Histopathology

Histopathology 2023, **82**, 376–384. DOI: 10.1111/his.14791

REVIEW

Dataset for reporting of gastrointestinal stromal tumours: recommendations from the International Collaboration on Cancer Reporting (ICCR)

Jason L Hornick,[1] Fleur Webster,[2] Angelo Paolo Dei Tos,[3,4] Chris Hemmings,[5,6] Markku Miettinen,[7] Yoshinao Oda,[8] Chandrajit P Raut,[9,10,11] Brian P Rubin,[12] Margaret Von Mehren,[13] Eva Wardelmann[14] & Christopher D M Fletcher[1]

[1]*Department of Pathology, Brigham and Women's Hospital, Harvard Medical School,* [9]*Department of Surgery, Brigham and Women's Hospital,* [10]*Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute,* [11]*Harvard Medical School, Boston, MA,* [7]*Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, National Institutes of Health Bethesda, Bethesda, MD,* [12]*Department of Cancer Biology, Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, OH,* [13]*Department of Hematology and Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA,* [2]*International Collaboration on Cancer Reporting, Sydney, NSW, Australia,* [3]*Department of Pathology, Azienda Ospedaliera Universitaria di Padova, Padova,* [4]*Department of Medicine, University of Padua School of Medicine, Padua, Italy,* [5]*Department of Anatomic Pathology, Canterbury Health Laboratories,* [6]*Department of Pathology and Biomedical Science, Christchurch Clinical School, University of Otago School of Medicine, Christchurch, New Zealand,* [8]*Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan and* [14]*Gerhard-Domagk-Institute of Pathology, University of Münster, Münster, Germany*

Hornick J L, Webster F, Dei Tos A P, Hemmings C, Miettinen M, Oda Y, Raut C P, Rubin B P, Von Mehren M, Wardelmann E & Fletcher C D M

(2023) *Histopathology* **82**, 376–384. https://doi.org/10.1111/his.14791

Dataset for reporting of gastrointestinal stromal tumours: recommendations from the International Collaboration on Cancer Reporting (ICCR)

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal tract and are among the most frequent sarcomas. Accurate diagnosis, classification, and reporting are critical for prognostication and patient management, including selection of appropriate targeted therapy. Here we report on international consensus-based datasets for the pathology reporting of biopsy and resection specimens of GIST. The datasets were produced under the auspices of the International Collaboration on Cancer Reporting (ICCR), a global alliance of major international pathology and cancer organizations. An international expert panel consisting of pathologists, a surgical oncologist, and a medical oncologist produced a set of core and noncore data items for biopsy and resection specimens based on a critical review and discussion of current evidence. All professionals involved were subspecialized soft tissue tumour experts and affiliated with tertiary referral centres. Commentary was provided for each data item to explain its clinical relevance and the rationale for selection as a core or noncore element. Following international public consultation, the datasets, which include synoptic reporting guides, were finalized and ratified, and published on the ICCR website. These first international datasets for GIST are intended to promote high-quality, standardised pathology reporting. Their widespread adoption will improve consistency of reporting, facilitate multidisciplinary communication, and enhance comparability of data, all of which will ultimately help to improve the management of patients with GIST. All the ICCR datasets, including these on GIST, are freely available worldwide on the ICCR website (www.iccr-cancer.org/datasets).

Address for correspondence: Professor J L Hornick, Professor of Pathology, Harvard Medical School. Director of Surgical Pathology and Immunohistochemistry, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115 USA. e-mail: jhornick@bwh.harvard.edu

Keywords: Checklist, dataset, protocol, synoptic report, guidelines, gastrointestinal stromal tumour, receptor tyrosine kinase, mutations

Introduction

Pathology structured reporting of cancer resection specimens provides essential information for patient management, clinical trials, tissue-based research, and cancer registries. Given the central role of pathology data in cancer care at an individual and population level, standardised and structured pathology reporting is critical to ensure that relevant information is complete and unambiguous and is delivered in a user-friendly format.

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal tract. GISTs range from minute, usually incidental and clinically insignificant lesions, to aggressive sarcomas; the latter are among the most common sarcoma types in adults. Diagnosis is generally straightforward upon histological review, in conjunction with the application of immunohistochemistry (IHC) using the Cajal cell lineage markers KIT (CD117) and DOG1 (ANO1). Assessment of the risk for malignant behaviour relies upon careful evaluation of clinical and pathologic features, chiefly including anatomic site, tumour size, and mitotic rate. The vast majority of GISTs are driven by activating mutations in *KIT* and *PDGFRA*, genes that encode transmembrane tyrosine kinase receptors; around 5% of GISTs are instead driven by inactivation of the succinate dehydrogenase (SDH) complex. Other molecular genetic drivers are rare. The specific underlying genetic alterations in clinically aggressive tumours predict response to (and therefore direct selection of) particular tyrosine kinase inhibitors; such therapies are administered not only to patients with metastatic disease but often for patients with "high risk" tumours in the neoadjuvant setting (to facilitate more limited resection) or following excision of localised tumours.

Several organizations, such as the College of American Pathologists (CAP) and the Royal College of Pathologists (RCPath), have independently developed datasets for pathology reporting of GIST.[1–3] The International Collaboration on Cancer Reporting (ICCR) coordinates the production of evidence-based international pathology reporting datasets with a consistent style and containing all the parameters needed to guide patient management. The ICCR is a collaboration of multiple pathology organizations and has alliances with international cancer organizations, including the International Agency for Research on Cancer (IARC), the Union for International Cancer Control (UICC), and the American Joint Committee on Cancer (AJCC).

Here we report on the development of the datasets for the pathology reporting of GIST, both on biopsy and resection specimens, and discuss the rationale for the inclusion of data items.

Methods

The ICCR developed a set of standard operating procedures for the process of dataset development and has also defined the selection process, roles, and responsibilities of the Chair, expert panel members, the ICCR Dataset Steering Committee representative(s) on the panel, ICCR Series Champion, and the Project Manager (http://www.iccr-cancer.org/datasets/dataset-development). The ICCR Series Champion provided guidance and support to the Chair of the Dataset Authoring Committee (DAC) regarding ICCR standards and ensured harmonization across the bone and soft-tissue suite of datasets. An international expert panel consisting of pathologists, a surgical oncologist, and a medical oncologist was established. Initial draft documents were produced by the Project Manager and Chair after assessment of core and noncore data items within existing international datasets for GIST. These drafts were circulated to the DAC and individual dataset items discussed at a series of coordinated videoconferences, following which an agreed version of the revised datasets was posted for open international consultation on the ICCR website for a period of 2 months. All comments received were then discussed by the DAC, and, where there was universal agreement from DAC members, resultant changes were incorporated into the datasets. The final datasets were ratified by the ICCR Dataset Steering Committee prior to publication. All the ICCR datasets, including these on GIST, are freely available worldwide on the ICCR website (www.iccr-cancer.org/datasets).

Results

SCOPE

Two separate ICCR datasets were developed for the pathology reporting of biopsy and resection specimens

for GIST. Metastatic GIST specimens were excluded from these datasets.

CORE ELEMENTS

Core elements are those that are essential for the clinical management, staging, or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council [NHMRC] levels of evidence[4]). In some circumstances, where level III-2 evidence is not available, an element may be made a core element where there is unanimous agreement of the DAC. The summation of all core elements is considered to be the minimum reporting standard for a specific cancer.

A summary of the core elements for each of the GIST datasets is outlined in Table 1 (biopsy specimens) and Table 2 (resection specimens), and each is described in further detail below.

Relevant syndrome

GISTs may arise in the setting of familial or nonfamilial syndromes. Familial syndromes include Carney–Stratakis syndrome (germline mutations in *SDHX* genes; affected patients develop gastric GISTs and extra-adrenal paragangliomas), neurofibromatosis type 1 (germline mutation in *NF1*; most GISTs in this setting arise in the small intestine), and familial GIST syndrome (germline mutation in *KIT* or *PDGFRA*).[5–8] The Carney triad is a nonfamilial syndrome most often driven by the *SDHC* promoter hypermethylation; this syndrome usually affects young women and is characterised by succinate dehydrogenase (SDH)-deficient gastric GIST, extra-adrenal paragangliomas, and pulmonary chondromas.[9,10] Clinical behaviour, therapy, and follow-up of GISTs in these syndromes are different from sporadic GISTs.

Table 1. Core elements for the pathology reporting of gastrointestinal stromal tumour – Biopsy specimens

CORE
Relevant syndrome
Operative procedure
Tumour site
Histological tumour type
Mitotic count
Ancillary studies

Table 2. Core and noncore elements for the pathology reporting of gastrointestinal stromal tumour – Resection specimens

CORE	NONCORE
Relevant syndrome	Neoadjuvant therapy
Operative procedure	Necrosis
Tumour site	Lymphovascular invasion
Tumour focality	Response to neoadjuvant therapy
Maximum tumour dimension	Lymph node status
Histological tumour type	Coexistent pathology
Mitotic count	Pathological staging
Tumour rupture	
Risk assessment	
Margin status	
Ancillary studies	
Histologically confirmed metastases	

Operative procedure

Depending on the anatomic location, GIST may be first sampled by core-needle biopsy, fine-needle aspiration (FNA) biopsy, or, for superficially located tumours, endoscopic biopsy. It is important that sufficient tumour tissue is obtained from the biopsy for IHC and molecular genetic analysis. If an FNA biopsy is obtained, a cell block should be prepared for IHC. It is not uncommon for endoscopic biopsies to obtain only uninvolved mucosa and/or ulcer bed without diagnostic tumour tissue; a repeat biopsy (or resection) may be required for definitive diagnosis.

The type of resection varies based on the anatomic site of involvement. Gastric primary GISTs may often be managed by a local or wedge resection with excision of limited uninvolved stomach; for large tumours, subtotal or total gastrectomy or oesophagogastrectomy may be required, depending on the specific location. GISTs of the small intestine (nonduodenal) are typically managed by segmental resection. Duodenal primary GISTs may require pancreatoduodenectomy (i.e. Whipple procedure). Depending on the tumour size and precise location, rectal primary GISTs may be managed by local excision, low anterior resection, or abdominoperineal resection. Rare primary colonic GISTs may be managed by right colectomy or segmental colectomy of other parts of the colon. Oesophageal

primary GISTs may be managed by local excision (for small tumours) or oesophagectomy. The dataset should also document other resected organs. Preoperative therapy may facilitate more limited resection, especially for oesophageal, duodenal, and rectal tumours.

Tumour site

GISTs most often arise in the stomach and nonduodenal small intestine, followed by the rectum and duodenum; primary GISTs of the oesophagus and colon are rare. Other sites may include the appendix and pancreas; however, these locations are exceptionally rarely involved. It is often difficult (or impossible) for the surgeon and the pathologist to distinguish between the jejunum and ileum, and there is no known prognostic difference for tumours arising at these sites; for these reasons, 'small intestine (nonduodenal)' is applied instead of jejunum or ileum.

So-called extragastrointestinal stromal tumours (EGISTs) are exceptionally rare and may present in the omentum, mesentery, or retroperitoneum; in some cases, attachment to the stomach or small intestine can be documented, whereas in other cases, no connection can be identified.[11,12] Many EGISTs likely represent gastric or small intestinal GISTs that arose from the outer layer of the wall and lost attachment to the respective organ.

The primary anatomic site is an important prognostic parameter; for example, gastric primary GISTs generally have a lower risk of metastasis than small intestinal GISTs.[13,14] For this reason, it is critical to specify the location as accurately as possible.

Tumour focality

Multifocal tumours are often associated with syndromic predisposition, such as neurofibromatosis type 1, Carney triad, and familial GIST syndrome.[5–8] However, minute gastric GISTs (so-called 'microGISTs' <1 cm) are common in the general population,[15,16] and may therefore accompany GISTs that present clinically in the absence of a tumour syndrome. Tumour focality is determined based on combined macroscopic and microscopic assessment. In the case of multiple synchronous tumours, the number of tumours should be recorded. A single dataset should be completed, in which the site and dimensions of the individual tumours are recorded; staging should be based on the largest tumour.

In some cases, it may be difficult to distinguish multifocality from metastatic disease; multifocal tumours most often arise in the muscularis propria, whereas metastases usually present on the serosa or within the mesentery or omentum.

Maximum tumour dimension

Tumour size is a critical parameter for assessment of risk of malignant behaviour. For multifocal tumours, a range of sizes should be reported.

Histological tumour type

Histological diagnosis is based on the 2020 World Health Organization (WHO) Classification of Soft Tissue and Bone Tumours, 5th edition.[17] GISTs are most often of spindle cell type, followed by epithelioid type and mixed epithelioid and spindle cell type[17]; the latter two histological types are most common in the stomach. The histological tumour type may be associated with mutational status (e.g. most *PDGFRA*-mutant GISTs are of epithelioid type)[18] or particular syndromes (e.g. Carney triad and Carney–Stratakis syndrome-associated GISTs are usually of epithelioid or mixed type),[10] although this is not always the case.

Pleomorphic morphology in GIST is rare (<2%).[19] Dedifferentiated GIST, defined as the abrupt transition from conventional spindle cell or epithelioid GIST to an anaplastic sarcomatous appearance, usually accompanied by loss of the expression of lineage markers (e.g. KIT and ANO1/DOG1), is exceptionally rare.[20]

Mitotic count

Mitotic count is the most important feature for the assessment of risk of malignant behaviour.[21] The mitotic count should be determined in the most mitotically active area of the tumour. The mitotic count should be reported per 5 mm^2. With older microscopes, 5 mm^2 is equivalent to 50 high-power fields (HPF). However, with most modern microscopes with wider fields, 5 mm^2 requires 20–25 HPFs using 40× lenses. The number of fields required to be counted to encompass 5 mm^2 should be calculated on individual microscopes.

In small biopsy specimens, mitotic count often cannot be reliably assessed. In such cases, it is appropriate to include a disclaimer statement to that effect, for example: "accurate assessment of mitotic count cannot be made based on this limited biopsy sample and is deferred to surgical resection." However, if the mitotic count in a limited biopsy sample is high, that information is helpful for prognostication.

Effective neoadjuvant tyrosine kinase inhibitor therapy limits the ability to accurately determine mitotic count; in such cases, it is appropriate to use 'cannot be assessed,' with an explanation.

Tumour rupture and risk assessment

The risk of malignant behaviour in GIST is associated with anatomic site, mitotic rate, and tumour size. Tumour rupture is associated with a particularly high

risk of recurrence.[22] Risk assessment plays a critical role for predicting metastatic potential in the management and follow-up of patients with GIST.[23] For example, patients with GISTs who are determined to be of moderate or high risk are often treated with adjuvant imatinib mesylate, following resection of localised primary tumours.

The most widely used risk assessment system was developed by Miettinen and Lasota (2006) (see Table 3),[21] which has been adopted by the WHO and many other organizations. Alternative risk assessment systems include prognostic nomograms and contour maps, which are quite often used by clinicians.[23–25]

Assessing the risk of malignant behaviour based on limited biopsy material is inaccurate in a large subset of cases, most often in gastric tumours, due to underestimates of mitotic activity (see section on *Mitotic count*).[26]

This risk assessment system should not be applied to SDH-deficient GISTs[27] or GISTs in patients with neurofibromatosis type 1 or other syndromes (*PDGFRA*-mutant syndrome, *KIT*/*PDGFRA* germline mutations, *BRAF* mutation).

Risk assessment cannot be determined following neoadjuvant therapy, since the mitotic count cannot be accurately determined in this context. It is also inappropriate to apply risk assessment to metastatic tumours.

Margin status

GISTs rarely recur locally at precisely the primary surgical site, even following excision with narrow margins. Surgical margins vary based on primary anatomic site for GISTs, in large part owing to anatomic constraints and surgical approaches. For example, narrow margins (several millimetres) are adequate for gastric GISTs; wedge resections are often sufficient for GISTs in the stomach. Since small intestinal GISTs are managed by segmental resection, the margins in such cases are typically greater. Because of anatomic constraints around the duodenum, a Whipple procedure (with wide surgical margins) is sometimes required. Resection of primary rectal GISTs often results in narrow circumferential (radial) margins; GISTs at this site are associated with a higher risk of local recurrence in the pelvis.

Ancillary studies

IHC plays a critical role in confirming the diagnosis of GIST. The tyrosine kinase receptor KIT (CD117) and the chloride channel ANO1 (DOG1), markers of interstitial cells of Cajal lineage, are highly sensitive and specific markers for GIST.[28–30] KIT expression is observed in 95% of cases, most often with a cytoplasmic staining pattern; a paranuclear dot-like or membranous pattern may also be seen. DOG1 is helpful to confirm the diagnosis in KIT-negative GISTs and those with weak or limited staining.[30,31] KIT-negative GISTs (and those with weak or limited staining for KIT) most often harbour *PDGFRA* mutations.[32,33] SDH-deficient GISTs show loss of staining for SDHB, irrespective of which *SDHX* gene is mutated (or if there is *SDHC* promoter hypermethylation; see

Table 3. Risk assessment for primary gastrointestinal stromal tumours

Tumour parameters		Risk of progressive disease[a] (%)			
Mitotic rate	Size	Gastric	Duodenum	Jejunum/Ileum	Rectum
≤5 per 5 mm^2	≤2 cm	None (0%)	None (0%)	None (0%)	None (0%)
	>2 to ≤5 cm	Very low (1.9%)	Low (8.3%)	Low (4.3%)	Low (8.5%)
	>5 to0 cm	Low (3.6%)	(Insufficient data)[b]	Moderate (24%)[b]	(Insufficient data)
	>10 cm	Moderate (10%)	High (34%)	High (52%)	High (57%)
>5 per 5 mm^2	≤2 cm	None[b]	(Insufficient data)	High[b]	High (54%)
	>2 to ≤5 cm	Moderate (16%)	High (50%)	High (73%)	High (52%)
	>5 to ≤10 cm	High (55%)	(Insufficient data)	High (85%)	(Insufficient data)
	>10 cm	High (86%)	High (86%)	High (90%)	High (71%)

Modified version reprinted from Semin Diagn Pathol, 23 (2), Miettinen M and Lasota J, Gastrointestinal stromal tumours: pathology and prognosis at different sites, Pages 70–83 (2006), with permission from Elsevier.[21]

[a]Defined as metastasis or tumour-related death.

[b]Denotes small number of cases.

below).[34,35] SDHB IHC can therefore be used to confirm the diagnosis of SDH-deficient GIST. SDHA loss is only observed in *SDHA*-mutant GISTs.[36] Despite the lack of *KIT* mutations, SDH-deficient GISTs are typically strongly positive for KIT (and DOG1).

KIT mutations are found in about 75% of GISTs, most often in exon 11 (66% overall) and exon 9 (6%); mutations in exon 13, exon 17, and other locations are rare (see Figure 1).[37,38] *PDGFRA* mutations are identified in 10–15% of GISTs, most often in exon 18 (10–12% overall; the most common is p.D842V), rarely in exon 12 or exon 14.[39,40] Genotype predicts the response to tyrosine kinase inhibitor therapy; for example, *KIT* exon 11-mutant GISTs have the best response to imatinib mesylate, whereas GISTs with *PDGFRA* D842V mutations show primary imatinib resistance, although such tumours respond to the tyrosine kinase inhibitor avapritinib.[41,42]

SDH-deficient GISTs account for about 5% of GISTs overall, including the majority of gastric GISTs that lack *KIT* and *PDGFRA* mutations and most tumours occurring in paediatric patients.[43] SDH-deficient GISTs typically show indolent behaviour, often with late and slowly progressive metastases, and show limited response to imatinib. As mentioned previously, conventional risk stratification systems do not apply to SDH-deficient GISTs.[27] SDH-deficient GISTs are often associated with germline mutations in *SDHA*, *SDHB*, *SDHC*, or *SDHD*; these mutations are sometimes associated with Carney–Stratakis syndrome (the dyad of gastric GIST and paraganglioma).[6] SDH-deficient GISTs that lack *SDHX* mutations usually show hypermethylation of the *SDHC* promoter; this epigenetic dysregulation is characteristic of the Carney triad (SDH-deficient GIST, paraganglioma, and pulmonary chondroma).[44]

Other genetic alterations in GIST are rare; these include *BRAF* V600E and *EGFR* mutations; biallelic *NF1* inactivation; and tyrosine kinase receptor gene rearrangements.[45,46]

Histologically confirmed metastases

GIST most often metastasizes to the peritoneum (serosa or omentum) and liver. Spread to other distant sites is rare outside of the setting of advanced, long-standing disease.

NONCORE ELEMENTS

Noncore elements are those that were unanimously agreed by the DAC to be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management. A summary of the noncore elements for resection specimens is outlined in Table 2 and each is described below. Note, there are no noncore elements for biopsy specimens.

Neoadjuvant therapy

In some cases, resection of GIST will be performed following neoadjuvant therapy with tyrosine kinase inhibitors (e.g. imatinib mesylate). Such approaches may be used for reducing tumour size to facilitate resection.

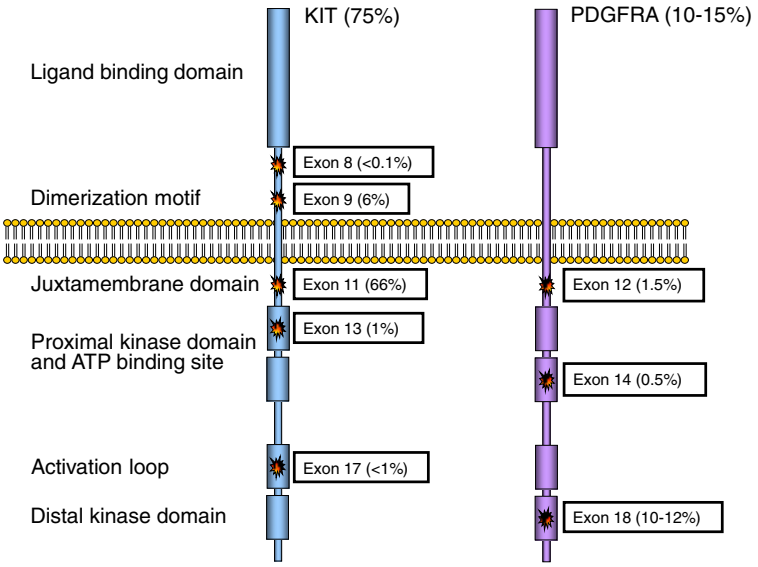

Figure 1. Distribution of *KIT* and *PDGFRA* mutations in gastrointestinal stromal tumours. Permission courtesy of Professor Jason L. Hornick.

Necrosis
The presence of necrosis is not associated with clinical behaviour in GIST. Neoadjuvant therapy may be associated with necrosis; however, most often, treated tumours show decreased cellularity and extensive hyalinised fibrotic or myxoid stroma.

Lymphovascular invasion
Lymphovascular invasion is most often seen in SDH-deficient GIST[43]; this finding is rare in *KIT* and *PDGFRA*-mutant GISTs.

Response to neoadjuvant therapy
Effective neoadjuvant tyrosine kinase inhibitor therapy is typically associated with markedly decreased cellularity and the presence of extensive hyalinised fibrotic or myxoid stroma[47]; less often, necrosis is seen. Highly cellular, mitotically active tumour is an indicator of no response; this may be seen as a clonal event within a tumour that otherwise shows extensive treatment effect. Such a finding should be documented.

Lymph node status
Lymph node metastases are rarely observed in GIST, other than for SDH-deficient tumours; such tumours frequently spread to regional lymph nodes.[27,43] Finding lymph node metastases should prompt evaluation for SDH deficiency.

Coexistent pathology
Coexistent pathology might include inflammatory conditions of the stomach, such as *Helicobacter pylori* gastritis or chronic atrophic (autoimmune) gastritis.

Pathological staging
The primary tumour T category in the TNM classification of the UICC[48] and the AJCC[49] includes the same size cutoffs as the risk assessment system developed by Miettinen and Lasota (2006).[21]

Lymph node metastases are often associated with SDH-deficient GISTs, but are rarely seen with *KIT* or *PDGFRA*-mutant GISTs.

GISTs most often metastasize to the liver and peritoneum. Other distant metastatic sites are rare, other than in patients with longstanding, advanced disease.

This staging system should not be applied to syndromic GISTs, which are often multifocal at presentation and usually show indolent behaviour.

Discussion

Here we report on the development and content of datasets for the pathology reporting of biopsy and resection specimens of GIST, which represents a consensus of an international, multidisciplinary group of GIST experts working in tertiary referral centres for this tumour type. The current evidence, including the relevant literature and existing guidelines, was carefully considered for the construction of these datasets.

The use of standardised reporting templates is not supported by all pathologists; application of such templates may be time-consuming and constrain reporting in cases of diagnostic uncertainty where nuance is needed.[50] However, it is widely recognised that structured pathology reporting ensures a more consistent, complete, and detailed diagnosis, thereby promoting better informed treatment decisions and patient outcomes.[51–53] Structured reporting facilitates data extraction by cancer registries and enables artificial intelligence-based studies. Utilization of standardised reporting will increase when supported by all members of a multidisciplinary team and compatible with laboratory and clinical information systems.

In summary, we here present two international datasets for standardised reporting of GIST, in order to improve diagnosis, prognostication, therapy, and outcome for affected patients.

Author Contributions

JLH wrote the article. All authors participated in discussions about the content and edited the article.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of Interest

None.

Conflict of Interest

The authors report no relevant conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article, as no datasets were generated or analysed during the current study.

References

1. Royal College of Pathologists. 2020. Dataset for histopathological reporting of gastrointestinal stromal tumours. Available from: https://www.rcpath.org/uploads/assets/6741f729-adf6-4ee6-b06144967e2d734a/g103-Dataset-for-histopathological-reporting-of-gastrointestinal-stromal-tumours.pdf (Accessed 16th June 2022).
2. College of American Pathologists. 2021. Protocol for the Examination of Biopsy Specimens From Patients With Gastrointestinal Stromal Tumor (GIST). Available from: https://documents.cap.org/protocols/Stomach.GIST.Bx_4.2.0.0.REL_CAPCP.pdf (Accessed 16th June 2022).
3. College of American Pathologists. 2021. Protocol for the Examination of Resection Specimens From Patients With Gastrointestinal Stromal Tumor (GIST). Available from: https://documents.cap.org/protocols/Stomach.GIST_4.2.0.0.REL_CAPCP.pdf (Accessed 16th June 2022).
4. Merlin T, Weston A, Tooher R. Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Med. Res. Methodol.* 2009; **9**; 34.
5. Maeyama H, Hidaka E, Ota H *et al*. Familial gastrointestinal stromal tumor with hyperpigmentation: association with a germline mutation of the c-kit gene. *Gastroenterology* 2001; **120**; 210–215.
6. Pasini B, McWhinney SR, Bei T *et al*. Clinical and molecular genetics of patients with the Carney-Stratakis syndrome and germline mutations of the genes coding for the succinate dehydrogenase subunits SDHB, SDHC, and SDHD. *Eur. J. Hum. Genet.* 2008; **16**; 79–88.
7. Andersson J, Sihto H, Meis-Kindblom JM, Joensuu H, Nupponen N, Kindblom LG. NF1-associated gastrointestinal stromal tumors have unique clinical, phenotypic, and genotypic characteristics. *Am. J. Surg. Pathol.* 2005; **29**; 1170–1176.
8. Miettinen M, Fetsch JF, Sobin LH, Lasota J. Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. *Am. J. Surg. Pathol.* 2006; **30**; 90–96.
9. Carney JA. Gastric stromal sarcoma, pulmonary chondroma, and extra-adrenal paraganglioma (Carney triad): natural history, adrenocortical component, and possible familial occurrence. *Mayo Clin. Proc.* 1999; **74**; 543–552.
10. Zhang L, Smyrk TC, Young WF Jr, Stratakis CA, Carney JA. Gastric stromal tumors in Carney triad are different clinically, pathologically, and behaviorally from sporadic gastric gastrointestinal stromal tumors: findings in 104 cases. *Am. J. Surg. Pathol.* 2010; **34**; 53–64.
11. Miettinen M, Felisiak-Golabek A, Wang Z, Inaguma S, Lasota J. GIST manifesting as a retroperitoneal tumor: clinicopathologic immunohistochemical, and molecular genetic study of 112 cases. *Am. J. Surg. Pathol.* 2017; **41**; 577–585.
12. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors presenting as omental masses—a clinicopathologic analysis of 95 cases. *Am. J. Surg. Pathol.* 2009; **33**; 1267–1275.
13. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am. J. Surg. Pathol.* 2005; **29**; 52–68.
14. Miettinen M, Makhlouf H, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. *Am. J. Surg. Pathol.* 2006; **30**; 477–489.
15. Kawanowa K, Sakuma Y, Sakurai S *et al*. High incidence of microscopic gastrointestinal stromal tumors in the stomach. *Hum. Pathol.* 2006; **37**; 1527–1535.
16. Agaimy A, Wünsch PH, Hofstaedter F *et al*. Minute gastric sclerosing stromal tumors (GIST tumorlets) are common in adults and frequently show c-KIT mutations. *Am. J. Surg. Pathol.* 2007; **31**; 113–120.
17. IARC. Soft tissue and bone Tumours. In WHO Classification of Tumours Editorial Board ed. *WHO Classification of Tumours*. Vol. **3**. 5th ed. Lyon, France: IARC Publications, 2020.
18. Wardelmann E, Hrychyk A, Merkelbach-Bruse S *et al*. Association of platelet-derived growth factor receptor alpha mutations with gastric primary site and epithelioid or mixed cell morphology in gastrointestinal stromal tumors. *J. Mol. Diagn.* 2004; **6**; 197–204.
19. Isidro RA, Hornick JL. The prognostic significance of pleomorphism in gastrointestinal stromal tumours. *Histopathology* 2022; **80**; 598–603.
20. Antonescu CR, Romeo S, Zhang L *et al*. Dedifferentiation in gastrointestinal stromal tumor to an anaplastic KIT-negative phenotype: a diagnostic pitfall: morphologic and molecular characterization of 8 cases occurring either de novo or after imatinib therapy. *Am. J. Surg. Pathol.* 2013; **37**; 385–392.
21. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin. Diagn. Pathol.* 2006; **23**; 70–83.
22. Hølmebakk T, Hompland I, Bjerkehagen B *et al*. Recurrence-free survival after resection of gastric gastrointestinal stromal tumors classified according to a strict definition of tumor rupture: a population-based study. *Ann. Surg. Oncol.* 2018; **25**; 1133–1139.
23. Joensuu H, Vehtari A, Riihimäki J *et al*. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. *Lancet Oncol.* 2012; **13**; 265–274.
24. Gold JS, Gönen M, Gutiérrez A *et al*. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. *Lancet Oncol.* 2009; **10**; 1045–1052.
25. Rossi S, Miceli R, Messerini L *et al*. Natural history of imatinib-naive GISTs: a retrospective analysis of 929 cases with long-term follow-up and development of a survival nomogram based on mitotic index and size as continuous variables. *Am. J. Surg. Pathol.* 2011; **35**; 1646–1656.
26. Mahdi Z, Zhang D, Gonzalez RS. Accuracy of risk-stratifying gastrointestinal stromal tumours using information available during biopsy. *Histopathology* 2022; **81**; 137–141.
27. Mason EF, Hornick JL. Conventional risk stratification fails to predict progression of succinate dehydrogenase-deficient gastrointestinal stromal tumors: a clinicopathologic study of 76 cases. *Am. J. Surg. Pathol.* 2016; **40**; 1616–1621.
28. Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. *Am. J. Pathol.* 1998; **152**; 1259–1269.
29. West RB, Corless CL, Chen X *et al*. The novel marker, DOG1, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of KIT or PDGFRA mutation status. *Am. J. Pathol.* 2004; **165**; 107–113.

30. Miettinen M, Wang ZF, Lasota J. DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors: a study of 1840 cases. *Am. J. Surg. Pathol.* 2009; **33**; 1401–1408.
31. Liegl B, Hornick JL, Corless CL, Fletcher CD. Monoclonal antibody DOG1.1 shows higher sensitivity than KIT in the diagnosis of gastrointestinal stromal tumors, including unusual subtypes. *Am. J. Surg. Pathol.* 2009; **33**; 437–446.
32. Debiec-Rychter M, Wasag B, Stul M *et al.* Gastrointestinal stromal tumours (GISTs) negative for KIT (CD117 antigen) immunoreactivity. *J. Pathol.* 2004; **202**; 430–438.
33. Medeiros F, Corless CL, Duensing A *et al.* KIT-negative gastrointestinal stromal tumors: proof of concept and therapeutic implications. *Am. J. Surg. Pathol.* 2004; **28**; 889–894.
34. Gaal J, Stratakis CA, Carney JA *et al.* SDHB immunohistochemistry: a useful tool in the diagnosis of Carney-Stratakis and Carney triad gastrointestinal stromal tumors. *Mod. Pathol.* 2011; **24**; 147–151.
35. Janeway KA, Kim SY, Lodish M *et al.* Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking KIT and PDGFRA mutations. *Proc. Natl. Acad. Sci. U. S. A.* 2011; **108**; 314–318.
36. Wagner AJ, Remillard SP, Zhang YX, Doyle LA, George S, Hornick JL. Loss of expression of SDHA predicts SDHA mutations in gastrointestinal stromal tumors. *Mod. Pathol.* 2013; **26**; 289–294.
37. Hirota S, Isozaki K, Moriyama Y *et al.* Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 1998; **279**; 577–580.
38. Rubin BP, Singer S, Tsao C *et al.* KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. *Cancer Res.* 2001; **61**; 8118–8121.
39. Heinrich MC, Corless CL, Duensing A *et al.* PDGFRA activating mutations in gastrointestinal stromal tumors. *Science* 2003; **299**; 708–710.
40. Corless CL, Schroeder A, Griffith D *et al.* PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. *J. Clin. Oncol.* 2005; **23**; 5357–5364.
41. Heinrich MC, Corless CL, Demetri GD *et al.* Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J. Clin. Oncol.* 2003; **21**; 4342–4349.
42. Klug LR, Khosroyani HM, Kent JD, Heinrich MC. New treatment strategies for advanced-stage gastrointestinal stromal tumours. *Nat. Rev. Clin. Oncol.* 2022; **19**; 328–341.
43. Miettinen M, Wang ZF, Sarlomo-Rikala M, Osuch C, Rutkowski P, Lasota J. Succinate dehydrogenase-deficient GISTs: a clinicopathologic, immunohistochemical, and molecular genetic study of 66 gastric GISTs with predilection to young age. *Am. J. Surg. Pathol.* 2011; **35**; 1712–1721.
44. Killian JK, Miettinen M, Walker RL *et al.* Recurrent epimutation of SDHC in gastrointestinal stromal tumors. *Sci. Transl. Med.* 2014; **6**; 268ra177.
45. Gasparotto D, Rossi S, Polano M *et al.* Quadruple-negative GIST is a sentinel for unrecognized Neurofibromatosis type 1 syndrome. *Clin. Cancer Res.* 2017; **23**; 273–282.
46. Agaimy A, Terracciano LM, Dirnhofer S *et al.* V600E BRAF mutations are alternative early molecular events in a subset of KIT/PDGFRA wild-type gastrointestinal stromal tumours. *J. Clin. Pathol.* 2009; **62**; 613–616.
47. Bümming P, Andersson J, Meis-Kindblom JM *et al.* Neoadjuvant, adjuvant and palliative treatment of gastrointestinal stromal tumours (GIST) with imatinib: a centre-based study of 17 patients. *Br. J. Cancer* 2003; **89**; 460–464.
48. International Union against Cancer. *TNM classification of malignant Tumours*. 8th ed. New York: Brierley J, Gospodarowicz M and C. W. Wiley-Blackwell, 2016.
49. Amin M, Edge S, Greene F *et al. AJCC cancer staging manual*. 8th ed. New York: Springer, 2017.
50. Swillens JEM, Sluijter CE, Overbeek LIH, Nagtegaal ID, Hermens R. Identification of barriers and facilitators in nationwide implementation of standardized structured reporting in pathology: a mixed method study. *Virchows Arch.* 2019; **475**; 551–561.
51. Baranov NS, Nagtegaal ID, van Grieken NCT *et al.* Synoptic reporting increases quality of upper gastrointestinal cancer pathology reports. *Virchows Arch.* 2019; **475**; 255–259.
52. Sluijter CE, van Workum F, Wiggers T *et al.* Improvement of care in patients with colorectal cancer: influence of the introduction of standardized structured reporting for pathology. *JCO Clin. Cancer Inform.* 2019; **3**; 1–12.
53. Gill AJ, Johns AL, Eckstein R *et al.* Synoptic reporting improves histopathological assessment of pancreatic resection specimens. *Pathology* 2009; **41**; 161–167.