The Royal College of Pathologists

Pathology: the science behind the cure

Standards and datasets for reporting cancers

Dataset for histopathological reporting of gastrointestinal stromal tumours

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	In accordance with the College's pre-publications policy, this dataset was on the Royal College of Pathologists' website for consultation from 4 September to 2 October 2019. Responses and authors' comments are available to view following final publication of this dataset.
	Dr Brian Rous
	Clinical Lead for Guideline Review

Contents

Foreword

The cancer datasets published by the Royal College of Pathologists (RCPath) are a combination of textual guidance, educational information and reporting proformas. The datasets enable pathologists to grade and stage cancers in an accurate, consistent manner in compliance with international standards and provide prognostic information, thereby allowing clinicians to provide a high standard of care for patients and appropriate management for specific clinical circumstances. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this guideline may therefore be required to report a specimen in a way that maximises benefit to the patient.

Each dataset contains core data items that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Data Set) in England. Core data items are items that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards (as defined by the Information Standards Board for Health and Social Care), and it is recommended that at least 95% of reports on cancer resections should record a full set of core data items. Other non-core data items are described. These may be included to provide a comprehensive report or to meet local clinical or research requirements. All data items should be clearly defined to allow the unambiguous recording of data.

The following stakeholders were contacted to consult on this document:

- Sarcoma UK
- British Society of Gastroenterology Pathology Section.

The evidence has been evaluated according to the modified SIGN guidance and the level of evidence for the recommendations has been summarised according to College guidance (see Appendix E). Unless otherwise stated, the level of evidence corresponds to 'Good practice point (GPP): Recommended best practice based on the clinical experience of the authors of the writing group'. The sections of this dataset that indicate compliance with each of the AGREE II standards are indicated in Appendix F.

No major organisational changes or cost implications have been identified that would hinder the implementation of the dataset.

A formal revision cycle for all cancer datasets takes place on a three-yearly basis. However, each year, the College will ask the author(s) of the dataset, in conjunction with the relevant subspecialty adviser to the College, to consider whether or not the dataset needs to be updated or revised. A full consultation process will be undertaken if major revisions are required, i.e. revisions to core data items (the only exception being changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Cellular Pathology and affiliated professional bodies; these changes will be implemented without further consultation). If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken whereby a short note of the proposed changes will be placed on the College website for two weeks for members' attention. If members do not object to the changes, the changes will be incorporated into the dataset and the full revised version (incorporating the changes) replace the existing version on the College website.

This dataset was reviewed by the Clinical Effectiveness department, Working Group on Cancer Services and Lay Governance Group and placed on the College website for consultation with the membership from 4 September to 2 October 2019. All comments received from the Working Group and membership were addressed by the authors to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review.

1 Introduction

The diagnosis and management of gastrointestinal stromal tumours (GISTs) is best accomplished within the multidisciplinary team (MDT) environment. The pathologist has a key role within this framework to provide accurate and comprehensive diagnostic and prognostic information.[1] These guidelines describe the core and non-core data that should be recorded in histopathological reports from GIST resection specimens to facilitate this process. The information within histopathology reports not only allows formulation of a definitive management plan but also is used to:

- provide accurate and complete data for cancer registration

- provide feedback to other clinical specialties, including surgery, radiology and oncology

- allow for high-quality clinical audit and research.

GISTs are now considered the most common connective tissue tumour of the gastrointestinal (GI) tract. They have been the subject of great interest over the past decade as a much deeper understanding of the underlying molecular biology of this tumour type and the therapeutic options, principally the use of tyrosine kinase inhibitors (TKIs), have emerged. Other diagnostic terms such as leiomyoblastoma and gastrointestinal autonomic cell tumour are no longer in use.[2–4]

[Level of evidence – B.]

The demonstration of mutations in the *KIT* gene in many GISTs[5,6] opened the way to the use of TKIs in the treatment of irresectable or metastatic tumours.[7] These gain-of-function mutations are an early event and are seen in very small lesions.[8] Subsequently, it was shown that only a small number of GISTs contained mutations, and these were not of *KIT* but of a gene encoding a related tyrosine kinase, *PDGFRA*.[9]

Traditionally, a GIST was referred to as 'wild type' when it did not harbour activating mutations in *KIT* or *PDGFRA*. However, more recently it was shown that some of these wild-type GISTs have a driving mutation in other genes such as *BRAF/RAS*, *NF1* or *SDH*. As a result, GISTs without *KIT* or *PDGFRA* mutations are currently being referred to as dual or double wild-type GISTs, and GISTs without *KIT/PDGFRA*, *BRAF/RAS*, *NF1* or *SDH* gene mutations are referred to as quadruple wild-type GISTs. It is expected that driving mutations in other genes will subsequently be demonstrated in quadruple wild-type GISTs. If so, the terminology will need revision.

Epidemiological studies have shown that the incidence of GISTs is higher[10,11] and the morphological spectrum of GISTs is wider than previously recognised.[12] The estimated incidence of GISTs is around 15 per million of population per annum, implying approximately 900 new cases per year in the UK. Most patients are adults with a median age of 50–60 years and the incidence is roughly equal in males and females. They are rare in childhood.[13]

While GISTs can occur anywhere in the GI tract, from the oesophagus to the rectum, most arise in the stomach (60–70%) or small intestine (20–30%). A few appear to arise primarily within the omentum,[14] but it is important to be sure that these do not represent spread from a primary lesion in the luminal GI tract.

It is important to be aware of the wide differential diagnosis of mesenchymal tumours of the GI tract, including true smooth muscle tumours, GI schwannomas, intra-abdominal fibromatosis, gastric glomus tumours, synovial sarcoma, inflammatory myofibroblastic tumour, plexiform fibromyxoma, calcifying fibrous tumour and melanoma.

While most cases of GIST are sporadic, there are four important syndromic settings in which they can arise. These include Carney's triad, in association with paraganglioma and pulmonary chondroma, as well as Carney-Stratakis syndrome or dyad, an association of GIST with paraganglioma alone.[15] As a rule, these Carney syndromic GISTs are deficient for *SDHB*. Additionally, there are rare familial GISTs that are associated with germline mutations of the *KIT*[16] or *PDGFRA* gene. There is also an increased incidence in type 1 neurofibromatosis (NF1),[17] which often causes multiple tumours to grow that are generally located in the small intestine.

4.1 Target users and health benefits of this dataset

The target primary users of the dataset are trainee and consultant cellular pathologists and, on their behalf, the suppliers of IT products to laboratories. The secondary users are surgeons, radiologists, oncologists, cancer registries and the National Cancer Registry and Analysis Service (NCRAS).

MDT working and standardisation of cancer reporting reduce the risk of histological misdiagnosis and help to ensure that clinicians have all of the relevant pathological information required for tumour staging, management and prognosis. Standardised cancer-specific data also provides information for healthcare providers and epidemiologists and facilitates national and international benchmarking and research.

2 Clinical information required on specimen request form

As GISTs may occur anywhere within the GI tract, as well as outside it (extra gastrointestinal stromal tumour [EGIST]), clinical information regarding the nature of the surgical resection and the site of the tumour is useful in   entimeter specimen handling. It also ensures that prognosis is related to site. A history of other possibly associated neoplasia such as neurofibromas or paragangliomas may be helpful in guiding mutation analysis studies.

While there is little published information specifically relating to EGIST, it is generally presumed that most of the basic principles and features of GIST apply to these tumours.

The size of the tumour on radiology is helpful. The surgeon's impression of the completeness of excision and the presence of peritoneal seedlings or liver metastases is also valuable. It is essential that a history of previous medical treatment (e.g. imatinib) is given as this may well modify the size, histological appearances and proliferation of a GIST. In addition, radiological assessment using Choi criteria is a helpful predictor of response.[18]

3 Specimen preparation before dissection

Owing to the varied anatomic sites from which GISTs arise, a wide array of specimen types may be encountered. Endoscopic biopsies are commonly taken, although the diagnostic yield of such sampling of submucosal or more deeply sited GI tumours is   entimeter to be low. Therefore, the use of endoscopic ultrasound-guided fine needle aspiration to sample such tumours is increasing and, if this is unavailable or unsuccessful, percutaneous core biopsy may be considered. Alternatively and depending on local practice and clinical circumstance, a patient with a suspected GIST but no tissue diagnosis may proceed straight to surgical removal.

In some circumstances it may be important to biopsy a GIST, for example tumours situated in the lower rectum and in the area of the duodenum or gastrooesophageal junction, in which neoadjuvant TKIs may allow less radical surgery. In these cases, mutation analysis is required following histopathological diagnosis as the presence of primary resistance mutations could preclude neoadjuvant therapy with TKIs. Provision of an adequate sample, permitting both immunohistochemical analysis and molecular genetic studies, may be challenging. MDT discussion is strongly advised in such cases.

Specimen preparation and handling is therefore somewhat dependent on site, although general principles apply. Ideally, and assuming the theatre and laboratory are well connected by a rapid delivery system, resection specimens should be received fresh (unfixed) as soon as possible after resection. The specimen is then inspected externally to locate the tumour and identify any serosal involvement. The circumferential resection margin may be marked with ink. The specimen is then opened in a manner appropriate for the anatomic location. The specimen is pinned out, if suitable or required, and fixed in the manner most appropriate for the anatomic site. If the tumour mass is very large, fixation will be facilitated by serial sectioning. The specimen should then be allowed to fix in an adequate volume of formalin for 24–48 hours. It is important to note that formalin-fixed paraffin-embedded tissue is suitable for routine mutation analysis. It is possible that other analyses, possibly research related, might require unfixed, fresh material. A sample of tissue may be taken and frozen if consent for such studies has been obtained from the patient.

4 Specimen handling and block selection

After adequate fixation, the specimen should be examined to locate the site of the tumour. The maximum tumour diameter should be measured, as should the distance to the closest surgical and circumferential resection margins. Evidence of extension into mucosa, ulceration and depth of invasion should be noted. The length of GI tract, including the tumour, should be serially sectioned at 5–10 mm intervals, and areas of necrosis, haemorrhage or myxoid change noted. Following neoadjuvant therapy, areas of unusual gross appearance may be seen including gelatinous or myxoid change and calcification. The slices should then be laid out and examined.

A permanent photographic record of the macroscopic specimen may be useful for presentation at a subsequent MDT meeting.

The following tissue blocks should be taken:

- margin – longitudinal and circumferential resection margin

- tumour – sufficient blocks of the tumour are taken to ensure that all macroscopically different areas are sampled (e.g. areas of haemorrhage or myxoid change). The number of blocks will depend on tumour size and heterogeneity. One block per centimetre of tumour diameter is recommended. These tumour blocks should include suspected mucosal infiltration/ulceration, possible blood vessel invasion, the closest circumferential margin and involvement of any adjacent organs. A block containing tumour and adjacent mucosa/muscularis propria is often useful in serving as an internal control for immunohistochemistry. A designated tumour block for molecular genetic analysis, selected for a high neoplastic cell content, may be helpful.

- one block of normal non-neoplastic tissue; more blocks may be required in cases of suspected familial GIST syndrome

- any lymph nodes identified, although involvement is seldom seen except in paediatric cases and GISTs associated with Carney syndromes

- blocks from any other co-existing macroscopic abnormality in the resected specimen or organ

- blocks from any suspected metastatic tumour synchronously resected from the liver or peritoneum.

5 Core data items

5.1 Summary

5.1.1 Clinical
- Specimen type.

- Site of tumour.

- Any previous treatment.

5.1.2 Macroscopic
- Tumour size, maximum diameter measured in centimetres or millimetres.

- Resection margins: distance of tumour to nearest longitudinal and circumferential resection margins.

- Evidence of serosal tumour rupture.

5.1.3 Microscopic
- Tumour type: spindle/epithelioid/mixed cell type.

- Mitotic count per 5 mm^2 – the total area to be counted should amount to 5 mm^2. With older microscopes, 50 high-power field (HPF) may be equivalent to 5 mm^2. However, 40x lenses in more modern microscopes have a much wider field of view and require far fewer HPFs to be surveyed (20–25) to assess the same area. The exact figure should be established by the individual user for their microscope.

- Mucosal invasion.

- Resection margins.

- In tumours treated with imatinib or other TKIs, presence of response to treatment.

5.1.4 Other
- Immunohistochemistry for CD117 (KIT) and DOG1.

- Prediction of tumour behaviour (i.e. risk category using the Armed Forces Institute of Pathology [AFIP] Lasota/Miettinen classification – see Table 1).

- Metastatic spread.

- Mutational analysis:
  - all resected moderate and high-risk GISTs of any site
  - all biopsies diagnostic of GIST prior to neoadjuvant TKI treatment
  - all biopsies from unresectable/widely metastatic GIST.

[Level of evidence – GPP.]

5.2 Clinical assessment

5.2.1 Specimen type
The type of resection specimen should be recorded, e.g. oesophagectomy, gastro-oesophagectomy, partial or total gastrectomy, small intestine resection, left or right

hemicolectomy, anterior resection or abdominoperineal resection. Gastrectomy specimens may vary from sleeve type gastrectomy specimens to partial or total gastrectomies with omental tissue. The presence of other resected organs, e.g. partial hepatectomy, must be recorded.

5.2.2 Site of tumour

The site of the tumour must be recorded. The most common sites are stomach and small intestine. Extra-gastrointestinal sites of origin are also encountered and this should be noted. Gastric GISTs generally have a better prognosis than small intestinal GISTs of similar size and mitotic activity. Oesophageal GISTs are very rare, tend to be diagnosed at a late stage and have a poorer prognosis.

5.2.3 Previous treatment

Any previous treatment should be recorded.

[Level of evidence – GPP.]

5.3 Macroscopic assessment

5.3.1 Maximum tumour diameter

There is a well-established relationship between maximum tumour diameter measured in centimetres and tumour behaviour, when taken together with mitotic count (see section 5.5.2).

5.3.2 Resection margins

The principal treatment for GISTs is surgery with wide local resection including a margin of 10–20 mm for most tumours. Radical resection such as total gastrectomy with lymphadenectomy is not required. Involvement of surgical margins may indicate a higher likelihood of local recurrence.

5.3.3 Serosal tumour rupture

While acknowledged to be a rare event, tumour rupture through a serosal/peritoneal surface is associated with a high risk of intra-abdominal recurrence of GIST and is independent of size and mitotic count in predicting survival. As such, serosal tumour rupture alone has been proposed as a defining criterion of a high-risk GIST and as an indication for adjuvant TKI therapy.

[Level of evidence – C.]

5.4 Microscopic assessment

5.4.1 Tumour type

GISTs may be of spindle cell type (70%), epithelioid type (20%) or mixed cell type (10%). Epithelioid and mixed cell types are much more common in the stomach.

5.4.2 Mitotic count

Taken together with maximum tumour dimension, mitotic count is used to predict tumour behaviour (see Table 1).

Mitotic count should be expressed as the number of mitoses per 5 mm^2. The count should be carried out in areas with the highest mitotic activity. Atypical mitotic figures are uncommon in GISTs. The proliferation marker Ki67 may be useful in assessing proliferation rate but has not been proven superior to mitotic count.

Table 1: AFIP/Lasota-Miettinen classification.

Tumour parameters		Tumour location and risk of progressive disease (metastasis or tumour-related death)			
Mitotic index	Size	Gastric	Duodenum	Jejunum/ileum	Rectum
≤5 (per 5 mm^2)*	≤2 cm	None (0%)	None (0%)	None (0%)	None (0%)
	>2–≤5 cm	Very low (1.9%)	Low (8.3%)	Low (4.3%)	Low (8.5%)
	>5–≤10 cm	Low (3.6%)	(Insufficient data)	Moderate (24%)	(Insufficient data)
	>10 cm	Moderate (10%)	High (34%)	High (52%)	High (57%)
>5 (per 5 mm^2)*	≤2 cm	(Insufficient data)	(Insufficient data)	High (limited data)	High (54%)
	>2–≤5 cm	Moderate (16%)	High (50%)	High (73%)	High (52%)
	>5–≤10 cm	High (55%)	(Insufficient data)	High (85%)	(Insufficient data)
	>10 cm	High (86%)	High (86%)	High (90%)	High (71%)

*With older microscopes, 50 HPF may be equivalent to 5 mm^2. However, 40x lenses in more modern microscopes have a much wider field of view and require far fewer HPFs to be surveyed (20–25) to assess the same area. The exact figure should be established by the individual user for their microscope.

5.4.3 Mucosal invasion

Mucosal invasion, characterised by diffuse spread of tumour cells in a 'lymphoma-like' pattern, has been associated with an adverse prognosis. This is not common.

5.4.4 Resection margins

The presence or absence of histological involvement of the circumferential and surgical margins should be recorded. If the distance measured histologically is more accurate than that measured macroscopically, it should be recorded instead.

5.4.5 Response to treatment

While surgery is the mainstay of treatment of resectable GISTs, imatinib may be used in a neoadjuvant manner in an attempt to render large or strategically placed tumours (e.g. those adjacent to the anal sphincter) resectable. The changes associated with a response to therapy include loss of cellularity, with the formation of a loose myxoid stroma and a reduction in mitotic activity or Ki67 proliferation index. Rarely, unusual changes, such as 'rhabdomyoblastic' transformation, may be seen in previously treated GISTs.

Acquired secondary resistance to TKIs is recognised and, in patients in whom there is focal clinical or radiological progression, surgical excision is appropriate therapy. In these specimens, there may be evidence of previous responsive therapy as well as a fully viable and proliferating tumour.

[Level of evidence – C.]

5.5 Other

5.5.1 Immunohistochemistry

Immunohistochemistry for CD117 (KIT) and DOG1 must be performed on every new tumour. A block of well-fixed tumour without necrosis or haemorrhage should be selected. The following immunohistochemical panel may be considered, but only CD117 and DOG1 are regarded as core data items:

- CD117: almost 95% positive

- DOG1: >95%

- CD34: 65% positive (40–72%)

- Desmin: negative (<2%)

- Smooth muscle actin: variably positive (34%)

- S100: variably positive (14%)

- Cytokeratin: very rarely positive.

Tumours morphologically typical of GISTs can be CD117 (KIT) negative by immunohistochemistry, and some of these do harbour *KIT* mutations.[19] Another third harbour *PDGFRA* mutations. CD117-negative GISTs are more commonly epithelioid and gastric. The antibody DOG1 is a useful addition to the immunohistochemistry panel as around 50% of KIT-negative tumours are positive for this marker.[20] Even when both CD117 and DOG1 are negative (approximately 1% of tumours),[20] it is legitimate to make the diagnosis of GIST on morphological grounds. However, this is a very strong indication that paraffin blocks should be referred to a centre capable of mutational analysis as a diagnostic adjunct (see section 5.5.4).

It must also be stressed that while both CD117 (KIT) and DOG1 are sensitive markers for GIST they are not specific. CD117 expression may be seen in other tumours within the differential diagnosis such as metastatic melanoma, synovial sarcoma and vascular neoplasms. Focal DOG1 expression can occur in melanomas, synovial sarcomas and leiomyosarcomas.

5.5.2 Prediction of tumour behaviour (prognostic index)

With the exception of very small tumours, all GISTs have the potential to behave aggressively. A scheme proposed under the aegis of the National Institutes of Health (NIH) defined the risk of aggressive behaviour using the twin criteria of tumour size and mitotic activity count irrespective of tumour location. A significant body of opinion holds that the NIH scheme underestimates the risk of small bowel tumours and overestimates those of gastric origin. As a result, its use in clinical practice has been replaced by one derived from the data collected by Lasota and Miettinen[21] (see Table 1). The AFIP or Lasota-Miettinen classification is based on tumour location, size (maximum dimension in centimetres) and mitotic activity (the total area to be counted should amount to 5 mm^2).

[Level of evidence – C and D.]

5.5.3 Metastatic spread

Lymph node involvement by metastatic GIST is rare, but it is good practice to submit any identified lymph nodes from resection specimens for histology. In particular, paediatric GISTs and GISTs associated with Carney syndromes are more likely to produce lymph node metastases.[22]

Direct extension of a tumour into other organs is also rare but must be recorded, especially with regard to margins.

Separately submitted specimens of peritoneal deposits of tumour and resected metastatic lesions (e.g. liver metastases) must be examined and recorded.

5.5.4 Mutational analysis

It is now clear that the precise mutation in GISTs is of prognostic and therapeutic importance both in the neoadjuvant and adjuvant treatment settings.[23]

[Level of evidence – B.]

Mutational (*KIT* and *PDGFRA*) analysis of all resected moderate-risk and high-risk GISTs, regardless of location, is recommended, as well as all diagnostic biopsies in which neoadjuvant therapy is contemplated and all biopsies of inoperable GIST.

If a patient develops recurrent GIST and is therefore being considered for TKI treatment, mutation analysis of the patient's tumour tissue is recommended if such analysis has not previously been undertaken. Mutational analysis of so-called microGISTs (<1 cm), most commonly encountered incidentally in cancer resection specimens, is not recommended.

As has been indicated, mutations of *KIT* or *PDGFRA* are detectable in over 80% of GISTs – both larger symptomatic tumours and in the common small incidental microGISTs. The largest group of *KIT* mutations (comprising around two-thirds of all *KIT* mutations) involve exon 11, which encodes the intracellular juxtamembrane domain, and are a heterogeneous group of deletions, substitutions and insertions. These correlate with the best response to imatinib. A further 15% or so affect exon 9, encoding the extracellular domain; these are mainly in frame tandem duplications. While they generally respond less well, they may respond with dose escalation of imatinib. Much smaller numbers of mutations occur in exons 13 and 17. As a general rule, primary *KIT* gene mutations are exclusive. However, in very rare cases, two or more primary mutations, most commonly in exon 11, are encountered. Correlation between mutation status and protein expression is imperfect. Some GISTs express CD117 but do not harbour *KIT* mutations, while others stain for CD117 but nevertheless have *KIT* mutations.[7,12,23,24]

A third of GISTs with a wild-type *KIT* gene have mutations in *PDGFRA*. Immunohistochemistry for PDGFα is unreliable, emphasising the value of mutational analysis. Of the 5–10% of GISTs containing *PDGFRA* mutations, the majority involve exon 18, especially within epithelioid type gastric tumours. The most common mutation (i.e. D842V) responds poorly to imatinib or sunitinib. Mutations have also been found in *PDGFRA* exons 12 and 14.

On rare occasions, GISTs with *SDH* gene mutations have been described. A subset of these are thought to be responsible for GISTs in patients with Carney syndrome and Carney-Stratakis dyad.[22] Furthermore, *BRAF* mutations have been reported in a very small subset of GISTs,[25,26] and RAS-mutated GISTs are even more rare. Immunohistochemistry for SDHB may be appropriate in certain cases but is only available in a few specialised centres.

Following TKI treatment, a broader range of unusual mutations, often associated with emerging resistance to therapy, may be discovered. These 'secondary' mutations involve other exons such as those encoding for the ATP binding pocket of the KIT receptor (exon 13 and 14) and in the KIT kinase activation loop domain (exon 17 and 18). These secondary mutations may show heterogeneity not just between metastatic deposits, but also within the same deposit. Therefore, the clinical utility of characterising secondary mutations to guide subsequent oncological management remains uncertain.

Most centres now offer mutational analysis on paraffin-embedded tissue blocks and this service should be subject to the UK NEQAS external quality assurance scheme. Mutational analysis should include assessment of primary *KIT* mutations in exons 9, 11, 13 and 17 and *PDGFRA* mutations in exons 12, 14 and 18 in the first instance. Further studies of other genes should be considered if deemed clinically appropriate.

Finally, in some cases, mutational analysis may be of direct diagnostic value. Identification of a typical mutation seen in GISTs may be of value in supporting the diagnosis of GIST,

particularly if a broader differential diagnosis had previously been considered. However, caution must be exercised in the interpretation of such data as other tumours, which may enter into the differential diagnosis of GIST such as malignant melanoma and inflammatory fibroid polyp, may harbour mutations in the *KIT* and *PDGFRA* genes, respectively.

6 Non-core data items

6.1 Macroscopic

The following items may be recorded:

- evidence of extension into mucosa, presence of mucosal ulceration and depth of invasion
- presence of necrosis.

6.2 Microscopic

The following items may be recorded:

- presence of haemorrhage
- presence of necrosis
- presence of ulceration
- lymphovascular space invasion
- lymph node status (the presence of lymph node metastases, especially with gastric epithelioid GISTs, is important in raising a suspicion of Carney's triad or Carney-Stratakis syndrome)
- other histological patterns, e.g. myxoid, nested, prominent giant cells
- adjacent cell of Cajal hyperplasia, which may indicate investigation for germ cell mutations of *KIT* or raise the possibility of NF1.

6.3 Other

Currently no molecular or other immunological markers have been accepted as superior to the AFIP/Lasota-Miettinen classification in predicting tumour behaviour. However, many other potential candidates have been proposed as alternatives or adjuncts including PDL1 expression[27] and tumour infiltrating lymphocytes.[28]

7 SNOMED coding

GISTs should be coded using the SNOMED CT system (see Appendix A). It is noted, however, that SNOMED is now in a practical transition phase, as part of the intended full implementation by the NHS and Public Health England of SNOMED CT. SNOMED ceased to be licensed by the International Health Terminology Standards Development Organisation from 26 April 2017. A list of applicable T and M SNOMED and SNOMED CT codes is provided in Appendix B. Mapping SNOMED CT terminology is provided.

8   Tumour staging

A staging system for GIST has been published by the Union for International Cancer Control (UICC).[29] However, it remains to be seen whether TNM staging of tumours confers any further useful information with regard to the treatment of patients when compared with current systems of prediction of tumour behaviour and mutational analysis of this group of tumours. While there is insufficient evidence to mandate the use of TNM at this time, it may provide useful additional information and so we include the TNM staging as an appendix (Appendix D).

9   Reporting of small biopsy specimens

The main aim in reporting a biopsy from a suspected (or unsuspected) GIST is to make the diagnosis, and only in unusual circumstances when mitoses may be very prominent would an attempt at prognostication be possible. Clearly, however, imaging of the lesion may give the requisite size that would allow a good estimate of the likely behaviour. With endoscopic biopsies, the difficulties often relate to the biopsy being too superficial or consisting of mucosa or ulcer slough. When neoadjuvant treatment with TKIs is planned, biopsy material is generally suitable for mutational analysis and this is recommended.

10   Reporting of post-neoadjuvant treatment resection specimens

The clinical setting of neoadjuvant TKI therapy should be clearly indicated on the request form. These resection specimens should be handled, dissected and blocked as for untreated resections. It should be noted that treated tumours may be smaller and atypical in gross appearance often with gelatinous change on the cut surface. There will be particular clinical interest in the resection margin status as preservation of anatomical function is a common clinical driver for neoadjuvant therapy. A thorough sampling of zones of divergent gross appearance may be helpful.

Microscopic changes including paucicellularity, myxoid degeneration and calcification are common. Alterations in CD117 expression, including complete loss of expression, may occur. Dedifferentiated histological components may be discovered with anaplastic or rhabdomyosarcomatous changes. Secondary resistance mutations may be seen on mutational analysis.

11   Multidisciplinary team meetings

All cases of GIST should be discussed at an appropriate MDT meeting. These are usually the upper GI MDT meetings but some cases may be discussed at the lower GI or sarcoma MDTs.

12   Criteria for audit

The following are suggested as some of the criteria that might be used in periodic reviews of GIST reporting:

- completeness of histopathology reports expressed as an average proportion of the core data items recorded, or as a proportion of the reports that successfully include 100% of the items. The standard is that all reports contain 100% of the items.

- the number (or proportion) of cases referred for mutational analysis

- the mutational spectrum of GISTs (for centres doing routine mutational analysis).

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Appendix A   SNOMED coding

Topography

Tumour site	SNOMED 2/3 code	SNOMED CT terminology	SNOMED CT code
Oesophagus	T-62000/T-56000	Entire oesophagus (body structure)	181245004
Stomach	T-63000/T-57000	Entire stomach (body structure)	181246003
Small intestine	T-64000/T-58000	Entire small intestine (body structure)	181250005
Duodenum	T-64300/T-58000	Entire duodenum (body structure)	181247007
Jejunum	T-65100/T-58400	Entire jejunum (body structure)	181248002
Ileum	T-65200/T-58600	Entire ileum (body structure)	181249005
Appendix	T-66000/T-59200	Entire appendix (body structure)	181255000
Colon	T-67000/T-59300	Entire colon (body structure)	302508007
Rectum	T-68000/T-59600	Entire rectum (body structure)	181261002
Anus	T-69000/T-59900	Entire anus (body structure)	181262009
Peritoneum	T-Y4400/T-D4400	Entire peritoneum (serous membrane) (body structure)	362698002
Omentum	T-63850/T-D4600	Entire omentum (body structure)	362710002
Liver	T-56000/T-62000	Entire liver (body structure)	181268008

Morphology

Morphological codes	SNOMED 2/3/ ICD-O code	SNOMED CT terminology	SNOMED CT code
Gastrointestinal stromal tumour, malignant	M89363	Gastrointestinal stromal sarcoma (morphologic abnormality)	128756002

Procedure

Local P codes should be recorded. At present, P codes vary according to the SNOMED system in use in different institutions.

Appendix B   Reporting proforma for gastrointestinal stromal tumours

Surname: …………………………Forenames:………………………Date of Birth: ………………Sex:….……..

Hospital:………………….…………….Hospital No: …………………..……NHS No:……………………..

Date of Surgery: ………………..…Date of Report Authorisation: …………….Report No:………………………...

Date of Receipt:…………………...Pathologist:………………………………Clinician:…………………….......

Macroscopic

Specimen type   …………………………..

Site of tumour   …………………………..

Maximum tumour dimension   ……………………… cm

Distance of tumour to nearest longitudinal resection margin   …………………cm

Distance of tumour to closest circumferential resection margin   …………………cm

Serosal tumour rupture   Present   Not identified

Microscopic

Tumour type   Spindle   Epithelioid   Mixed cell type

Mitotic count   ………………… /5 mm^2*

Mucosal invasion   Not applicable   Present   Not identified

Involvement of longitudinal margins   Yes   No

Involvement of circumferential margins   Yes   No

Features indicating a response to treatment   Not applicable   Present   Not identified

Metastatic spread

Number of lymph nodes present   …………………………..

Number of lymph nodes positive   …………………………..

Peritoneal metastasis   Present   Not identified

Liver metastasis   Present   Not identified

Other metastasis (specify)   …………………………..

Immunohistochemistry

CD117   Positive   Negative   Not tested

DOG1   Positive   Negative   Not tested

AFIP/Lasota-Miettinen risk category

None   Very low   Low   Moderate   High

Mutational analysis

Mutational analysis requested   Yes   No

The result when available will be issued in a supplementary report.

SNOMED codes   …………………

Signature………………………   **Date**……………………..

*With older microscopes, 50 HPF may be equivalent to 5 mm^2. However, 40x lenses in more modern microscopes have a much wider field of view and require far fewer HPFs to be surveyed (20–25) to assess the same area. The exact figure should be established by the individual user for their microscope.

Appendix C   Reporting proforma for gastrointestinal stromal tumours in list format

Element name	Values	Implementation notes
Specimen type	Free text	
Site of tumour	Free text	
Maximum tumour dimension	Size in cm	
Distance of tumour to nearest longitudinal resection margin	Size in cm	
Distance of tumour to nearest circumferential resection margin	Size in cm	
Serosal tumour rupture	Single selection value list: • Present • Not identified	
Tumour type	Single selection value list: • Spindle • Epithelioid • Mixed cell type	
Mitotic count (per 5 mm^2)	Integer	
Mucosal invasion	Single selection value list: • Not applicable • Present • Not identified	
Involvement of longitudinal margins	Single selection value list: • Yes • No	
Involvement of circumferential margins	Single selection value list: • Yes • No	
Features indicating a response to treatment	Single selection value list: • Not applicable • Present • Not identified	
Number of lymph nodes present	Integer	
Number of lymph nodes positive	Integer	
Peritoneal metastasis	Single selection value list: • Present • Not identified	
Liver metastasis	Single selection value list:	

	• Present • Not identified	
Other metastasis	Single selection value list: • Present • Not identified	
Other metastasis, specify	Free text	Only applicable if 'Other metastasis, Present' is selected.
Immunohistochemistry performed, CD117	Single selection value list: • Positive • Negative • Not tested	
Immunohistochemistry performed, DOG1	Single selection value list: • Positive • Negative • Not tested	
AFIP/Lasota-Miettinen risk category	Single selection value list: • None • Very low • Low • Moderate • High	
Mutational analysis requested	Single selection value list: • Yes • No	
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.	

Appendix D   TNM staging for gastrointestinal stromal tumours (UICC TNM8)

Primary tumour (T)

TX   Primary tumour cannot be assessed

T0   No evidence for primary tumour

T1   Tumour 2 cm or less

T2   Tumour more than 2 cm but not more than 5 cm

T3   Tumour more than 5 cm but not more than 10 cm

T4   Tumour more than 10 cm in greatest dimension

Regional lymph nodes (N)

NX   Regional lymph nodes cannot be assessed*

N0   No regional lymph node metastasis

N1   Regional lymph node metastasis

Note: *NX: Regional lymph node involvement is rare for GISTs, so cases in which the nodal status is not assessed clinically or pathologically could be considered N0 instead of NX or pNX.

Distant metastasis (M)

M1   Distant metastasis

Histopathological grading (G)

Grading for GISTs is dependent on mitotic rate:*

Low mitotic rate: 5 or fewer per 5 mm^2

High mitotic rate: Over 5 per 5 mm^2

Note: *With older microscopes, 50 high power field (HPF) may be equivalent to 5 mm^2. However, 40x lenses in more modern microscopes have a much wider field of view and require far fewer HPFs to be surveyed (20–25) to assess the same area. The exact figure should be established by the individual user for their microscope.

Stage

Note: *Staging criteria for gastric tumours can be applied in primary, solitary omental GISTs. Staging criteria for intestinal tumours can be applied to GISTs in less common sites such as oesophagus, colon, rectum and mesentery.

Gastric GIST*

Stage	T	N	M	Mitotic rate
Stage IA	T1, T2	N0	M0	Low
Stage IB	T3	N0	M0	Low
Stage II	T1, T2	N0	M0	High
	T4	N0	M0	Low
Stage IIIA	T3	N0	M0	High
Stage IIIB	T4	N0	M0	High
Stage IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate

Small intestinal GIST*

Stage	T	N	M	Mitotic rate
Stage I	T1, T2	N0	M0	Low
Stage II	T3	N0	M0	Low
Stage IIIA	T1	N0	M0	High
	T4	N0	M0	Low
Stage IIIB	T2, T3, T4	N0	M0	High
Stage IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate

Appendix E Summary table – explanation of grades of evidence

(modified from Palmer K *et al. BMJ* 2008;337:1832)

Grade (level) of evidence	Nature of evidence
Grade A	At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target cancer type or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target cancer type.
Grade B	A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in A.
Grade C	A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high-quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in B.
Grade D	Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix F AGREE II guideline monitoring sheet

The cancer datasets of the Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this dataset that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Introduction
2 The health question(s) covered by the guideline is (are) specifically described	Introduction
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6 The target users of the guideline are clearly defined	Introduction
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword and Introduction
12 There is an explicit link between the recommendations and the supporting evidence	2–11
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	2–11
16 The different options for management of the condition or health issue are clearly presented	2–11
17 Key recommendations are easily identifiable	2–11
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Appendices A–D
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	12
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interests of guideline development group members have been recorded and addressed	Foreword