

The Management of Oesophago-Gastric Cancer

Pathway of Care

Publication date	April 2020
Expected review date	April 2022
Version number	7.0
Version status	FINAL

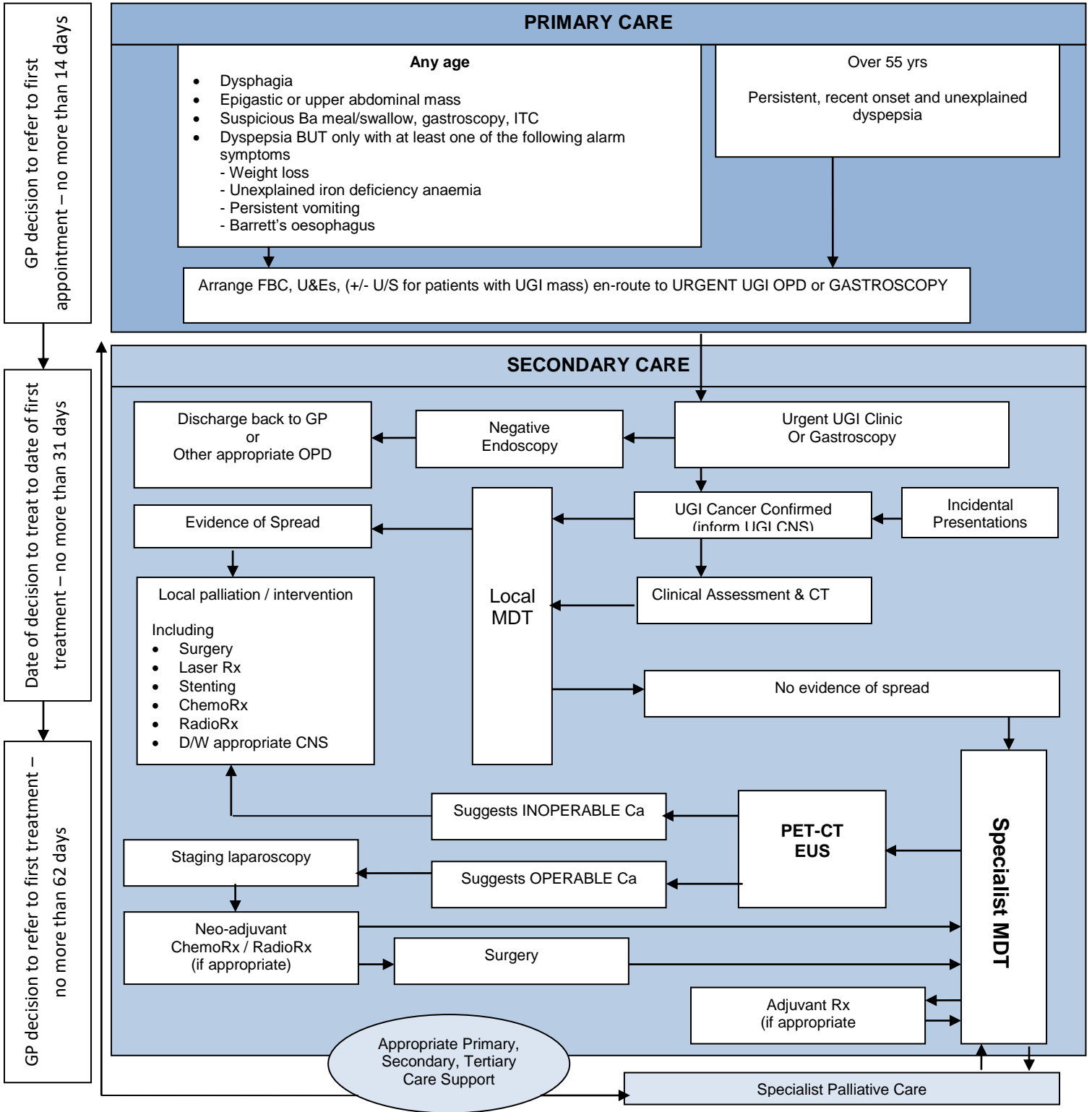
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1.0 Pathway Overview

Symptomatic Patient



2.0 Terminology

A. Tumours:

- Cancer of the oesophagus
- Cancer of the oesophago-gastric junction
- Cancer of the stomach

A Pathway of Care for patients with hepato-biliary & pancreatic cancers has been defined separately by the Upper GI Tumour Site Specific Group (TSSG) Pancreatic Cancer Reference Group.

3.0 Referral Guidelines and Process

3.1 The Rapid Access Route

Indications for an urgent (rapid access) referral for a suspected new malignancy, based on NICE guidance "Suspected cancer: recognition and referral" 2015

3.1.1 High Index of Suspicion of Cancer

Patients of any age with one or more of the following:

1. Dysphagia Epigastric or upper abdominal mass
2. Suspicious imaging
3. Unintentional weight loss of at least 5% body mass (*in addition to one or more of the following alarm symptoms and signs*)
 - a) Dyspepsia
 - b) Upper abdominal pain
 - c) Reflux

Dyspepsia is defined as any symptom of the Upper GI tract present for $\geq 4/52$ including upper abdominal pain or discomfort, nausea or vomiting. **It excludes heart burn and acid reflux.**

Note: General practitioners should be encouraged to:

- Provide information on all current medication
- Performance status
- Any significant comorbidities
- The results of all recent investigations:
 - Barium meal / swallow / gastroscopy results
 - FBC, LFTs and U&Es results
- Arrange an urgent ultrasound in place of a gastroscopy for patients with an upper GI mass
- Make referrals using the appropriate referral proforma for patients in whom there is a high index of suspicion cancer as defined above.
- *Dyspepsia, heartburn and/or acid reflux on their own do not warrant referral under the 2-week referral system.*

3.1.3 Incidental findings of Cancer

Patients who are diagnosed with upper GI cancer by other secondary care teams should always be referred to the upper GI cancer MDT at the earliest opportunity.

Referrals should be made by following locally agreed protocols

Patients who are diagnosed with upper GI cancer by independent diagnostic centres should be referred to the upper GI cancer MDT by their GP and under the 2-week rule

4.0 Local Specialist Clinic

Patients referred under the 2-week criteria should be seen within 2-weeks of referral.

The Local Specialist Clinic should be managed by members of the local specialist upper GI cancer multi-disciplinary team.

Patients who are endoscopy negative and without a palpable abdominal mass or other alarm symptoms will be referred back to their General Practitioner. If symptoms of dyspepsia persist patients should be referred to an appropriate UGI team for reassessment.

Patients diagnosed with upper GI cancer who are considered potentially fit enough to undergo active intervention should be urgently referred to the specialist upper GI cancer team using the agreed proforma (of which a copy is available on the KMCC website via the following link:

<http://www.KMCC.nhs.uk/tumour-sites/upper-gi-tssg/>

Note: To help reduce any delays in the diagnostic/staging pathway, the following investigations should be ordered by the local team:

- CT Chest & abdomen, including the liver

With the exception of patients with T1 disease referrals should also be made to oncology.

Patients being considered for curative resection should be referred to a dietician.

Potentially operable patients with a high degree of dysphagia may be offered oesophageal stenting locally after discussion with the specialist centre.

4.1 Further investigations by specialist team

PET-CT +/- EUS should be used to assess operability. Patients with wide spread disease can be spared major surgery, offered appropriate palliation and support more quickly using this type of triage.

Patients with oesophageal adenocarcinoma, but NOT squamous carcinoma, in whom EUS and CT suggest operability should undergo staging laparoscopy.

Patients with gastric adenocarcinoma, but NOT squamous carcinoma, in whom CT / PET-CT suggests operability should undergo staging laparoscopy.

4.2 Imaging Guidelines

Full KMCC imaging guidelines are located on the KMCC website on the following link:
<http://www.KMCC.nhs.uk/tumour-sites/sub-groups-or-cross-cutting-groups/>

4.3 Pathology

All KMCC reporting pathologists follow The Royal College of Pathologists Histopathology Reporting on Cancers guidelines – a copy of which is available through the KMCC website:-
<http://www.KMCC.nhs.uk/tumour-sites/pathology-ccag/>

Note: The Upper GI TSSG has agreed that tumour markers should not routinely be requested.

5.0 Patients deemed suitable for Curative Resection

Patients deemed suitable for curative surgery should be referred to the specialist team using the agreed proforma, an example of which is attached at the end of this document.

Referral arrangements between the centre and the unit will be based on TSSG agreed pathways and policies.

Patients should be considered for pre-operative chemotherapy.

Patients should be followed up, initially, by the specialist team. However, follow up should be transferred to the local team and/or the Specialist Palliative Care Team and/or Primary Care as soon as appropriate.

Full discharge documentation from the centre to the unit on discharge should be provided and include:

- Information given to patient
- Operative procedure performed
- Pathology results
- Any other investigative/staging results
- Details of post-surgical follow up arrangements – surgical, oncological, supportive palliative care, dietetic and nursing

6.0 Patients in whom there is evidence of spread

Patients in whom there is evidence of spread indicating inoperable disease will be managed locally.

Local palliative intervention will include:

- Stenting & other endoscopic interventions
- Laser treatment
- Chemotherapy
- Surgery

Biopsy samples from inoperable gastric tumours should be tested for HER-2 positivity

7.0 Oncology Specification

The Upper GI Non-Surgical Oncology Group is responsible for defining and maintaining the Non-Surgical Oncological Pathways of Care for Upper GI Cancers (including neuroendocrine tumours).

Note: For further information on oncological management – please refer see the documentation on the KMCC website: <http://www.KMCC.nhs.uk/tumour-sites/upper-gi-tssg/>

8.0 Neuroendocrine Tumour Multidisciplinary Team (MDT)

8.1 Neuroendocrine Tumours – an overview

Neuroendocrine tumours are uncommon tumours that arise from diffuse endocrine cells in the embryonic gut, characterised by the presence of neurosecretory intracytoplasmic granules containing peptide or amine hormones. They are distinguished from carcinomas by the immunohistochemical detection of antigens that are also common in nerve elements such as synaptophysin, neuron-specific enolase, chromogranins A, B and C, and CD56.

Neuroendocrine tumours may arise from various sites, and can be broadly categorised as arising from foregut (bronchus, oesophagus, stomach, duodenum & pancreas), midgut (jejunum, ileum, appendix, right colon) or hindgut (transverse colon, left colon & rectum). They have a wide spectrum of clinical behaviour, ranging from essentially benign tumours to highly malignant small cell carcinomas. The WHO classification categorises tumours according to their propensity for malignant behaviour on the basis of histological differentiation, proliferation index, size, and the presence of angioinvasion. It also recognises a number of distinct clinical entities among the group of well-differentiated slow-growing neuroendocrine tumours and carcinomas based on their localization and functional features.

Secretion of active hormones by these tumours can produce various syndromes of hormonal excess. The most common of these is the carcinoid syndrome, which results from the secretion of 5-hydroxytryptamine, and possibly other vasoactive amines and tachykinins, mainly from well differentiated carcinomas of the mid gut. The syndrome is characterised by diarrhoea, flushing and bronchospasm. Right sided cardiac valvular fibrosis can also develop, leading to tricuspid and pulmonary incompetence, and ultimately to right ventricular failure. Rarer hormonal syndromes include insulinoma, glucagonoma, Werner-Morrison syndrome (caused by hypersecretion of vasoactive intestinal peptide – VIP), and Zollinger-Ellison syndrome (caused by hypersecretion of gastrin). Conversely, some tumours produce no recognisable syndrome, either because they do not secrete hormones, or because they produce hormones that have no discernable clinical effect.

Neuroendocrine tumours have an annual incidence of around 20-30 per 1 000 000 population. They can occur at any age but are more common in the 5th and 6th decades. Presenting symptoms may be those of hormonal hypersecretion, mass effect due to primary or metastatic disease or as an incidental finding during investigation of an unrelated condition. Metastatic disease is present at the time of diagnosis in a large proportion of patients. Prognosis is dependent on stage and grade of disease at presentation. Median survival for patients with metastatic well differentiated neuroendocrine carcinomas is approximately 5 years, hence the prevalence of this condition is relatively high despite its low incidence.

8.2 Treatment of neuroendocrine tumours

8.2.1 Localised Disease

Surgery is the only curative therapy for neuroendocrine tumours, but in most cases there is evidence of disease spread at diagnosis and curative surgery cannot be undertaken. Surgery for localised disease should generally follow oncological principles identical to the surgical management of adenocarcinomas of the same organ. This should include regional lymphadenectomy in view of the risk of lymphatic spread and loco-regional lymph node metastases. The exceptions to this are small type 1 and type 2 gastric neuroendocrine tumours, which do not require surgical resection due to their generally benign course, and small (<2cm) neuroendocrine tumours of the appendix, for which appendicectomy is sufficient surgical therapy; right hemicolectomy is reserved for tumours > 2cm in size or showing deep (>3mm) mesoappendiceal invasion, or for tumours involving the base of the appendix where the completeness of excision is uncertain. Small (<1cm) neuroendocrine tumours of the rectum can also be managed with endoscopic resection.

8.2.2 Palliative management of advanced disease

Advanced neuroendocrine carcinomas frequently follow an indolent clinical course. The selection of palliative treatment options will depend on many factors including the rate of disease progression, the site of the primary tumour, the extent and distribution of metastatic disease, the expression of somatostatin receptors by tumour cells, the presence of comorbidity, and the wishes of the patient. Frequently patients will require a number of different modalities of palliative therapy at different times during the course of their illness, and the appropriate selection and sequencing of therapies is an important consideration in their management.

Palliative Surgery

Palliative surgery of primary neuroendocrine carcinomas of the small intestine in the presence of small volume slowly growing metastatic disease is recommended to prevent local complications of the primary tumour, particularly bowel obstruction and mesenteric ischaemia, which can be difficult to palliate once established. Palliative debulking surgery for metastatic disease in the liver in combination with resection of the primary tumour may prolong survival, particularly if >90% of the disease volume can be removed, although the evidence supporting this approach is from retrospective analyses of historical data.

Local ablative therapies for Hepatic Metastatic disease

Debulking of hepatic metastatic disease can be undertaken using a number of non-surgical techniques, including radiofrequency ablation, microwave ablation, transarterial embolisation or chemoembolisation, and selective internal radiotherapy using Yttrium-labelled glass beads administered via the hepatic artery.

Medical Therapy

Medical therapy for neuroendocrine carcinomas has two main objectives: control of symptoms of hormone hypersecretion and control of tumour

Somatostatin Analogues

The first objective can be achieved by the use of somatostatin analogues, which bind to somatostatin receptors on tumour cells and inhibit hormone secretion. These analogues have an antiproliferative effect, and prolong time to disease progression in well differentiated neuroendocrine carcinomas.

Interferon

Interferon-alpha produces a biochemical and symptomatic response in around 30-50% of patients with the carcinoid syndrome, with tumour shrinkage in about 10% of patients. However, many patients find interferon difficult to tolerate due to side effects of asthenia, anorexia and weight loss, bone marrow toxicity, hepatotoxicity, depression and mental disturbances. Interferon is therefore considered mainly in cases of disease progression and symptomatic breakthrough on somatostatin analogue therapy.

Chemotherapy

Chemotherapy is indicated for metastatic well differentiated neuroendocrine carcinomas of the pancreas. Streptozotocin-based combination chemotherapy with either doxorubicin or a fluoropyrimidine produces response rates of between 40-60% in this patient group. In contrast, well differentiated neuroendocrine carcinomas arising in the mid-gut do not show significant chemosensitivity, and chemotherapy should only be considered in this population if disease is progressing rapidly, with a high proliferation rate shown by Ki67 staining of >20% of tumour cell nuclei in tumour biopsies. Poorly differentiated neuroendocrine carcinomas arising at any site may also be chemosensitive, and are usually treated with a combination of cisplatin or carboplatin and etoposide.

Targeted agents

The mTOR inhibitor everolimus is indicated for progressive pancreatic well differentiated NETs, and also for non-functional pulmonary and small bowels NETs. The multitargeted tyrosine kinase inhibitor, sunitinib is indicated for progressive well differentiated pancreatic NETs.

Peptide Receptor Radionuclide Therapy

Peptide Receptor Radionuclide therapy has become established as an important treatment modality for this group of patients, exploiting the frequent expression of somatostatin receptors by these tumours to target radiotherapy to the tumour cells. Leutetium dotatate radiopeptide therapy is indicated for progressive well differentiated gastroenteropancreatic NETs. Radiopeptide therapy is currently provided by Medway Maritime Hospital, Maidstone Hospital, Kings College Hospital and Guys Hospital nuclear medicine departments.

Note: Details of oncological treatment are located in the UGI Oncology Treatment Guidelines on the KMCC website: <http://www.KMCC.nhs.uk/tumour-sites/upper-gi-tssq/>

8.3 Referral to the Neuroendocrine Tumour MDT

Once a diagnosis of a GI related Neuroendocrine tumour is confirmed patients should be referred to the Neuroendocrine MDT at Maidstone Hospital, which will also liaise with the Kings College Hospital NET MDT where indicated

9.0 Gastrointestinal Stromal Tumours (GISTs)

9.1 Introduction

Gastrointestinal stromal tumours (GISTs) are tumours of mesenchymal origin that arise in the GI tract. The most common sites of disease are the stomach (40%), small intestine (32%), rectum (10%), and less frequently in the oesophagus, colon, mesentery or omentum. The incidence of GIST is around 15 per million population per year. Presenting symptoms are often non-specific and depend on the size and site of the lesion. Gastric GISTs may present with bleeding, pain, fatigue or malaise, but small GISTs under 2 cm in size are usually asymptomatic and are detected during investigation of unrelated problems with imaging or endoscopy. Small intestinal GISTs may present with symptoms of intestinal obstruction, bleeding or perforation, and rectal GISTs may also produce obstructive symptoms and lower GI bleeding.

All cases of suspected oesophageal, gastric or small intestinal GIST should be referred to the centre upper GI MDT meeting prior to definitive therapy or biopsy, unless there is an urgent indication for surgical intervention such as gastrointestinal haemorrhage, obstruction or perforation. Suspected colonic or rectal GISTs should be discussed in the relevant lower GI MDT meeting, but in cases where complete surgical resection is thought unlikely to be feasible, oncological advice should be sought via the upper GI MDT meeting. Dr Waters is the nominated GIST oncologist for Kent and Medway.

9.2 Investigation

1. Patients suspected of having a GIST should undergo CT of chest, abdomen and pelvis to assess primary tumour extension and the presence of metastatic disease.
2. Endoscopic ultrasound examination (EUS) should be considered for oesophageal, gastric, duodenal and rectal tumours.
3. MRI may be useful to further characterise rectal tumours.
4. The role of PET/CT is not well established, but may be useful when there is diagnostic uncertainty following standard imaging.
5. Endoscopic biopsy should be obtained if there is diagnostic uncertainty, supplemented by EUS guided FNA or preferably EUS guided core biopsy.
6. In the presence of metastatic disease, endoscopic, per-cutaneous or laparoscopic biopsy should be obtained to establish a pathological diagnosis prior to systemic therapy. Ideally the biopsy should sample multiple areas and include normal tissue.

9.3 Histopathology and immunohistochemistry

The diagnosis of GIST is made definitively by histopathological examination of a surgical specimen or tumour biopsy. Characteristic morphological appearances fall into 3 types comprising a spindle cell type, an epithelioid type and a mixed type. These features are supplemented by immunohistochemical staining for CD117 (positive in 96% of GISTs) and/or DOG1 (positive in 98% of GISTs, including PDGFRA mutant GISTs that may be CD117 negative). GISTs may also show positive staining for CD34 (60-70%) and SMA (30-40%). Desmin and S-100 are rarely positive in GISTs, which helps to distinguish them from smooth muscle tumours and schwannomas respectively, which are also CD117 negative.

The histopathological report should include the tumour size and the mitotic index, measured as the number of mitoses identified in 50 high-power fields, both of which have prognostic significance following complete surgical resection of a primary GIST.

9.3.1 Mutational analysis

The majority of GISTs carry an activating mutation in the c-kit gene (75-80%) or the PDGFRA gene (10%). Mutational analysis of these genes can therefore be useful in cases of suspected GIST where immunohistochemistry for CD117 and/or DOG1 is negative. Furthermore, the specific location of the activating mutation in these genes is predictive of response to imatinib therapy. Mutations in exon 9 of c-kit predict for a poorer chance of response to standard dose imatinib, and a shorter progression-free survival for patients with advanced disease than seen in the more common exon 11 mutants. These patients may benefit from escalated-dose imatinib as initial therapy. Hence mutational analysis of c-kit and PDGFRA genes is recommended for all patients with intermediate or high risk completely resected GIST, and for patients with metastatic or locally advanced GIST for whom systemic therapy is being considered.

9.4 Treatment – Resectable Disease

Surgery is the only established curative therapy for GISTs. All GISTs should be considered to have malignant potential, and therefore surgery should be undertaken by a surgeon with appropriate site-specific expertise. Kent & Medway patients with a GIST of oesophagus, stomach, duodenum or small intestine should be referred to the central upper GI cancer surgical team for resection. Patients with a GIST of colon or rectum should be referred to the local colorectal cancer surgical team.

Principles of surgery are to resect the tumour completely with a wide local excision. Surgery should aim to preserve function, but not at the expense of an R0 resection. Lymph node metastases are very uncommon so an extended lymphadenectomy of macroscopically normal lymph nodes is not required. Laparoscopic resection is appropriate where feasible. If there is involvement of adjacent organs, en bloc resection should be undertaken whenever possible.

In cases of locally advanced GIST, where surgery would require multivisceral resection or result in significant functional impairment, neoadjuvant systemic therapy may also be considered. (see section 9.7)

9.5 Prognosis and Follow Up

Important prognostic factors for completely resected GIST include tumour size, mitotic index, site of primary tumour, and presence of tumour perforation (table 1).

Follow up is determined by the risk category. High risk patients should have CT scan and clinical evaluation 3-monthly for 2 years, 6 monthly for 2 years then annually. Intermediate risk patients should have CT scan and clinical evaluation at 3-months, 6 monthly for 2 years then annually to 5 years. Low risk patients should have CT scan and clinical evaluation at 3-months and then clinical follow up every 6 months for 5 years. Patients with very low risk tumours do not require specialist follow up.

Patients at high or intermediate risk of recurrence should be referred to the medical oncologist for follow up.

1. Table 1 - Prognostic factors following complete resection of GIST

Risk category (recurrence risk)	Tumour size (cm)	Mitotic index (per 50 HPFs)	Primary tumour site
Very Low (<2%)	<2.0	≤5	Any
Low (2-10%)	2.1-5.0	≤5	Any
Intermediate (10-50%)	2.1-5.0	>5	Gastric
	<5.0	6-10	Any
	5.1-10.0	≤5	Gastric
High (50-100%)	Any	Any	Tumour rupture
	>10	Any	Any
	>5.0	>5	Any
	2.1-5.0	>5	Non-gastric
	5.1-10.0	≤5	Non-gastric

Adapted from Joensuu H. *Hum Pathol* 2008; 39:1411-1419

9.6 Adjuvant Imatinib

Imatinib is licensed as an adjuvant treatment for patients following resection of a GIST who are at significant risk of recurrence. This licence was granted on the basis of data showing a statistically significant reduction in the risk of relapse following treatment with imatinib 400 mg for 1 year following complete surgical excision of a GIST measuring ≥3cm in size (DeMatteo et al. *Lancet* 2009; 373: 1097-1104). Relapse at 1 year was reduced from 17% to 2% (hazard ratio 0.35; 95% confidence interval 0.22-0.53; p < 0.0001). However this trial has not shown a difference in survival, although it was not powered to do so.

A subsequent study comparing adjuvant imatinib for 1 year versus 3 years showed both a progression free and overall survival benefit for the patients who received 3 years of treatment. Adjuvant imatinib for 3 years is therefore now recommended for all patients with imatinib-sensitive tumours based on mutational analysis of c-kit and PDGFRA genes.

9.7 Neoadjuvant Imatinib

Patients who have a locally advanced GIST in whom surgery is considered to carry a risk of substantial loss of organ function or in whom complete surgical excision may not be possible should be considered for neoadjuvant therapy with imatinib, which produces a complete or partial response in 50-67% of patients. Mutational analysis should be performed to identify the small group of patients that are unlikely to respond to imatinib therapy, and these patients should be considered for surgery if at all feasible, even at the expense of organ dysfunction. Patients with exon 9 mutations should be considered for initial therapy at a dose of 400mg bd, whereas other patients should be treated with a standard dose of 400mg daily. In the patients responding

to imatinib, surgery should be reconsidered after 6-12 months of imatinib therapy, when maximal response is likely to have been achieved. Decisions regarding suitability for neoadjuvant imatinib should be made in conjunction with the central upper GI MDT, and in consultation with the Royal Marsden Hospital Sarcoma MDT.

9.8 Advanced Disease

Patients with advanced or recurrent GIST should be referred to the medical oncologist for consideration of imatinib therapy. Suitable patients may be referred to the Royal Marsden Hospital sarcoma unit for consideration of inclusion in a clinical trial.

Note: Details of oncological treatment are located in the UGI Oncology Treatment Guidelines on the KMCC website: <http://www.KMCC.nhs.uk/tumour-sites/upper-gi-tssq/>

10.0 Specialist Palliative Care and Support

All patients with upper GI cancer will have access to specialist palliative care and support at every stage of the patient journey.

Open and frank discussions with patients should take place at all stages of their journey so that patients are not confused about their prognosis or have unrealistic expectations of any of the forms of treatment offered to them.

Relatives and carers will need to be appropriately supported and given appropriate information. However, in accordance with the recommendations set out in the revised Improving Outcomes Guidance in Upper GI Cancer, relatives and carers should not be given information different to that given to the patient.

Frail and terminally ill patients with upper GI cancer should always be discussed with the specialist palliative care team.

Palliative care provision should be made for all patients:

- Hospital teams, including the Clinical Nurse Specialists for upper GI cancer patients
- Primary Health Care Team would provide for palliative care at home
- General Practitioner should be informed within 24 hours of the diagnosis, treatment plan and medication

The management of symptoms, psychological, social and spiritual issues, and the communication of the diagnosis, and any associated problems, should be within the domain of all health care professionals.

Referral to specialist palliative care services should be considered when these issues have not been resolved and in particular for patients with:

- Complex symptom management issues, which are difficult to manage
- Difficulties in adjusting to the diagnosis or disease progression
- Psychological and family issues – such as communication problems within the family
- Spiritual issues – such as the challenging of belief system/faith/cultural values as a result of the cancer

Consideration of specialist palliative care or support should be given throughout the patient pathway, particularly:

- At the Multidisciplinary Team Meeting
- When no active treatment is considered
- After active treatment
- At relapse
- In the terminal stages

All patients should have unlimited access to an upper GI cancer nurse specialist who is a member of the specialist upper GI cancer team.

11.0 Clinical Trials

Suitability for entry into network agreed clinical trials should be a standard component of the MDM discussion on each patient with upper GI cancer.

12.0 Follow Up

- Patients (their relatives and carers) should have unlimited access to clinical nurse specialists.
- **Patients should be followed-up as close to home as possible.**

Post oesophagectomy:

Patients will be seen three weeks post operatively at the surgical centre. If the patient's condition is satisfactory he/she will be given a three month appointment at the centre.

Post Gastrectomy:

Patients will be seen six weeks post operatively at the surgical centre. Following this, patients should only be followed up by the specialist MDT if there is a clinical reason for doing so. In general patients should be referred back to the local team for follow-up.

The specialist MDT will ensure that local teams and General Practitioners are fully informed about the following:

- Outcome of surgery – including prognosis
- Information given to patients and carers by the specialist MDT
- Planned date of discharge
- Specialist follow-up arrangements – if any
- Investigations required to be carried out by the local MDT

Nurse specialists will be responsible for ensuring information is exchanged between Primary, Secondary and Tertiary Nurse Support Teams in a timely manner.

13.0 Data

Collection of data at each stage of the pathway is the responsibility of the team looking after the patient at that time. The minimum dataset agreed by the TSSG will be a combination of those data items that meet national requirements, and additional items as agreed by the TSSG.

National data requirements will include:

- Cancer Waiting Times monitoring, including Going Further on Cancer Waits. The data items required will be as defined in ISB0147 at the time of referral and/or treatment.

Details of the Cancer Waiting Times dataset are available from:

http://www.datadictionary.nhs.uk/data_dictionary/messages/clinical_data_sets/data_sets/national_cancer_waiting_times_monitoring_data_set_fr.asp

Cancer Waiting Times data will be submitted according to the timetable set out in the National Contract for Acute Services.

- The Cancer Outcomes and Services Dataset. The data items will be as defined in ISB1521, and any subsequent versions, at the time of diagnosis and/or treatment. The requirement will include those fields listed in the "Core" section of the dataset, and any additional tumour site specific sections, as applicable.

Details of the COSD are available from:

http://www.ncin.org.uk/collecting_and_using_data/data_collection/cosd.aspx

Cancer Registration and Cancer Outcomes and Services (COSD) data will be submitted according to the timetable set out by the National Cancer Registration Service (NCRS).

- Where applicable, teams will also collect additional data items as defined in any corresponding National Clinical Audit Support Programme (NCASP) audit dataset.

Details of these datasets are available from:

<http://www.ic.nhs.uk/services/national-clinical-audit-support-programme-ncasp/cancer>

Data for NCASP audits will be submitted, where applicable, according to timetables as agreed by the TSSG, and within the overall submission deadlines for each audit.

Submission of data to meet these national requirements will be the responsibility of each individual Trust.

Note that these standards are subject to variation from time to time, and where these requirements change, the data items required to be collected by the team will also change in line with national requirements.

Local data requirements will include any additional data items as agreed by the TSSG. These must be selected to avoid overlap with any existing data items, and where possible must use standard coding as defined in the NHS Data Dictionary.

Where possible and applicable, InfoFlex will be used for the collection and storage of data.

Additional areas of the COSD, relating to pathology, radiotherapy, Systemic Anti-Cancer Therapy (SACT), diagnostic imaging and basic procedure details will feed into the dataset from other nationally mandated sources. It is the responsibility of each team to ensure that the whole of the relevant dataset is collected, and it is acknowledged that this may come from a variety of sources.

14.0 Appendix 1 - Barrett's oesophagus (Columnar Lined Oesophagus CLO) Guidance

14.1 Rationale for Surveillance

The incidence of oesophageal adenocarcinoma has increased three-fold in the last decade. Patients are often without symptoms until the tumour has grown to be inoperable, and the survival for this cancer remains poor. Early diagnosis is crucial to improve survival.

Barrett's oesophagus (BE) is the pre-cancerous lesion. 90% of oesophageal adenocarcinomas arise in the presence of Barrett (CLO) Oesophagus. Although the absolute risk of developing carcinoma remain low, this is increased in male patients aged >45 years, with extensive CLO (>8cm) and longstanding reflux. Improved 5 year survival rates of 62-100% have been reported in patients with oesophageal carcinoma diagnosed at surveillance OGD. Surveillance should be considered, particularly in high-risk patients who are fit for oesophagectomy or mucosal resection. Routine endoscopic screening of patients with heartburn is not recommended.

Endoscopic therapy is reserved for high risk Barrett's demonstrating dysplasia. High grade dysplasia (HGD), carries a rate of progression to OAC of up to 60% over 5 years, and is often associated with more advanced pathology. Techniques to treat HGD or intramucosal cancer include Endoscopic Mucosal Resection (EMR), Radiofrequency Ablation and, for small islands, APC. Photodynamic Therapy has been superseded by RFA and is seldom used. These techniques should be performed at centres where endoscopic and surgical options can be offered to patients – Guys & St Thomas' (GSTT) is the local referral centre for the Kent & Medway Cancer Collaborative. All patients with dysplasia or early cancer, for whom therapy is considered, should be discussed at the specialist MDT for oesophago-gastric cancer. This team should include an interventional endoscopist, upper GI cancer surgeon, radiologist and a GI pathologist (minimum standard).

The guidance for low grade dysplasia (LGD) set out in this document highlights the emerging evidence for Endoscopic therapy in this group, with consideration for RFA at specialist centre in those with high risk features (Age, long segment, LGD on 2 occasions, genetic abnormalities). The organisation of dedicated surveillance and mutual audit to improve quality and dysplasia detection rate is also discussed.

Definition

Diagnosis of Barrett's oesophagus is described in the recent BSG guidance as –

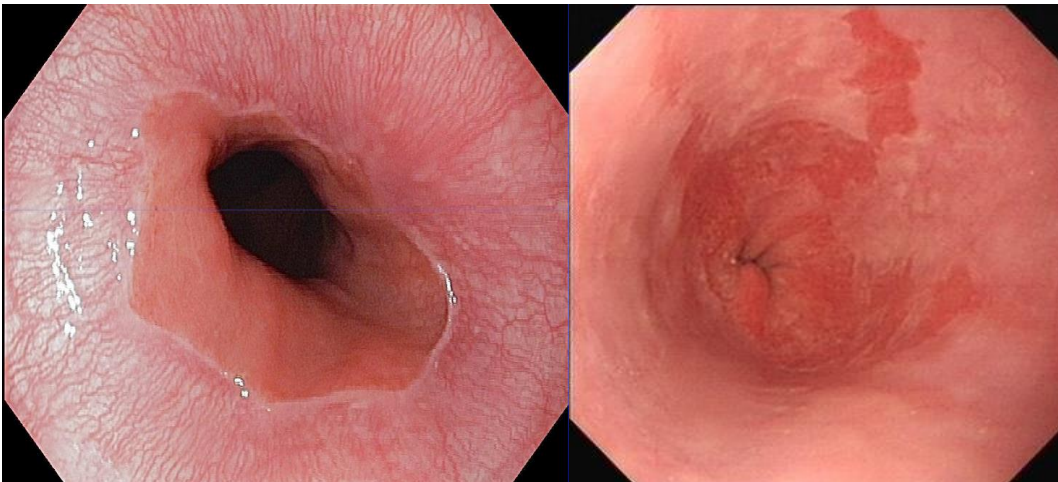
An oesophagus in which any portion of the normal distal squamous epithelial lining has been replaced by metaplastic columnar epithelium, which is clearly visible endoscopically (≥ 1 cm) above the GOJ and confirmed histopathologically from oesophageal biopsies (Recommendation grade C).

Or

- Presence of visible columnar mucosa above the top of gastric folds
- Presence of Intestinal metaplasia if length <3cm

It is therefore essential to accurately document the level of the GOJ, which is often difficult as the majority of patients will have a hiatus hernia.(2) For the purposes of this guidance we recommend the top of gastric folds (rather than extent of palisade vessels as is used in Japan) is the Z-line, and a measurement of columnar lined mucosa 1 cm above this is sufficient for a diagnosis of Barrett's oesophagus (see Figure 1).

Figure 1 Normal Z-line (left), Barrett's oesophagus (right) COM3 - On histopathological correlation there was evidence of specialised intestinal metaplasia, no dysplasia



14.2 Surveillance Technique

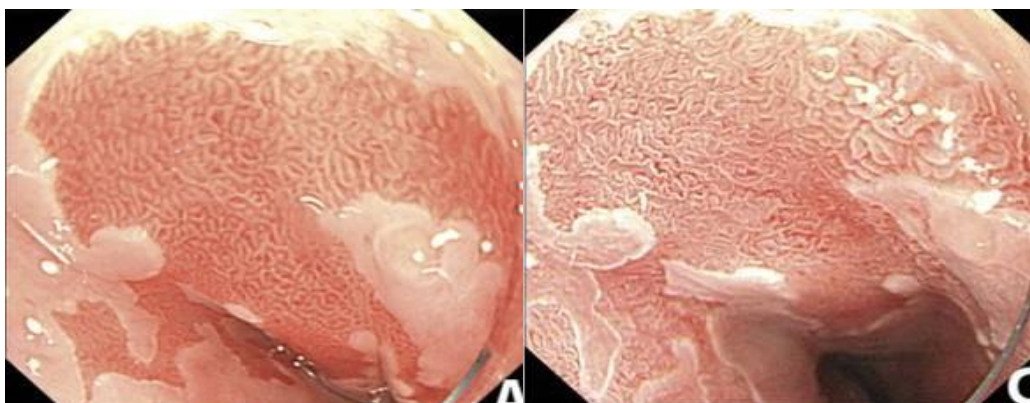
Endoscopy

The BSG recommends High-resolution endoscopy should be used in Barrett's oesophagus surveillance. Advanced imaging modalities, such as chromoendoscopy or 'virtual chromoendoscopy' (i.e. Narrow Band Imaging (Olympus), I-scan (Pentax) or FICE (Fuji)) are not superior to standard white light endoscopy in Barrett's oesophagus surveillance and are therefore not recommended for routine use.(3)

Withdrawal time should be 1min per cm of circumferential Barrett's, following publication of PROMs by UEG.

Situations when these advanced techniques may be more advantageous are in patients where the intention is a target biopsy in the first instance. Such situations may include previous LGD/IND or those with very long segment Barrett's (i.e. ≥ 10 cm). The technique for acetic acid chromoendoscopy is as follows:–

1. Make up 20-50 mls of 2.5% acetic acid (comes as 5% acetic acid from pharmacy, dilute 50:50 with water)
2. Wash entire mucosa with acetic acid using spray catheter
3. Wash over surface with water
4. Assess for areas of LAWS (loss of aceto-whitening sign)



14.3 Lesion recognition

Target biopsy is recommended prior to embarking on the Seattle protocol four quadrant biopsy technique. This is primarily to target nodular disease (see Figure 3), with the proviso from the BSG guidance that 'visible lesions should be considered malignant until proven otherwise'. Nodules should be described according to the Paris classification, see Figure 4.

Figure 3 Nodule arising in Barrett's post treatment with RFA. The lesion is at 32cm Posterior/Left wall or at 7 o'clock, Paris IIa/c.

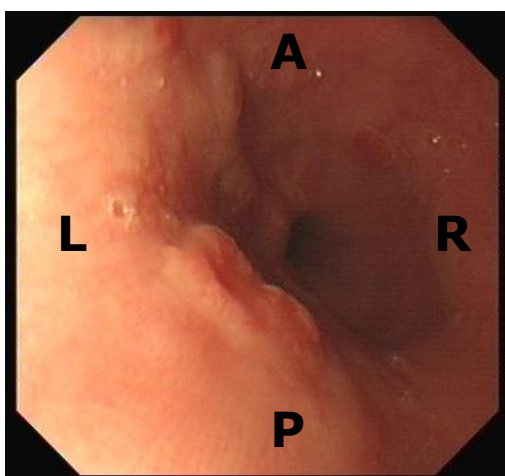










Figure 4 Paris Classification

Endoscopic appearance	Paris class		Description
Protruded lesions	Ip		Pedunculated polyps
	Ips		Subpedunculated polyps
	Is		Sessile polyps
Flat elevated lesions	0-IIa		Flat elevation of mucosa
	0-IIa/c		Flat elevation with central depression
Flat lesions	0-IIb		Flat mucosal change
	0-IIc		Mucosal depression
	0-IIc/IIa		Mucosal depression with raised edge

The presence of ulcers and strictures are also indicative of prevalent malignancy and should be reassessed without delay, including multiple targeted biopsies or diagnostic EMR if appropriate. If severe ulceration and stricturing is evident, but initial biopsy is negative for dysplasia, it is recommended to start high dose PPI (Nexium 40mg bd or equivalent) and reassess within 8 weeks.

14.4 Prague Classification

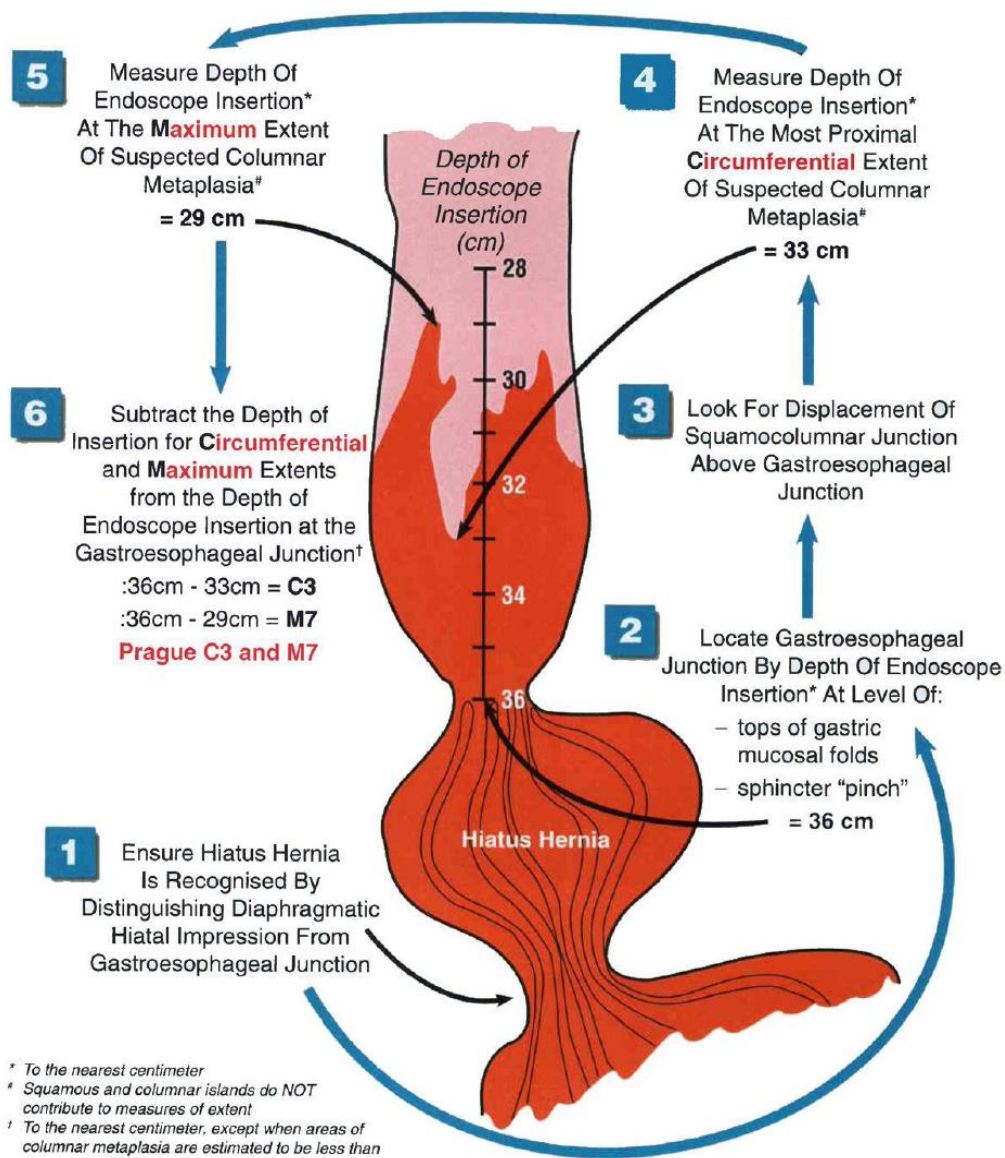
Prague C & M Criteria

To further accurately document the nature of Barrett's CLO the International Working Group for Classification of Oesophagitis (IWGCO) developed the Prague C&M criteria.(4) This scoring system is based on the circumferential (C value, in cm) and the maximal extent (M value, in cm) of BE above the gastro-oesophageal junction (GOJ). For example, if BE was circumferential for 2 cm above the GOJ and the maximal extent of non-circumferential BE was 5 cm (i.e., with 3 cm of BE "tongues") above the GOJ, this would be recorded as C2M5. The consensus group in this study decided that 'true islands of squamous and columnar mucosa should not influence the measurement of extent of BE and that only segments of contiguous BE are measured'. The proposed scoring system was validated in a study using 29 digital recordings of endoscopies. Internal validation yielded a high reliability coefficient value for agreement on the presence of BE >1 cm (r =0.72).

Figure 5 Prague criteria

PRAGUE CRITERIA - For Endoscopically Suspected Oesophageal Columnar Metaplasia / Barrett's Oesophagus

Developed by the Barrett's Oesophagus Subgroup of the International Working Group for the Classification of Reflux Oesophagitis (IWGCO).

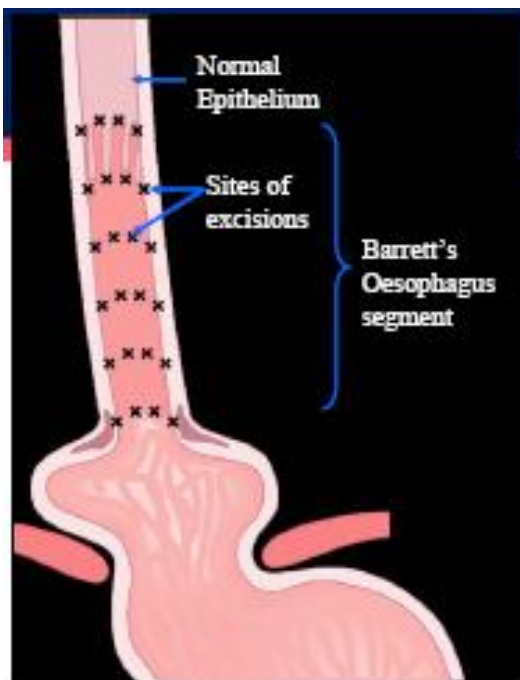


14.5 Biopsy protocol

A four quadrant biopsy protocol (the 'Seattle' protocol) consisting of jumbo forceps biopsies from every 2cm of columnar mucosa, was first proposed for surveillance of patients with BE in 1993,(5) and national guidelines of many countries recommend this protocol as standard.

Four quadrant biopsies should be taken and labelled at the site i.e not distal oesophagus. Ensure each level is in a separate pot. For example ---Barrett's oesophagus C4M5 (33-39cm). Quad bx at 39M (for multiple), 37M, 35M, 33M.

Figure 6 Seattle protocol



Biopsies taken in 4 quadrants every 2cm through Barrett's segment.

Individually labelled pots per level.

Surveillance follow up intervals

- Repeat endoscopy should be considered at 3-5 year intervals Barrett's segments ≤ 3 cm or 2-3 years for segments ≥ 3 cm
- Patients with a Barrett's segment >5 cm should be screened on dedicated lists by an endoscopist with particular expertise in this area.
- Very long segments of Barrett's (>10 cm) should probably be referred to a tertiary centre for surveillance
- BSG Guidance advises patients are maintained on **high dose** PPIs long term

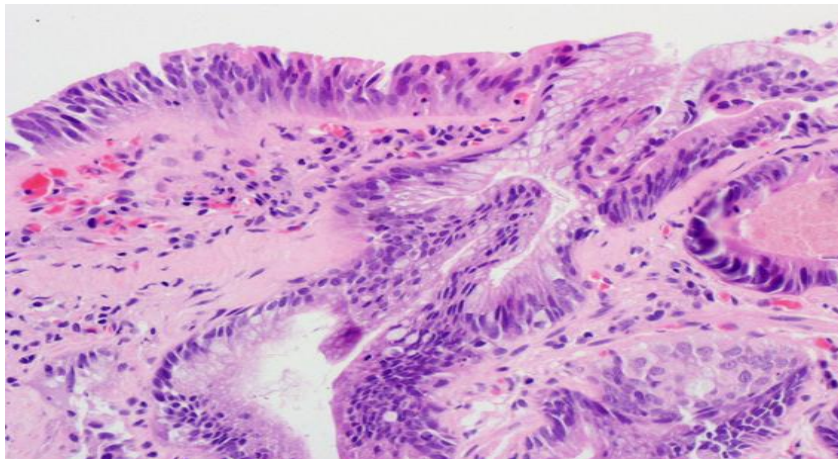
15.0 Dysplasia Management

Management of Low grade dysplasia/Indefinite for dysplasia

Low grade dysplasia (LGD) is characterized by crypts with relative preservation of simple glandular architecture. Epithelial cell nuclei are oval or elongated and generally retain polarity. The nuclei are hyperchromatic with mild irregularity of nuclear membrane contour. Nuclear stratification is present and usually occupies the lower half of the thickness of the epithelium; full-thickness stratification is not present (see figure 9). Other features include mucin depletion, decreased number of goblet cells, and increased epithelial mitotic figures. Importantly, there is lack of maturation at the surface such that these changes are present on surface epithelium.

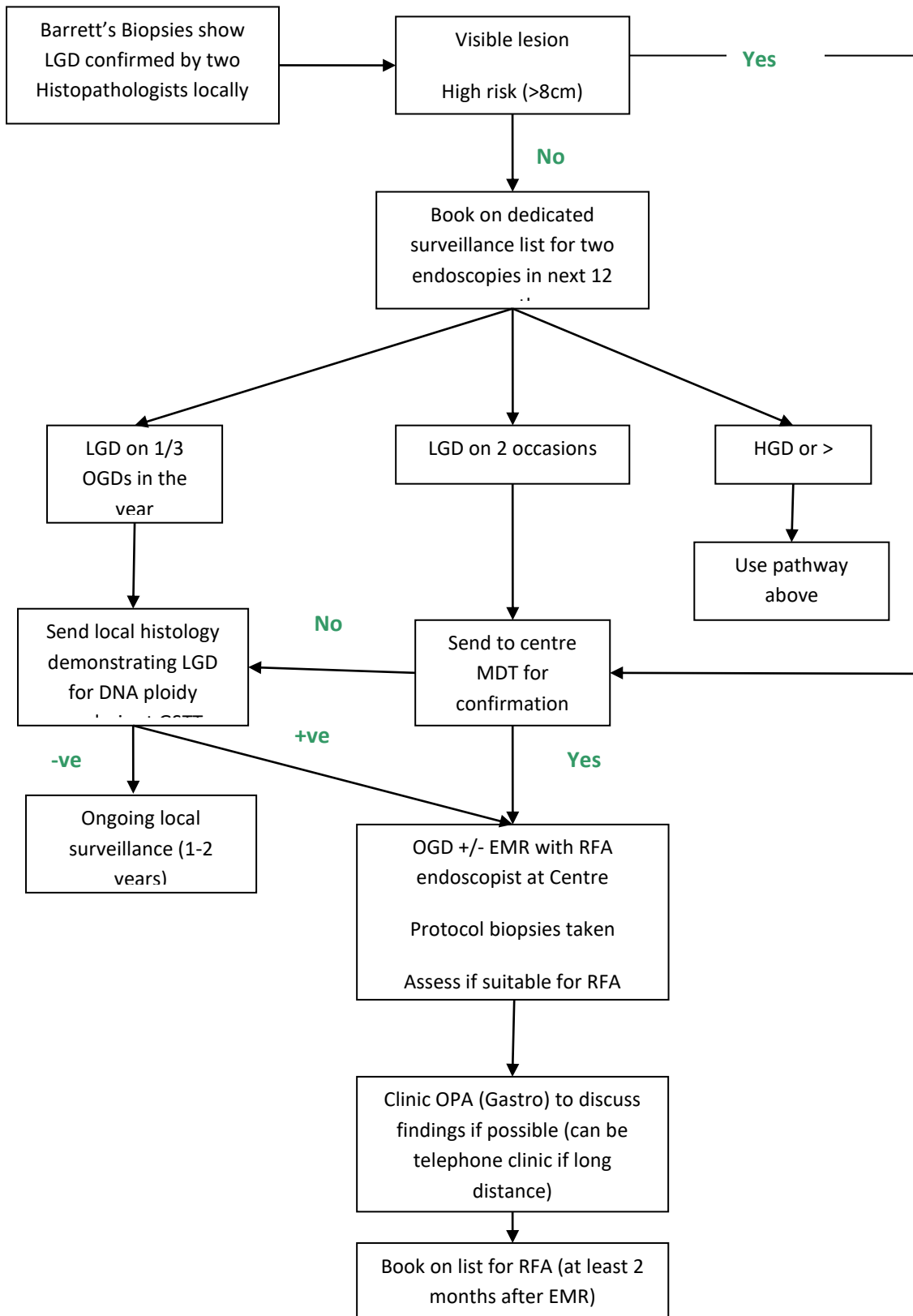
Figure 9 Haemotoxylin and eosin stain of low grade dysplasia

(Courtesy of Professor Novelli – the sharp cut off between normal and atypia favours dysplasia)



The uncertainty of the risk of cancer has led to great debate about the advantages and disadvantages of treating low grade dysplasia, particularly with the advent of minimally invasive endoscopic therapies. The results of a multicentre RCT for RFA compared with endoscopic surveillance in a large cohort of patients with LGD did demonstrate a significantly lower risk of progression to HGD/cancer, and as a result of this it is now recommended that confirmed LGD be treated in Endotherapy centres. The below diagram demonstrates a pathway for the management of LGD.

15.1 Low Grade Dysplasia in Barrett's Oesophagus

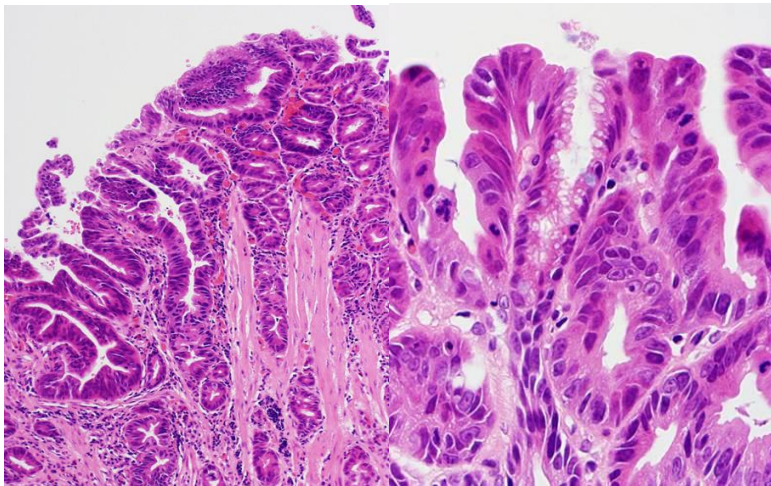


15.2 Management of High grade dysplasia

High grade dysplasia (HGD) is characterised by architectural changes which include increased budding, branching, and crowding, villiform surface configuration, and the presence of intraluminal bridges or papillae. Cytological features of HGD include marked nuclear pleomorphism (ie, variation in nuclear size and shape), loss of polarity (ie, loss of normal nuclear orientation, in which the long axis of the nucleus is perpendicular to the basement membrane and basally oriented), and full-thickness nuclear stratification (see figure 7). Mitotic figures, especially atypical ones, are often present and may involve the surface epithelium. The diagnosis is subject to low inter-observer variability between pathologists, with studies demonstrating agreement 80% of the time.(6)

Figure 7 Haemotoxylin and eosin stain of high grade dysplasia

(courtesy of Professor Novelli- Left x100, right x400)



HGD is at present the most robust routinely used clinical marker of cancer progression in Barrett's oesophagus; its presence confers a 16-59% risk of developing cancer within 5 years of the diagnosis of HGD.(7-10) It is generally accepted that a diagnosis of HGD is an indication for treatment and the British Society of Gastroenterology (BSG) guidance, from 2005, states the following:

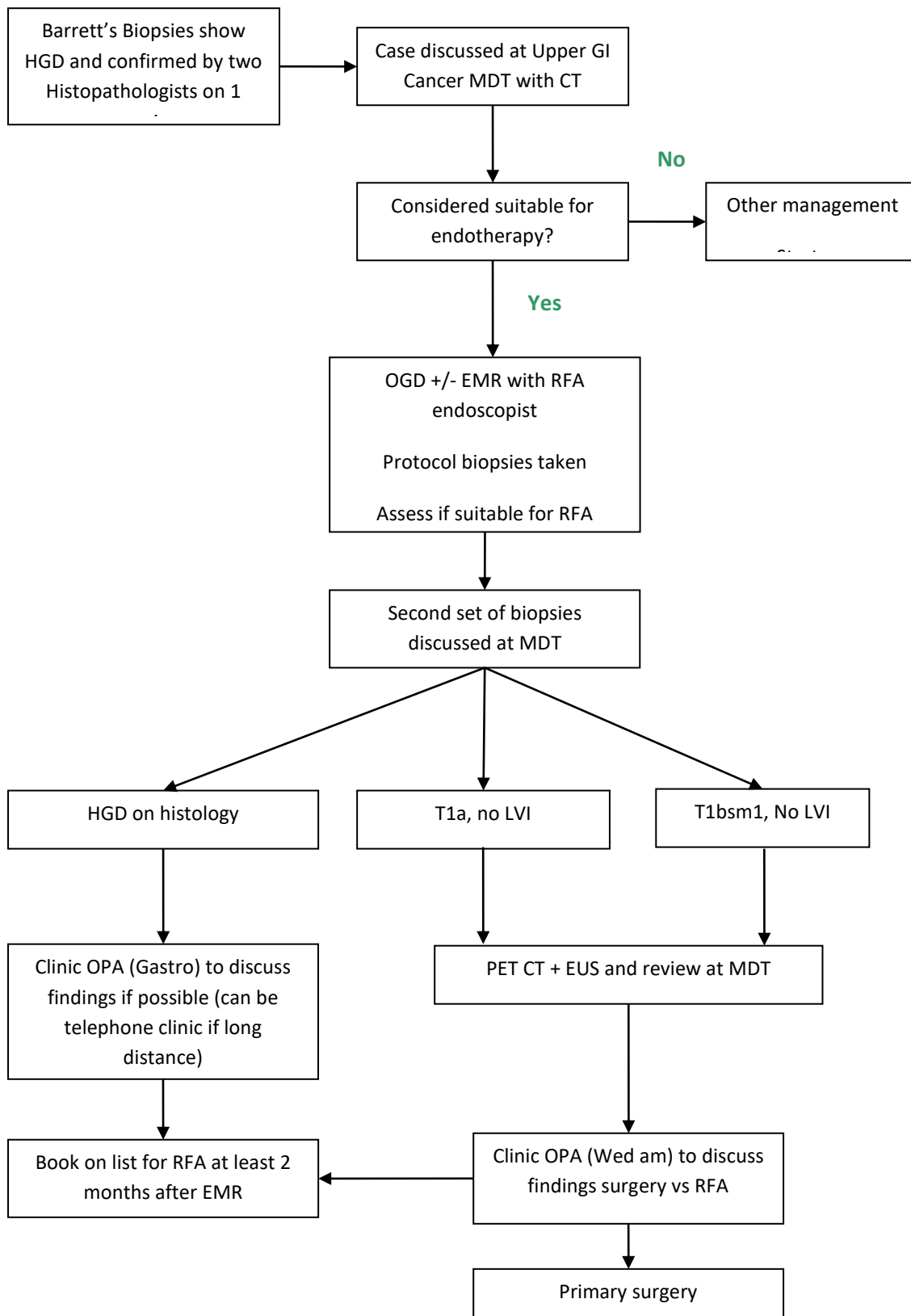
*High-grade dysplasia is associated with a focus of invasive adenocarcinoma in 30–40% of patients. For this reason, **if the changes persist after intensive acid suppression and are confirmed by two expert pathologists**, oesophagectomy in a specialised unit is currently recommended in patients considered fit for surgery*

(Recommendation grade C).(11)

Two important changes were made in the recently updated 2013 version (Figure 8). One is the timing of referral to tertiary referral centre. These guidelines state that ***a diagnosis of HGD on one occasion is sufficient for referral to UGI MDT for evaluation***. The reason is that these patients will often have more severe disease. Nodules or changes in surface pit pattern are often apparent in HGD, and can be removed by Endoscopic Mucosal Resection (EMR) which will result in upstaging to cancer 40% of the time. High resolution endoscopy undertaken by specialist endoscopist may improve the pick-up rate of visible lesions. An eight week period of intensive acid suppression therefore delays accurate staging, and subsequent potential for minimally invasive therapy (EMR/RFA).

The second important change is the adoption of minimally invasive therapy as a first line treatment for HGD or IMC arising in Barrett's oesophagus. This makes accurate early staging by an endoscopist with a special interest in RFA/EMR a critical step in the patient pathway – see below. The National OG cancer Audit now includes HGD, and forms are shown in appendix A.

A patient with HGD should be referred at first diagnosis to Centre MDT



15.3 Environment

Organisation of surveillance programmes is key to structured follow up. Non-adherence has been reported as high as 50% in a US community setting and is associated with significantly decreased dysplasia detection. There is a growing body of evidence that dedicated surveillance lists improve endoscopic technique and dysplasia detection rate (DDR). In the recent AspECT study there was a significant increase in four quadrant biopsy technique (32% to 86%) and number of biopsies taken post trial adoption at site.(28) A recent report from the UKBOR cohort on 817 patients, demonstrated a large proportion of dysplastic disease (>90%) was detected on specific surveillance endoscopies, though variation in surveillance practice for BE was observed throughout the UK.(25) A study by Abela *et al.* in a UK setting showed that there was a 13 fold increase in detection of prevalent dysplasia between patients who underwent four quadrant biopsies every 2cm (median biopsy number; 16) compared to those who had non-systematic biopsies (median biopsy number; 4).(29) This study showed an increased DDR; 18.9% vs 1.6% for LGD; 2.8% vs 0% for HGD.

The group at GSTT recently published a pilot study undertaken at 2 sites in London, GSTT and Lewisham [7]. It was shown that moving BE surveillance to dedicated lists run by trained endoscopists significantly reduced variation (as evidenced by better documentation and adherence to biopsy protocol) with a subsequent significant increase in the dysplasia detection rate (DDR) for all grades (Low grade Dysplasia (LGD) and high grade dysplasia (HGD)). Importantly there was no difference in quality at a teaching or district general hospital, and therefore this model may be applicable to BE surveillance at a regional level.

One area of research that may be conducted through KMCC is a study assessing the impact of the introduction of dedicated surveillance lists. Funding for a pilot study QUEBOC (Quality Endoscopy for Barrett's Oesophagus Collaborative) has been applied for.

Audit

One role of the lead at each centre would be the organisation of an annual audit which will be rolled out throughout the KMCC. Auditable criteria include the following

- Prague documentation
 - Aim for >80%
- Number of bx per 2cm
 - Aim for >70%
- DDR
 - Aim at least 7% for all grades
- Dual pathology review of LGD/IND
 - 90%
- Central pathology review of high grade dysplasia
 - 100%
- Time to centre referral for HGD (one only x 2 pathol) or persistent IND/LGD (2 times , x 2 pathol)
 - Within 2 weeks 90%
- Surveillance intervals correct according to guidelines
 - As above, 80%

16.0 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://www.KMCC.nhs.uk/tumour-sites/>

17.0 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
GSTT	Guys & St Thomas' NHS 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
MDT	Multi-Disciplinary Team
MTW	Maidstone & Tunbridge Wells NHS Trust
NOG	Non-Surgical Oncology Group (<i>Permanent oncologist sub group of the TSSGs with a specific responsibility for chemo/rad pathways and advice to the TSSG, KMCC and geographical locations on new drugs</i>)
PoC	Pathway of Care (<i>KMCC agreed disease site specific clinical guidelines</i>)
QEQM	Queen Elizabeth the Queen Mother Hospital, Margate (EKHUFT)
QoL	Quality of life
RAT	Research and Trial Group (<i>Permanent sub-group of the TSSGs with a specific responsibility for taking forward the clinical trials agenda</i>)
RMH	Royal Marsden Hospital
RNOH	Royal National Orthopaedic Hospital
TSSG	Tumour Site Specific Group
QVH	Queen Victoria Foundation Trust Hospital East Grinstead
UCLH	University College Hospital London
WHH	William Harvey Hospital, Ashford (EKHUFT)
WK	West Kent

18.0 Document Administration

Document Title	The Management of Oesophago-Gastric Cancer – Pathway of Care
Principle author (s)	A.Piotrowicz/G.Smith-Laing/A.Jackson
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Current version number	7.0
Current status	FINAL
Original publication date	September 2005
Expected review date by	April 2022

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Revision History			
Date of revision	New Version Number	Nature of Revision	Confirmation of Accuracy by
Sept 05	0.1	Initial Draft - All sections reviewed; New Flow Chart; New Section on Follow Up	A.Jackson
Oct 05	0.2	2 nd Draft - Flow Chart revisions; text revisions; Oncology section revisions	A.Jackson/ G. Smith-Laing/ J.Waters
Jan 06	0.3	3 rd Draft - Changes agreed at DOG	A.Jackson
Jan 06	0.4	4 th Draft – Modifications to referral/dyspepsia pathway	A.Jackson/ G.Smith-Laing/ J.Waters
Feb 06	0.5	Final Draft – Final updates from 01/02/06 DOG	A.Jackson
June 06	1.0	Published - Clarification of data collection section	A.Jackson
May 09	1.1	Review Draft – General overhaul by DOG	A.Jackson
June 09	2.0	Published – New appendices for Dyspepsia & Barrett's	G.Smith-Laing/ R.Ede/M.Philpott
Nov 09	2.1	Review draft – New section on Neuroendocrine Tumours; New section on GISTs	J.Waters
Mar 10	2.2	Review Draft – Updated Barrett's Guidance	R.Ede
Mar 10	3.0	Published – Admin Updates	A.Jackson
Mar 12	3.1	Draft – updated all weblinks inc. imaging, pathology & contacts; general formatting & content checking	S.Stanley/C.Tsatsaklas
September 2012	4.0	FINAL – Data Collection updated / Amendments added as agreed at UGI DOG 05/09/12 – agreed/published	UGI DOG/A Piotrowicz /I.Vousden
August 2014	4.1	Draft - Removed text relating to DOGs, PCTs, KMCN – replaced with TSSGs, CCGs, Cancer Team, updated weblinks etc	C.Tsatsaklas
November 2015	4.2	Changed contact details for enquiries	N.Aluwalia
September 2016	4.3	Updates by A.Piotrowicz. To be ratified in the TSSG 22/9/16	A.Piotrowicz/ N.Aluwalia

April 2017	4.4	Copy circulated to the TSSG. Updates added by Jason Dunn. Updates added to reflect referral proforma. Ratification process underway.	J.Dunn/N.Aluwalia
May 2017	5.0	Final ratified version approved for website upload	O&Q Group/ N.Aluwalia
February 2020	5.1	Draft – Updates from Justin Waters & Walter Melia	W. Melia/A. Wiltshire
April 2020	6.0	Final version agreed and circulated to TSSG members	J. Waters/W. Melia/A. Wiltshire
April 2021	6.1	Draft – New TSSG chair	J. Lordan/A. Wiltshire
June 2021	7.0	Final version agreed and circulated to TSSG members	J. Lordan/A. Wiltshire