dissection would risk an involved margin.

Extra-Levator Abdominal Perineal Excision (ELAPE):

For locally advanced low rectal cancers (within 6cm from the anal verge) there is a national drive to promote extra-levator technique of abdominal perineal excision (ELAPE). This process has gained popularity because of the associated low intra-operative tumour perforation rates and subsequent local recurrence. It involves excision of the anus outside the levator plate to ensure enough clear tissue around the tumour.

TME Hartmann's:

Frail, elderly or incontinent patients with rectal cancer technically suitable for restorative surgery in whom there is a desire to avoid restoration of bowel continuity. An alternative to APERi.

**Metastatic / Disseminated Disease:**

- Unexpected/suspicious metastases within the abdomen should be biopsied. Biopsy/FNA liver lesions within the liver substance should not be undertaken without prior discussion with regional hepatobiliary surgeons.

**Early rectal cancer - local excision – see 2.5 below**

- Following pre-operative T1 stage assessment by EUS & MR
- Performed by an adequately trained surgeon after discussion at MDT.

### 2.4.4 Neo-adjuvant chemotherapy and radiotherapy

Discussion about the use of neo-adjuvant chemo/radiotherapy takes place at the MDT meeting.
**Preoperative**

Long course chemo-radiotherapy will be considered when:

- MR predictive of positive circumferential margin (R2) or threatened <1mm margin (R1)
- Schedule: 45-50 Gy in 25-28 fractions in 5 weeks given to a planned volume using a 3 - 4 field technique covering the tumour and an adequate margin
- Chemotherapy (5 Fluorouracil and folinic acid) is given daily in the first and fifth weeks of treatment
- Patients are reassessed after 2 - 4 weeks with further imaging ± PR or EUA.

Short-course radiotherapy will be considered when:

- MRI predictive of R0 resection but advanced T3 tumour / major lymph node involvement
- Schedule: 25 Gy in 5 fractions in 1 week. Surgery is scheduled within 7 days of completion.

**Post-Operative Multidisciplinary Team (MDT) Meeting**

Surgical treatment must be judged as curative or palliative.
Consider the place of post-operative radiotherapy or chemotherapy:

**Postoperative Radiotherapy**

MDT to consider long-course chemo-radiotherapy when:

- Circumferential margin is +ve (R2) or threatened <1mm (R1)
- The schedule is a 5 week course of 45-50 Gy and 25 fractions using a 3-4 field technique covering the posterior pelvis
- Chemotherapy (5 Fluorouracil and folinic acid) is given daily in the first and fifth weeks of treatment
- Patients with co-morbidity may receive radiotherapy as above or as a short course, both without chemotherapy.

**Postoperative adjuvant chemotherapy**

- Adjuvant chemotherapy usually recommended for all T4 NX tumours and TX N1-2, also for high risk T3 N0 tumours as judged by extramural vascular invasion. Patients should be counselled on the relative risks and benefits of treatment and understand that a "no chemotherapy" approach is an option
- Patients with favourable T3 tumours less than 80 years of age may be offered a discussion with the oncologist to discuss the potential but small benefits of therapy
- Chemotherapy may not be appropriate for patients with significant co-morbidity (WHO performance status), high frailty index or extremes of age when unacceptable toxicity a high

probability, or their likelihood of death from those diseases affects any reduction in the risk of cancer recurrence or death.

**Palliative chemotherapy**

Patients who have un-resectable disease or undergo palliative surgery should be considered for palliative chemotherapy and offered the opportunity to meet with an oncologist. Patients unfit for chemotherapy should receive best supportive care

### 2.5 Management of Early Rectal Cancer

#### 2.5.1 Investigation and Staging

Preoperative staging includes:

- Digital rectal examination
- Endoscopic evaluation with biopsy
- CT chest / abdomen / pelvis
- MR rectum
- Endoscopic ultrasound is highly recommended.

Accurate staging will determine which patients may be candidates for local excision.
In 'fit' patients local excision by TART or preferably TEMS (or equivalent technique) may be considered for early rectal cancers with good prognostic features:

- T1 (sm1) cancer on TRUS
- Small (<4 cm) tumours
- Good histological prognostic features (well to moderately differentiated adenocarcinoma)
- Mobile

In patients unfit for major resection local excision of more advanced early rectal cancers, with or without radiotherapy, may be considered to try and achieve local control.

### 2.5.2 Post-operative MDT

Discovery of poor prognostic features on histopathology, including deeper or margin involvement, poor differentiation, and or vascular or perineural invasion, should lead to a discussion about the merits of a formal resection or post-operative chemo-radiotherapy.

Most early rectal cancers are diagnosed when a local excision is performed for a benign lesion and incidental cancer is found. If TEMS / TART or EMR has achieved a clear margin with good prognostic histological features, no further intervention will be necessary.

Mr Mike Thomas (UH Bristol) and Mr Neil Borley (Cheltenham) provide the Network TEMS service.

## 2.6 Management of Colon Cancer

### 2.6.1 Diagnosis

Diagnosis usually occurs after a colonoscopy and a biopsy. Histological confirmation of radiologically diagnosed cancer is desirable but not essential; however, every effort should be made when radiology is equivocal and especially for right-sided cancers.

### 2.6.2 Investigation and Staging

- Patient's general health and operative risk (ASA, WHO PS & PPOSSUM)
- Bloods (FBC, U&E, LFT) Baseline CEA
- Colonoscopy or CT colonography to visualise the non-visualised colon prior to surgery (or within 6 months of potentially curative surgery performed as an emergency)
- CT scan chest, abdomen & pelvis to exclude metastatic disease
- MRI liver if liver metastases to assess suitability for hepatic resection. All patients with liver metastases will be referred to the regional hepatobiliary MDT for their opinion about optimal management
- All patients with potentially resectable lung metastases will be referred to the regional lung MDT for their opinion about optimal management
- PET will be considered when there is a high clinical or biochemical suspicion of systemic, metastatic or local recurrence in the context of negative or equivocal CT where there are further treatment options
- All investigations and histopathology results are discussed at the local MDT before treatment.

### 2.6.3 Surgery

**Preparation for surgery – refer to Appendix 1**

**Colonic resection**

- Laparoscopy is offered to every suitable patient in the CAG in accordance with NICE Guidelines
- For most fit patients, excision will be by segmental resection to include high ligation of feeding arterial supply with associated lymph nodes
- Biopsy any suspicious lesions within the abdomen
- Do not biopsy / FNA liver lesions within liver substance unless discussed with the regional hepatobiliary MDT
- De-functioning stomas may be required (consider if cancer not resectable or bypass not possible).

**Colonic Stenting (SEMS)**

- Consider this option to ameliorate obstructive symptoms where disseminated disease is present or the patient is too unfit for surgical resection
- SEMS as a bridge-to-surgery in patients with acute bowel obstruction by probable cancer should be discussed with the patient as an alternative to Hartmann's procedure and you are encouraged to enter patients in an accredited randomised trial.

### 2.6.4 Post-Operative Multidisciplinary Team (MDT) Meeting

Surgical treatment must be judged as curative or palliative.

Consider the place of post-operative chemotherapy:

#### 2.6.4.1 Postoperative adjuvant chemotherapy

- Adjuvant chemotherapy usually recommended for all T4 NX tumours and TX N1-2, also high risk T3 N0 tumours as judged by extra-mural vascular invasion. Patients should be counselled on the relative risks and benefits of treatment and understand that a "no chemotherapy" approach is an option
- Patients with favourable T3 tumours less than 80 years of age may be offered a discussion with the oncologist to discuss the potential but small benefits of therapy
- Chemotherapy may not be appropriate for patients with significant co-morbidity (WHO performance status), high frailty index or extremes of age when unacceptable toxicity is a high probability, or their likelihood of death from those diseases affects any reduction in the risk of cancer recurrence or death.

#### 2.6.4.2 Palliative chemotherapy

Patients who have un-resectable disease or undergo palliative surgery should be considered for palliative chemotherapy and offered the opportunity to meet with an oncologist. Patients unfit for chemotherapy should receive best supportive care.

## 3. The CAG agreed Clinical Guidelines for Anal Cancer

This service is centralised at University Hospitals Bristol NHS Foundation Trust and Gloucestershire Royal Hospitals NHS Foundation Trust.

### 3.1 Diagnosis

- Achieved by biopsy - histological confirmation is essential
- Consider examination under anaesthesia in difficult cases
- FNAC any palpable or radiologically enlarged inguinal lymph nodes.

### 3.2 Investigation and Staging

- Patient's general health (WHO performance status)
- CT scan chest, abdomen & pelvis
- Consider the role of pelvic MRI to aid staging
- Serology screening for the human papillomavirus.

### 3.3 Multidisciplinary Team meeting (MDT) Meeting, UH Bristol

Radiotherapists and surgeons who are part of the specialist MDT at UH Bristol and GLOS treat anal cancer. The SWAG CAG recognises that the principle management of anal squamous cell carcinoma (SCC) is chemo-radiotherapy rather than resectional surgery.

Individual Trust based MDTs should confirm the histological diagnosis and stage of the disease, and then refer on to the Network Anal Cancer MDT (Consultant Clinical Oncologist and /or his Deputy) for discussion about the various options (radical chemo-radiotherapy or palliative radiotherapy) in light of the local extent of the tumour, the patient's co-morbidities and wishes.

Patients requiring pre-treatment stomas are to be referred back to the referring surgeon and CNS.

### 3.4 Treatment Options

- Histologically confirmed complete excision of an early lesion may be the sole treatment
- Radical chemo-radiotherapy will be the standard treatment
- Consider palliative radiotherapy for advanced disease / comorbid patients
- Consider palliative defunctioning stoma for advanced disease / comorbid patients
- Eligibility of entry into the national portfolio of clinical trials
- Salvage surgery: consider other specialities e.g. plastic surgery, urology and gynaecology

- Where palliative treatment is performed or best supportive care advised consider further supportive therapies and follow-up by the Palliative Care Team
- MDT decision and follow-up plan to be documented in patient's notes & conveyed to the patient/carers, referring surgical team/CNS, and the patient's GP.

**4. Management of Liver Metastases**

Colorectal MDTs should refer patients with liver metastases, selected according to the network guidelines, to the liver resection MDT.

All patients with potentially curable liver metastases from colorectal cancer will be considered for liver resection, and referred for discussion to the regional hepatobiliary MDT at UHB (Basingstoke from RUH Bath, Birmingham from Cheltenham/Gloucester)

Unsuitable cases for referral include patients with uncontrollable extra-hepatic disease defined as:

- Non-treatable primary tumour
- Wide-spread pulmonary disease
- Loco-regional recurrence
- Peritoneal disease
- Retroperitoneal, mediastinal or portal nodes
- Bone or CNS metastases.

Or, the patient is unwilling to have further treatment or is unfit for further treatment. Whilst patients with more than 5 multifocal metastases are less likely to benefit from surgery, each case will be looked at individually.

All patients with liver metastases with a performance status appropriate for chemotherapy +/- surgery will be referred to the regional hepatobiliary MDT. Patients with unresectable liver disease should be considered for chemotherapy +/- cetuximab as per the NICE Guidelines. The decision to undertake RAS testing will usually be made at the local MDT.

**4.1 Staging investigations at presentation of primary cancer**

All patients will have undergone a staging CT scan of the chest, abdomen and pelvis with intravenous contrast (ideally at a maximum collimation of 5mm), the whole colon visualised (barium enema or colonoscopy) and a baseline CEA measurement performed. Increasingly, PET scanning is requested and can be requested by the HPB MDT or the local MDT if the indication is obvious.

**4.2 Synchronous liver metastases**

Colorectal cancer and liver resection are not normally performed synchronously. Patients found to have synchronous liver metastases at the time of their initial presentation should undergo a contrast enhanced liver MRI scan and be referred to/discussed at the designated Network HPB MDT (Bristol Royal Infirmary / Basingstoke / Birmingham).

Patients with potentially resectable disease, who have undergone radical resection of their primary bowel cancer, should be considered for 3 months of adjuvant chemotherapy (FOLFOX 4) prior to any liver resection. These patients will be restaged at 3 months by MRI. A further 3 months of chemotherapy will be considered post any potentially curative liver resection.

### 4.3 Metachronous liver metastases

Follow-up after resection of the primary colorectal cancer will be according to local protocol. The CAG recommends that a CT scan of the chest, abdomen and pelvis are performed as a minimum in the 2 years following completion of treatment of the primary tumour. Patients found to have liver metastases during follow up will have a treatment plan discussed at the Network HPB MDT.

If there is no extrahepatic disease on axial CT scanning, all patients will have a contrast enhanced MRI scan. Biopsy of liver lesions would not be performed without prior discussion at the Network HPB MDT. Patients should be considered for 3 months of neoadjuvant chemotherapy before any liver resection.

### 4.4 Chemotherapy

All patients with liver only metastases with a performance status appropriate for surgery +/- chemotherapy will be referred to the regional hepatobiliary MDT.

In all cases of metastatic colorectal cancer, molecular analyses to determine the presence of mutations in KRAS and NRAS (collectively known as RAS) should be performed as soon as the diagnosis is made and treatment is being considered.

RAS Mutation – Anti-EGFR targeted therapy should not be incorporated into the treatment algorithm of patients with RAS mutations

RAS Wild type – Anti-EGFR targeted therapy can be incorporated into the treatment algorithm of patients with wild-type RAS

The decision to undertake RAS testing will usually be taken at the CRC MDT.

Patients with potentially resectable liver metastases without unresectable extrahepatic disease should be considered for neoadjuvant chemotherapy (+/- cetuximab as per the NICE Technology Appraisal 176 Guidelines). See management

Algorithmhttp://www.eastmidlandscancernetwork.nhs.uk/Library/NeoadjuvantColorectal.pdf

Patients with unresectable liver metastases +/- extrahepatic disease should be considered for palliative chemotherapy. RAS mutation testing is requested via the CDF for these patients by an oncologist. The following metastatic colorectal cancer patient treatment algorithms are routinely funded by NHS England via the cancer drug fund (12 March 2015 V4.0 )

Algorithm http://www.eastmidlandscancernetwork.nhs.uk/Library/mCRC.pdf

**RAS Testing Guidelines for mCRC**

**RAS Testing Overview**

- In order to guide molecularly targeted therapy, and in line with the product licenses of currently approved treatments, NICE TAG 176 and CDF treatment access criteria, RAS testing requests should be made at the earliest opportunity to inform the 1st line treatment clinical decision making process.

- RAS test requests will typically be initiated by oncologists at the CRC MDT.

- Systematic and robust testing pathways should ensure that every patient who qualifies for a test is offered one in a timely manner, with results being accessible by the treating oncologist at the time of the patient's first line treatment consultation

- Clear and unambiguous local responsibilities for RAS test requests, tissue sample handing, molecular analysis and reporting of the results should exist within each local Trust to ensure that necessary tests are requested timely and avoid unnecessary delays to patient access to treatment.

- Where RAS testing is performed on demand, rapid turnaround times (from test request to result) are critical to avoid treatment delays. Molecular genetics laboratory turnaround times for RAS testing should be ≤7 working days from receipt of the specimen in the testing laboratory to issuing of the final report, for >90% of specimens

- Pathology laboratories should ensure that their RAS diagnostic testing covers all relevant genes that appear in the Summary of Product Characteristics published of the available treatment options.

- For RAS testing of CRC patients, these should include analysis of at least KRAS codons 12, 13, 59, 61, 117 and 146 and NRAS codons 12, 13, 59 and 61.

- When integrated into pathology reports, RAS test results should accurately convey the information the clinician needs to treat the patient on whom the test was performed, with sufficient information to allow correct interpretation of the results.

RAS tests are funded by NHS England.

**4.5 Ablative therapy**

Patients not suitable for liver resection (e.g. extensive co-morbidity, patient choice, irresectable disease) may be offered ablative treatment (radiofrequency ablation). This would be discussed at the HPB MDT.

### 4.6 Follow up after liver resection

Follow up will be agreed in collaboration with the HPB MDT according to HPB and Colorectal MDT guidelines, in order to direct follow up for both liver and colorectal disease. CEA levels should be monitored at least 6 monthly.

Six monthly reviews should be considered for 3 years and then on an annual basis thereafter. Follow up will be shared between either the HPB team and the oncology team or base colorectal team. In patients who develop a local liver recurrence it may be appropriate to consider referral for re-resection and/or ablation as well as chemotherapy.

Patients will remain under the care of the local colorectal team for surveillance colonoscopy according to local protocol.

## 5. Management of Advanced Colorectal Cancer

### 5.1 Presentation

- Inoperable primary disease
- Inoperable metastatic disease
- Loco-regional recurrence.

### 5.2 Treatment

For patients with inoperable rectal cancer, (fixed or tethered on clinical examination and/or MRI indicates that margins are potentially at risk i.e. R1 or R2 resections) without evidence of metastatic spread, preoperative long course chemo-radiotherapy should be offered to downstage the cancer in the hope of making it resectable for potential cure.

Although there is less good evidence, for patients with apparently inoperable colonic cancer on CT scanning, without evidence of metastatic spread, preoperative chemotherapy may be offered to downstage the cancer in the hope of making it resectable for cure or could become palliative.

### 5.3 Metastatic Disease

- Colorectal MDTs should refer patients with liver metastases, selected according to the network guidelines, to the liver resection MDT (see above)
- Colorectal MDTs should refer patients with lung metastases, selected according to the network guidelines, to the appropriate chest MDT.

Lung resection to be considered in patients where:

- Primary disease has been radically removed
- Resectable colorectal metastases confined to the lung and/or liver.

### 5.4 Chemotherapy

Patients with incurable disease, and who are fit enough, should be offered the opportunity to discuss the benefits and disadvantages of chemotherapy with palliative intent.

### 5.5 Radiotherapy

Radiotherapy can be an effective form of treatment for palliation of rectal bleeding, tenesmus and rectal pain. It should be considered for patients with inoperable advanced disease and recurrent disease (not suitable for resection).

### 5.6 Palliative Care

Palliative care is an integral component of the management of incurable cancer and should be practised by all the members of the MDT. The key components are:

- A focus on quality of life, which includes good symptom control
- A whole person approach, taking into account past experiences and current situation
- Respect for patient autonomy and choice
- Open and sensitive communication between patients, carers and professional colleagues.

### 5.7 Referral for Specialist Palliative Assessment

The patient should meet one or both of the following criteria:

- Incurable disease with the focus being on quality of life
- The patient has one or more of the following needs, which cannot be met by the referring team:
    - Uncontrolled / complicated symptoms
    - Complex psychological / emotional issues
    - Complex social / family issues
    - Difficult decision making about appropriate future carers.

## 6. Follow up Guidelines

### Colon Cancer & Rectal Cancer

It is expected that most Trusts in the SWAG Network will adhere to the NICE guidelines on follow-up after resection of colon and rectal cancer. There is a national move towards 'remote' surveillance programmes minimising the need for patient attendance at clinic. Consideration may be given to specialist nurse lead clinics and telephone follow-up.

### 6.1 NICE Guidance: Follow-up after apparently curative resection

Offer follow-up to all patients with primary colorectal cancer undergoing treatment with curative intent. Start follow-up at a clinic visit 4–6 weeks after potentially curative treatment.

Offer patients regular surveillance with:

- a minimum of two CTs of the chest, abdomen, and pelvis in the first 3 years **and**
- regular serum carcinoembryonic antigen tests (at least every 6 months in the first 3 years).

Offer a surveillance colonoscopy at 1 year after initial treatment. If this investigation is normal consider further colonoscopic follow-up after 5 years, and thereafter as determined by cancer networks. The timing of surveillance for patients with subsequent adenomas should be determined by the risk status of the adenoma.

Start reinvestigation if there is any clinical, radiological or biochemical suspicion of recurrent disease.

Stop regular follow-up:

- when the patient and the healthcare professional have discussed and agreed that the likely benefits no longer outweigh the risks of further tests **or**
- when the patient cannot tolerate further treatments.

### 6.2 Follow up of Patients with Anal Cancer

Follow-up of patients with anal cancer is the responsibility of the anal cancer MDT at UH Bristol. The majority of these patients will be under the follow-up of the Lead Clinical Oncologist. Patients with disease relapse will be discussed at the UH Bristol Colorectal Cancer MDT (de facto Anal Cancer MDT) for the consideration of salvage surgery. The CAG salvage surgery service is run by Mr M Thomas and his colleagues in UH Bristol.

**6.3 Risk Assessment and Clinical Surveillance in patients with a Family History of colorectal cancer**

Referral for screening colonoscopy and / or specialist genetic counselling will be considered for the following patients:

- CRC in single first degree relative (FDR) <50 years or 2 FDR of any age.
  Risk 1 in 12. Once-only colonoscopy at age 55

- CRC in 2 FDR mean age <60 years or 3 FDR with **first degree kinship***
  Risk between 1 in 6 and 1 in 10 – suggest referral to geneticist
  Colonoscopy age 50 then 5 yearly colonoscopy to age 75

- Less strong family history of CRC. Risk >1 in 12. No colonoscopy offered
  (UK background population risk for colorectal cancer is 1 in 18)

**N.B. first degree kinship*** - affected relatives who are first-degree relatives of each other AND at least one is a first degree relative of the patient

- Colorectal cancer associated with other characteristic tumours in same individual/ family (ovary, urothelium, small bowel, biliary tree)

- Surveillance and genetic testing should be offered to all Familial Adenomatous Polyposis (FAP) families and Hereditary Non-polyposis Colorectal Cancer (HNPCC) / Lynch families that either meet the Amsterdam or Amsterdam II criteria (3 affected relatives inn 2 successive generations of which one is under the age of 50) or have confirmed mismatch repair gene mutations.

# 7. Appendices

### 7.1 Appendix 1

**Preparation for Surgical Procedures**

- Informed consent, detailing the benefits and risks of the procedure versus alternatives including no surgery, will be obtained by the operating surgeon or delegated trainee with sufficient knowledge and training
- Appropriate treatment options will be discussed fully with all patients including laparoscopic intervention
- Consider iron infusion to restore iron deficiency anaemia prior to elective surgery
- Bowel preparation according to the local surgeon's preference / mechanical bowel preparation provided there is no incipient obstruction
- Anti-thrombotic & antibiotic prophylaxis according to local policy
- Group and save will be sufficient for most colorectal cancer resections dependent upon local transfusion facilities. Consider cross-match for pelvic resections and pre-operative transfusion if haemoglobin level (Hb) < 8 or if the patient is symptomatic)
- Counselling, guidance and support
- Stoma marking if applicable
- HDU / ITU facilities if required.

### 7.2 Appendix 2

**Pulmonary Metastasectomy in Colorectal Cancer - Guidelines for referral and eligibility for the PulMiCC trial (currently being updated)**

**Authors:**
Tim Batchelor, Consultant Thoracic Surgeon (UH Bristol)
Katrina Hurley, Research Nurse (UH Bristol)

**Introduction**

There is an absence of good quality evidence to support the role of pulmonary metastasectomy in colorectal cancer. Subsequently, there is great variation in clinicians' practices regarding selection of patients suitable for the procedure. From the multiple case series in the literature we know that multiple pulmonary metastases, a raised CEA and a short disease-free interval are poor prognostic factors. Conversely, almost all patients with a solitary pulmonary nodule, a normal CEA and a long disease-free interval would be considered for surgery.

A randomised trial of pulmonary metastasectomy in colorectal cancer (PulMiCC) has opened in the UK, initially as a feasibility study. Bristol is the sixth centre to start recruiting. The null hypothesis is that pulmonary metastasectomy does not alter the natural history of the disease.

The PulMiCC study has allowed us to formulate selection criteria for pulmonary metastasectomy whether a patient wishes to be enrolled in the study or whether they would prefer to proceed with surgery (or indeed no surgery) off trial. Consequently, those patients with one nodule should be referred for surgery while those with 5 or more nodules are not eligible for surgical management. Those patients with 2-4 nodules (the so-called "group of uncertainty") should be considered for the PulMiCC trial. If a patient does not wish to be randomised they should be referred for surgery.

**The solitary pulmonary nodule**

Patients on routine follow up following resection of primary colorectal cancer may have a solitary pulmonary nodule discovered on routine surveillance CT scans or as a result of some specific trigger such as symptoms or a raised CEA. The possibility that this is a primary lung cancer must be considered by the lung multidisciplinary team (MDT). The patient should then be referred for surgical resection.

**Eligibility for surgery:**

- Patients with primary colorectal cancer who have undergone resection of the primary cancer with intent to cure
- Local control has been confirmed and no clinical indications of other active colorectal cancer other than the known pulmonary nodule **(PET-CT required)**
- Pulmonary function adequate to sustain good performance after the largest likely loss of parenchyma **(spirometry required)**
- ECOG performance status 0-1
- Any recommended systemic or other non- surgical treatment has been completed.

**5 or more pulmonary metastases**

Those patients who are discovered to have 5 or more pulmonary metastases will not be considered for pulmonary metastasectomy. Furthermore, they will not be considered eligible for the PulMiCC trial. They should be treated as per local practice guidelines.
Referral to thoracic surgery for a lung biopsy should be considered if the diagnosis is in doubt and a diagnosis cannot be achieved by less invasive procedures.

**The "group of uncertainty": 2 to 4 pulmonary metastases**

Patients on routine follow up following resection of primary colorectal cancer may have pulmonary metastases discovered on routine surveillance CT scans, or as a result of some specific trigger such as symptoms or a raised CEA. The results should be discussed in the colorectal MDT meeting where radiological evidence of pulmonary metastases will be first presented by the radiologist. **If there is agreement within the colorectal MDT that the multiple pulmonary nodules most likely represent metastatic colorectal cancer then the patient's case does not need to be discussed at a lung MDT meeting.**

Patients fulfilling the following criteria will be eligible for registration for evaluation for the PulMiCC trial. Even if a patient does not want to be considered for the trial they should be encouraged to register.

**Inclusion criteria for surgery or registration for PulMiCC:**

- Patients with primary colorectal cancer who have undergone resection of the primary cancer with intent to cure
- Local control has been confirmed
- No clinical indications of other active colorectal cancer other than the known lung metastases (PET-CT required)
- Pulmonary function adequate to sustain good performance after the largest likely loss of parenchyma (spirometry required)
- ECOG performance status 0-1.

**Exclusion criteria:**

- Previous malignancy likely to interfere with protocol treatment or measurement of endpoints
- Any concurrent illness which could interfere with the treatment protocol or confound survival
- Unavailable for follow up and assessment according to protocol
- Psychiatric or mental incapacity that precludes fully informed consent.

**Exceptions**
Surgery will not normally be considered for 5 or more pulmonary metastases. However, rare cases where the nodules are unilateral and preferably within one lobe will be considered after specific discussion with the thoracic surgeons

**The PulMiCC trial**

Informed consent for registration

The clinical team member at the base hospital designated to inform potentially eligible patients of the MDT findings will explain the situation, indicating explicitly the uncertainty surrounding the management of pulmonary metastases. The trial will be introduced and interested patients will be given a patient information leaflet and DVD to take home.

Arrangements will be made for a follow up discussion in the thoracic surgical clinic in Bristol when patients who express an interest in the study will be invited to discuss the trial further and ask questions. Patients who confirm that they are willing to join stage 1 of the trial will be asked to sign a registration for evaluation consent form.
Patients who do not wish to be considered for registration will be offered surgery off trial.

Evaluation following registration

Patients should be evaluated according to local practice but investigations should also include the following:

- ECOG performance status assessment
- PET-CT (half body)
- Histology/cytology to confirm the nature of the nodules if there is clinical uncertainty concerning their nature (this is not mandatory)
- Full blood count, serum biochemistry and liver function tests
- CEA measurement
- Lung spirometry
- Further lung function tests if there is uncertainty about fitness for surgery according to BTS guidelines
- Weight.

Evaluation for randomisation

Following completion of investigations all patients should be evaluated according to local practice guidelines.

Some teams may offer systemic treatment. This can be given and the patients re-evaluated according to the template below following treatment.

If the best course of action with respect to surgery of the lung metastases seems clear (i.e. no surgery if 5 or more metastases or unfit for lung surgery; or surgery if only one nodule) at this point, these patients will not take any further part in the trial. However, the status of these patients at one year after registration will be recorded by the centre using information from the MDT.

Patients for whom uncertainty exists whether surgery would improve survival and/or quality of life are eligible for the second stage of the trial. Patients fulfilling the following criteria will be eligible for randomisation.

Inclusion criteria for randomisation:

- One or more nodules histologically/cytologically confirmed as metastases from colorectal cancer OR >90% likelihood of being metastases from colorectal cancer
- Pulmonary function adequate to sustain good performance after the largest likely loss of parenchyma (calculated as the predicted postoperative FEV1 according to BTS guidelines)
- ECOG performance status 0-1
- Any recommended systemic or other non-surgical treatment has been completed
- Available for trial assessments and follow up
- Consent form has been signed.

Exclusion criteria:

- Patients with a nodule which is proven or is likely to be lung cancer
- Concurrent disease that may interfere with protocol treatment or measurement of endpoints.

Informed consent for randomisation and ‘accept or decline’ questionnaire

Following evaluation and any systemic non-surgical treatment, eligible patients will be approached by the thoracic surgeon or other designated member of the clinical team and asked if they are willing to consider the second stage of the trial. They will be offered another copy of the patient information leaflet and the chance to ask questions.

All patients eligible for Stage 2 of the trial, whether or not they choose to proceed to randomisation, will be invited to complete a questionnaire exploring reasons for accepting or declining trials.

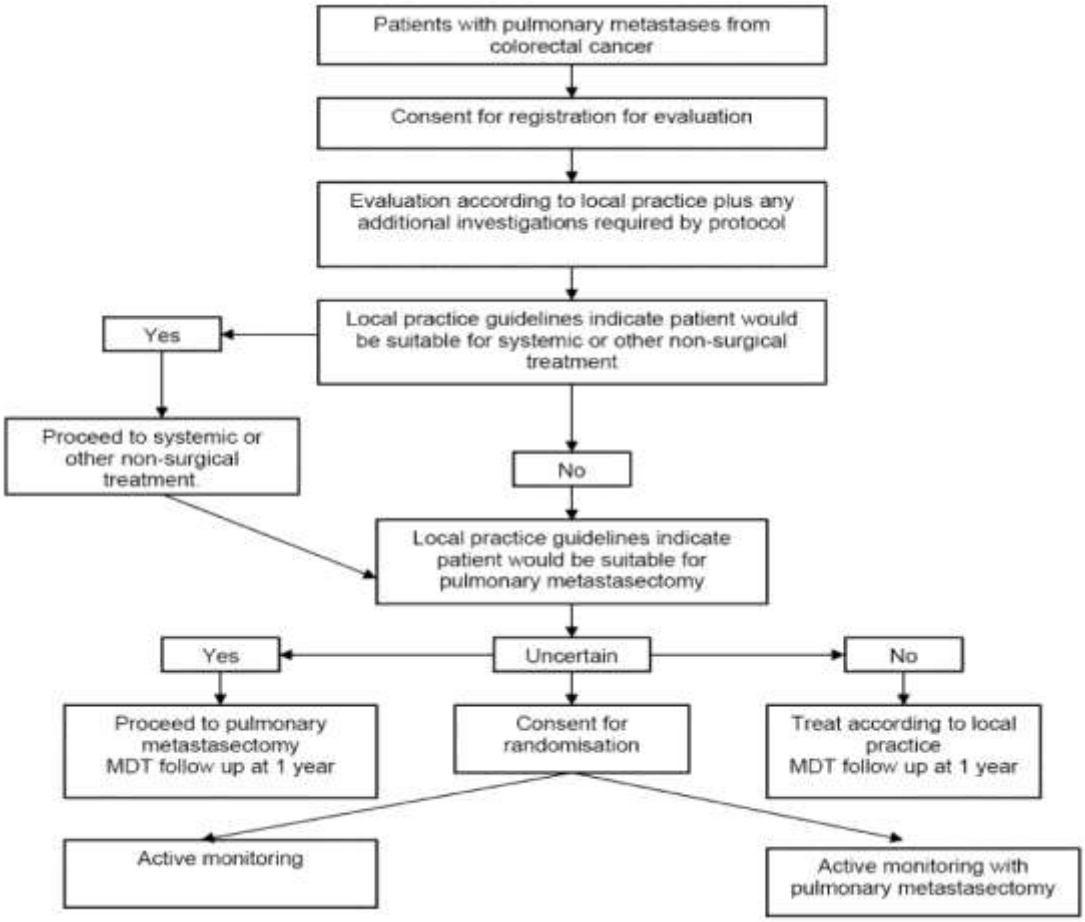
Patients who confirm that they are willing to be randomised will be asked to sign a second consent form and complete a set of baseline questionnaires.

**Contacts**

Karen Bobruk (Research nurse, UH Bristol)
Tel: 0117 342 4532 Fax: 0117 342 4834
Department of Thoracic Surgery (UH Bristol)
Tel: 0117 342 3132 Fax: 0117 342 3522

## 7.3 Appendix 3
## PulMiCC trial design

This is a two-stage randomised feasibility study. Patients will be registered first for evaluation and if subsequently eligible, randomised to active monitoring versus active monitoring with pulmonary metastasectomy.



Assessments will be carried out from the date of randomisation. All patients will be seen 3 monthly during Year 1, 6 monthly during Year 2 and then annually up to five years. Investigations will be according to routine practice, but lung function and CEA measurements will be performed at each visit. A CT scan will be performed at 3 months, 1 year, 2 years and 3 years. Patients will be assessed for quality of life and anxiety at baseline and at 3, 6, 12 and 24 months.

## 7.4: Appendix 4

## SWAG Management and Surveillance Guidelines for people with a Lynch syndrome mutation

- All people with a Lynch syndrome mutation are referred to a clinical geneticist for genetic counselling and provision of information to families about the condition
- All people identified as being at high risk of Lynch syndrome on MMR IHC and/or MSI testing (as described in NICE Diagnostic Guidance 27 for example) are referred to a clinical genetics service for further assessment
- All people with a Lynch syndrome mutation are recommended to take long term low dose aspirin (75mg) if tolerated.

| Site of Cancer: | Examination | Age range | Interval (years) |
|---|---|---|---|
| **Colorectum** | • All people with a Lynch syndrome mutation are to be offered total colonic surveillance<br>• Colonoscopy in MMR mutation carriers | • 25 years or 2-5 years before the youngest age of diagnosis of CRC in the family if diagnosed before age 25 years. Considerations: start at age 30 years in MSH6 and 35 in PMS2 families | • 1-2<br>• 1 |
| **Uterus** | • All women diagnosed with a Lynch syndrome mutation should be referred to the | • 30-35 years | • 1-2 |

| | | | |
|---|---|---|---|
| | gynaecology service for discussion of potential risks<br>• Gynaecological screening should be confined to ruling out endometrial cancer, with an annual pelvic examination, transvaginal ultrasound and aspiration biopsy | | |
| **Stomach** | • Upper gastrointestinal endoscopy is only recommended in Lynch syndrome families from countries with high incidence of gastric cancer, preferably in a research setting; all people with a Lynch syndrome mutation are to be screened for H pylori infection | • 25 years | • 1-2 |
| **Urinary tract** | • Surveillance (by urine cytology and ultrasound) of MSH2 carriers should only be performed in a research setting or if results are systematically collected in a Lynch syndrome registry | • 30-35 | • 1 |

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