

ICCR Gastrointestinal Stromal Tumour (GIST) Histopathology Reporting Guide – Resection Specimens, 1st edition

Elements in black text are CORE

Elements in grey text are NON-CORE

o indicates single select values

□ indicates multi-select values

Definition of Core elements	<p>Core elements are those which 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 evidence¹). In rare circumstances, where level III-2 evidence is not available an element may be made a core element where there is unanimous agreement in the expert committee. An appropriate staging system, e.g., Pathological TNM staging, would normally be included as a core element. The summation of all core elements is considered to be the minimum reporting standard for a specific cancer.</p> <p>Reference</p> <p>1 Merlin T, Weston A and Tooher R (2009). Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. <i>BMC Med Res Methodol</i> 9:34.</p>
Definition of Non-core elements	<p>Non-core elements are those which are unanimously agreed should 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.</p> <p>Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either core or non-core elements by consensus of the Dataset Authoring Committee.</p>
Scope of this dataset	<p>The dataset has been developed for the pathology reporting of resection specimens for gastrointestinal stromal tumour (GIST). A separate International Collaboration on Cancer Reporting (ICCR) dataset is available for reporting of biopsy specimens of GIST.¹</p> <p>Metastatic GIST specimens are excluded from this dataset. A separate ICCR dataset for soft tissue sarcoma is available.²</p> <p>References</p> <p>1 International Collaboration on Cancer Reporting (2021). <i>Gastrointestinal Stromal Tumour (GIST) Histopathology Reporting Guide - Biopsy Specimens</i>. Available from: http://www.iccr-cancer.org/datasets/published-datasets/soft-tissue-bone (Accessed 19th April 2021).</p> <p>2 International Collaboration on Cancer Reporting (2021). <i>Soft Tissue Sarcoma Histopathology Reporting Guide - Resection Specimens</i>. Available from: http://www.iccr-cancer.org/datasets/published-datasets/soft-tissue-bone (Accessed 19th April 2021).</p>

Core/ Non-core	Element name	Values	Commentary	Implementation notes
Non-core	NEOADJUVANT THERAPY	<ul style="list-style-type: none"> o Information not provided o Not administered o Administered, <i>describe</i> 	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.	
Core	RELEVANT SYNDROME	<ul style="list-style-type: none"> o Information not provided o Carney triad o Carney-Stratakis syndrome o Neurofibromatosis type 1 o Familial GIST syndrome o Other, <i>specify</i> 	<p>Gastrointestinal stromal tumours (GISTs) may arise in the setting of familial or non-familial syndromes. Familial syndromes include Carney-Stratakis syndrome (germline mutations in <i>SDHX</i> genes; affected patients develop gastric GISTs and extra-adrenal paragangliomas), neurofibromatosis type 1 (germline mutation in <i>NF1</i>; most GISTs in this setting arise in the small intestine), and familial GIST syndrome (germline mutation in <i>KIT</i> or <i>PDGFRA</i>).¹⁻⁴ Carney triad is a non-familial syndrome most often driven by <i>SDHC</i> promoter hypermethylation; this syndrome usually affects young women and is characterised by succinate dehydrogenase (SDH)-deficient gastric GIST, extra-adrenal paragangliomas, and pulmonary chondromas.^{5,6} Clinical behaviour, therapy, and follow-up of GISTs in these syndromes are different from sporadic GISTs.</p> <p>References</p> <p>1 Maeyama H, Hidaka E, Ota H, Minami S, Kajiyama M, Kuraishi A, Mori H, Matsuda Y, Wada S, Sodeyama H, Nakata S, Kawamura N, Hata S, Watanabe M, Iijima Y and Katsuyama T (2001). Familial gastrointestinal stromal tumor with hyperpigmentation: association with a germline mutation of the c-kit gene. <i>Gastroenterology</i> 120(1):210-215.</p>	

Core/ Non-core	Element name	Values	Commentary	Implementation notes
			<p>2 Pasini B, McWhinney SR, Bei T, Matyakhina L, Stergiopoulos S, Muchow M, Boikos SA, Ferrando B, Pacak K, Assie G, Baudin E, Chompret A, Ellison JW, Briere JJ, Rustin P, Gimenez-Roqueplo AP, Eng C, Carney JA and Stratakis CA (2008). 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. <i>Eur J Hum Genet</i> 16(1):79-88.</p> <p>3 Andersson J, Sihto H, Meis-Kindblom JM, Joensuu H, Nupponen N and Kindblom LG (2005). NF1-associated gastrointestinal stromal tumors have unique clinical, phenotypic, and genotypic characteristics. <i>Am J Surg Pathol</i> 29(9):1170-1176.</p> <p>4 Miettinen M, Fetsch JF, Sobin LH and Lasota J (2006). Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. <i>Am J Surg Pathol</i> 30(1):90-96.</p> <p>5 Carney JA (1999). Gastric stromal sarcoma, pulmonary chondroma, and extra-adrenal paraganglioma (Carney Triad): natural history, adrenocortical component, and possible familial occurrence. <i>Mayo Clin Proc</i> 74(6):543-552.</p> <p>6 Zhang L, Smyrk TC, Young WF, Jr., Stratakis CA and Carney JA (2010). Gastric stromal tumors in Carney triad are different clinically, pathologically, and behaviorally from sporadic gastric gastrointestinal stromal tumors: findings in 104 cases. <i>Am J Surg Pathol</i> 34(1):53-64.</p>	
Core	OPERATIVE PROCEDURE	<ul style="list-style-type: none"> o Not specified □ Resection, <i>specify type</i> □ Lymph nodes, <i>specify site(s)</i> □ Other, <i>specify</i> 	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 oesophago-gastrectomy may be required, depending upon the specific location. GISTs of the small intestine (non-duodenal) are typically managed by segmental resection. Duodenal primary GISTs may require pancreatoduodenectomy (i.e., Whipple procedure). Depending upon 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.	
Core	TUMOUR SITE	<ul style="list-style-type: none"> o Not specified □ Oesophagus □ Gastro-oesophageal junction □ Stomach □ Duodenum □ Small intestine (non-duodenal) □ Colon (non-rectal) □ Rectum □ Other, <i>specify</i> 	<p>Gastrointestinal stromal tumours (GISTs) most often arise in the stomach and non-duodenal 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 (non-duodenal)' is applied instead of jejunum or ileum.</p> <p>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.^{1,2} 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.</p> <p>Primary anatomic site is an important prognostic parameter; for example, gastric primary GISTs generally have a lower risk of metastasis than small intestinal GISTs.^{3,4} For this reason, it is critical to specify location as accurately as possible.</p> <p>References</p> <p>1 Miettinen M, Felsiak-Golabek A, Wang Z, Inaguma S and Lasota J (2017). GIST Manifesting as a Retroperitoneal Tumor: Clinicopathologic Immunohistochemical, and Molecular Genetic Study of 112 Cases. <i>Am J Surg Pathol</i> 41(5):577-585.</p> <p>2 Miettinen M, Sobin LH and Lasota J (2009). Gastrointestinal stromal tumors presenting as omental masses--a clinicopathologic analysis of 95 cases. <i>Am J Surg Pathol</i> 33(9):1267-1275.</p> <p>3 Miettinen M, Sobin LH and Lasota J (2005). Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. <i>Am J Surg Pathol</i> 29(1):52-68.</p>	

Core/ Non-core	Element name	Values	Commentary	Implementation notes
			4 Miettinen M, Makhlof H, Sobin LH and Lasota J (2006). 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. <i>Am J Surg Pathol</i> 30(4):477-489.	
Core	TUMOUR FOCALITY	<ul style="list-style-type: none"> o Cannot be assessed o Unifocal o Multifocal <ul style="list-style-type: none"> Specify number of tumours ____ Specify site(s) ____ 	<p>Multifocal tumours are often associated with syndromic predisposition, such as neurofibromatosis type 1, Carney triad, and familial GIST syndrome.¹⁻⁴ However, minute gastric GISTs (so-called 'microGISTs' <1 centimetres) are common in the general population,^{5,6} 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.</p> <p>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.</p> <p>References</p> <ol style="list-style-type: none"> 1 Maeyama H, Hidaka E, Ota H, Minami S, Kajiyama M, Kuraishi A, Mori H, Matsuda Y, Wada S, Sodeyama H, Nakata S, Kawamura N, Hata S, Watanabe M, Iijima Y and Katsuyama T (2001). Familial gastrointestinal stromal tumor with hyperpigmentation: association with a germline mutation of the c-kit gene. <i>Gastroenterology</i> 120(1):210-215. 2 Pasini B, McWhinney SR, Bei T, Matyakhina L, Stergiopoulos S, Muchow M, Boikos SA, Ferrando B, Pacak K, Assie G, Baudin E, Chompret A, Ellison JW, Briere JJ, Rustin P, Gimenez-Roqueplo AP, Eng C, Carney JA and Stratakis CA (2008). 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. <i>Eur J Hum Genet</i> 16(1):79-88. 3 Andersson J, Sihto H, Meis-Kindblom JM, Joensuu H, Nupponen N and Kindblom LG (2005). NF1-associated gastrointestinal stromal tumors have unique clinical, phenotypic, and genotypic characteristics. <i>Am J Surg Pathol</i> 29(9):1170-1176. 4 Miettinen M, Fetsch JF, Sobin LH and Lasota J (2006). Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. <i>Am J Surg Pathol</i> 30(1):90-96. 5 Kawanowa K, Sakuma Y, Sakurai S, Hishima T, Iwasaki Y, Saito K, Hosoya Y, Nakajima T and Funata N (2006). High incidence of microscopic gastrointestinal stromal tumors in the stomach. <i>Hum Pathol</i> 37(12):1527-1535. 6 Agaimy A, Wünsch PH, Hofstaedter F, Blaszyk H, Rümmele P, Gaumann A, Dietmaier W and Hartmann A (2007). Minute gastric sclerosing stromal tumors (GIST tumorlets) are common in adults and frequently show c-KIT mutations. <i>Am J Surg Pathol</i> 31(1):113-120. 	
Core	MAXIMUM TUMOUR DIMENSION	____ mm OR ____ mm to ____ mm ^a o Cannot be assessed, <i>specify</i>	Tumour size is a critical parameter for assessment of risk of malignant behaviour. For multifocal tumours, a range of sizes should be reported.	^a Include the range of sizes for multifocal tumours.
Core	HISTOLOGICAL TUMOUR TYPE	<ul style="list-style-type: none"> o Spindle cell type o Epithelioid type o Mixed type o Other, <i>specify</i> 	<p>Histological diagnosis is based on the 2020 World Health Organization (WHO) Classification of Soft Tissue and Bone Tumours, 5th edition.¹ GISTs are most often of spindle cell type, followed by epithelioid type and mixed epithelioid and spindle cell type;¹ the latter two histological types are most common in the stomach. The histological tumour type may be associated with mutational status (e.g., most <i>PDGFRA</i>-mutant GISTs are of epithelioid type)² or particular syndromes (e.g., Carney triad and Carney-Stratakis syndrome-associated GISTs are usually of epithelioid or mixed type),³ although this is not always the case.</p> <p>Pleomorphic morphology in GIST is rare (<2%). 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</p>	<p>This Value list based on the WHO of Soft Tissue and Bone Tumours (2020).</p> <p>Note that permission to publish the WHO Classification of Tumours may be</p>

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			<p>lineage markers (e.g., KIT and ANO1/DOG1), is exceptionally rare.⁴</p> <p>References</p> <ol style="list-style-type: none"> 1 WHO Classification of Tumours Editorial Board (2020). <i>Soft Tissue and Bone Tumours. WHO Classification of Tumours, 5th Edition, Volume 3</i>. IARC Publications, Lyon. 2 Wardelmann E, Hrychuk A, Merkelbach-Bruse S, Pauls K, Goldstein J, Hohenberger P, Losen I, Manegold C, Büttner R and Pietsch T (2004). Association of platelet-derived growth factor receptor alpha mutations with gastric primary site and epithelioid or mixed cell morphology in gastrointestinal stromal tumors. <i>J Mol Diagn</i> 6(3):197-204. 3 Zhang L, Smyrk TC, Young WF, Jr., Stratakis CA and Carney JA (2010). Gastric stromal tumors in Carney triad are different clinically, pathologically, and behaviorally from sporadic gastric gastrointestinal stromal tumors: findings in 104 cases. <i>Am J Surg Pathol</i> 34(1):53-64. 4 Antonescu CR, Romeo S, Zhang L, Nafa K, Hornick JL, Nielsen GP, Mino-Kenudson M, Huang HY, Mosquera JM, Dei Tos PA and Fletcher CD (2013). 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. <i>Am J Surg Pathol</i> 37(3):385-392. 	needed in your implementation. It is advisable to check with the International Agency for Research on Cancer (IARC).
Core	MITOTIC COUNT	<p>___ /5 mm²</p> <p>o Cannot be assessed, <i>specify</i></p>	<p>Mitotic count is the most important feature for the assessment of risk of malignant behaviour.¹ The mitotic count should be determined in the most mitotically active area of the tumour. The mitotic count should be reported per 5 mm². With older microscopes, 5 mm² is equivalent to 50 high power fields (HPF). However, with most modern microscopes with wider fields, 5 mm² requires 20 to 25 HPFs using 40X lenses. The number of fields required to be counted to encompass 5 mm² should be calculated on individual microscopes.</p> <p>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.</p> <p>Reference</p> <ol style="list-style-type: none"> 1 Miettinen M and Lasota J (2006). Gastrointestinal stromal tumors: pathology and prognosis at different sites. <i>Semin Diagn Pathol</i> 23(2):70-83. 	
Non-core	NECROSIS	<p>o Cannot be assessed</p> <p>o Not identified</p> <p>o Present</p> <p>___ %</p>	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 hyalinized fibrotic or myxoid stroma.	
Core	TUMOUR RUPTURE	<p>o Not identified</p> <p>o Present</p>	<p>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.¹ Risk assessment plays a critical role for predicting metastatic potential in the management and follow-up of patients with GIST.² For example, patients with GISTs that are determined to be of moderate or high risk are often treated with adjuvant imatinib mesylate, following resection of localised primary tumours.</p> <p>The most widely used risk assessment system was developed by Miettinen and Lasota (2006) (see Table 1),³ which has been adopted by the WHO and many other organisations. Alternative risk assessment systems include prognostic nomograms and contour maps, which are quite often used by clinicians.^{2,4,5}</p> <p>This risk assessment system should not be applied to succinate dehydrogenase (SDH)-deficient GISTs⁶ or GISTs in patients with neurofibromatosis type 1 or other syndromes (<i>PDGFRA</i>-mutant syndrome, <i>KIT/PDGFRA</i> germline mutations, <i>BRAF</i> mutation).</p>	

Core/ Non-core	Element name	Values	Commentary	Implementation notes
			<p>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.</p> <p>Table 1 (See the end of document for Table)</p> <p>References</p> <ol style="list-style-type: none"> 1 Hølmek T, Hompland I, Bjerkehagen B, Stoldt S, Bruland Ø S, Hall KS and Boye K (2018). Recurrence-Free Survival After Resection of Gastric Gastrointestinal Stromal Tumors Classified According to a Strict Definition of Tumor Rupture: A Population-Based Study. <i>Ann Surg Oncol</i> 25(5):1133-1139. 2 Joensuu H, Vehtari A, Riihimäki J, Nishida T, Steigen SE, Brabec P, Plank L, Nilsson B, Cirilli C, Braconi C, Bordoni A, Magnusson MK, Linke Z, Suflarsky J, Federico M, Jonasson JG, Dei Tos AP and Rutkowski P (2012). Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. <i>Lancet Oncol</i> 13(3):265-274. 3 Miettinen M and Lasota J (2006). Gastrointestinal stromal tumors: pathology and prognosis at different sites. <i>Semin Diagn Pathol</i> 23(2):70-83. 4 Gold JS, Gönen M, Gutiérrez A, Broto JM, García-del-Muro X, Smyrk TC, Maki RG, Singer S, Brennan MF, Antonescu CR, Donohue JH and DeMatteo RP (2009). Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. <i>Lancet Oncol</i> 10(11):1045-1052. 5 Rossi S, Miceli R, Messerini L, Bearzi I, Mazzoleni G, Capella C, Arrigoni G, Sonzogni A, Sidoni A, Toffolatti L, Laurino L, Mariani L, Vinaccia V, Gnocchi C, Gronchi A, Casali PG and Dei Tos AP (2011). Natural history of imatinib-naïve 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. <i>Am J Surg Pathol</i> 35(11):1646-1656. 6 Mason EF and Hornick JL (2016). Conventional Risk Stratification Fails to Predict Progression of Succinate Dehydrogenase-deficient Gastrointestinal Stromal Tumors: A Clinicopathologic Study of 76 Cases. <i>Am J Surg Pathol</i> 40(12):1616-1621. 	
Core	RISK ASSESSMENT	<ul style="list-style-type: none"> o Not applicable o No risk o Very low risk o Low risk o Moderate risk o High risk o Overtly malignant/metastatic o Cannot be assessed, <i>specify</i> 	<p>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.¹ Risk assessment plays a critical role for predicting metastatic potential in the management and follow-up of patients with GIST.² For example, patients with GISTs that are determined to be of moderate or high risk are often treated with adjuvant imatinib mesylate, following resection of localised primary tumours.</p> <p>The most widely used risk assessment system was developed by Miettinen and Lasota (2006) (see Table 1),³ which has been adopted by the WHO and many other organisations. Alternative risk assessment systems include prognostic nomograms and contour maps, which are quite often used by clinicians.^{2,4,5}</p> <p>This risk assessment system should not be applied to succinate dehydrogenase (SDH)-deficient GISTs⁶ or GISTs in patients with neurofibromatosis type 1 or other syndromes (<i>PDGFRA</i>-mutant syndrome, <i>KIT/PDGFRA</i> germline mutations, <i>BRAF</i> mutation).</p> <p>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.</p> <p>Table 1 (See the end of document for Table)</p>	

Core/ Non-core	Element name	Values	Commentary	Implementation notes
			References <ol style="list-style-type: none"> 1 Hølmekbakk T, Hompland I, Bjerkehagen B, Stoldt S, Bruland Ø S, Hall KS and Boye K (2018). Recurrence-Free Survival After Resection of Gastric Gastrointestinal Stromal Tumors Classified According to a Strict Definition of Tumor Rupture: A Population-Based Study. <i>Ann Surg Oncol</i> 25(5):1133-1139. 2 Joensuu H, Vehtari A, Riihimäki J, Nishida T, Steigen SE, Brabec P, Plank L, Nilsson B, Cirilli C, Braconi C, Bordoni A, Magnusson MK, Linke Z, Suflarsky J, Federico M, Jonasson JG, Dei Tos AP and Rutkowski P (2012). Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. <i>Lancet Oncol</i> 13(3):265-274. 3 Miettinen M and Lasota J (2006). Gastrointestinal stromal tumors: pathology and prognosis at different sites. <i>Semin Diagn Pathol</i> 23(2):70-83. 4 Gold JS, Gönen M, Gutiérrez A, Broto JM, García-del-Muro X, Smyrk TC, Maki RG, Singer S, Brennan MF, Antonescu CR, Donohue JH and DeMatteo RP (2009). Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. <i>Lancet Oncol</i> 10(11):1045-1052. 5 Rossi S, Miceli R, Messerini L, Bearzi I, Mazzoleni G, Capella C, Arrigoni G, Sonzogni A, Sidoni A, Toffolatti L, Laurino L, Mariani L, Vinaccia V, Gnocchi C, Gronchi A, Casali PG and Dei Tos AP (2011). Natural history of imatinib-naïve 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. <i>Am J Surg Pathol</i> 35(11):1646-1656. 6 Mason EF and Hornick JL (2016). Conventional Risk Stratification Fails to Predict Progression of Succinate Dehydrogenase-deficient Gastrointestinal Stromal Tumors: A Clinicopathologic Study of 76 Cases. <i>Am J Surg Pathol</i> 40(12):1616-1621. 	
Non-core	LYMPHOVASCULAR INVASION	<ul style="list-style-type: none"> o Not identified o Present o Indeterminate 	<p>Lymphovascular invasion is most often seen in succinate dehydrogenase (SDH)-deficient GIST;¹ this finding is rare in <i>KIT</i> and <i>PDGFRA</i>-mutant GISTs.</p> <p>Reference</p> <ol style="list-style-type: none"> 1 Miettinen M, Wang ZF, Sarlomo-Rikala M, Osuch C, Rutkowski P and Lasota J (2011). Succinate dehydrogenase-deficient GISTs: a clinicopathologic, immunohistochemical, and molecular genetic study of 66 gastric GISTs with predilection to young age. <i>Am J Surg Pathol</i> 35(11):1712-1721. 	
Non-core	RESPONSE TO NEOADJUVANT THERAPY	<ul style="list-style-type: none"> o No prior treatment o No response o Response, <i>describe</i> o Cannot be assessed, <i>explain reasons</i> 	<p>Effective neoadjuvant tyrosine kinase inhibitor therapy is typically associated with markedly decreased cellularity and the presence of extensive hyalinized fibrotic or myxoid stroma;¹ 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.</p> <p>Reference</p> <ol style="list-style-type: none"> 1 Bümming P, Andersson J, Meis-Kindblom JM, Klingenstierna H, Engström K, Stierner U, Wängberg B, Jansson S, Ahlman H, Kindblom LG and Nilsson B (2003). Neoadjuvant, adjuvant and palliative treatment of gastrointestinal stromal tumours (GIST) with imatinib: a centre-based study of 17 patients. <i>Br J Cancer</i> 89(3):460-464. 	
Core	MARGIN STATUS	<ul style="list-style-type: none"> o Cannot be assessed o Not involved Distance of tumour from closest margin ____ mm Specify closest margin, <i>if possible</i> o Involved Specify margin(s), <i>if possible</i> 	<p>Gastrointestinal stromal tumours (GISTs) rarely recur locally at precisely the 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.</p>	

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Non-core	LYMPH NODE STATUS	<ul style="list-style-type: none"> o Cannot be assessed o No nodes submitted or found o Number of lymph nodes examined <ul style="list-style-type: none"> o Not involved o Involved <ul style="list-style-type: none"> Number of involved lymph nodes o Number cannot be determined 	<p>Lymph node metastases are rarely observed in GIST, other than for succinate dehydrogenase (SDH)-deficient tumours; such tumours frequently spread to regional lymph nodes.^{1,2} Finding lymph node metastases should prompt evaluation for SDH deficiency.</p> <p>References</p> <ol style="list-style-type: none"> 1 Miettinen M, Wang ZF, Sarlomo-Rikala M, Osuch C, Rutkowski P and Lasota J (2011). Succinate dehydrogenase-deficient GISTs: a clinicopathologic, immunohistochemical, and molecular genetic study of 66 gastric GISTs with predilection to young age. <i>Am J Surg Pathol</i> 35(11):1712-1721. 2 Mason EF and Hornick JL (2016). Conventional risk stratification fails to predict progression of succinate dehydrogenase-deficient gastrointestinal stromal tumors: a clinicopathologic study of 76 cases. <i>Am J Surg Pathol</i> 40(12):1616-1621. 	
Non-core	COEXISTENT PATHOLOGY	<ul style="list-style-type: none"> o None identified o Present, <i>specify</i> 	Coexistent pathology might include inflammatory conditions of the stomach, such as <i>Helicobacter pylori</i> gastritis or chronic atrophic (autoimmune) gastritis.	
Core	ANCILLARY STUDIES	<p>Immunohistochemistry</p> <ul style="list-style-type: none"> o Not performed o Performed <ul style="list-style-type: none"> □ KIT (CD117), <i>record results</i> □ DOG1 (ANO1), <i>record results</i> □ SDHB, <i>record results</i> □ Other (e.g., SDHA), <i>specify test(s) and result(s)</i> <p>Molecular genetic testing</p> <ul style="list-style-type: none"> o Not performed o Performed, <i>record methodology and result(s)</i> <p>Other ancillary studies</p> <ul style="list-style-type: none"> o Not performed o Performed, <i>specify test(s) and result(s)</i> 	<p>Immunohistochemistry (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 cell of Cajal lineage, are highly sensitive and specific markers for GIST.¹⁻³ 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.^{3,4} KIT-negative GISTs (and those with weak or limited staining for KIT) most often harbor <i>PDGFRA</i> mutations.^{5,6} Succinate dehydrogenase (SDH)-deficient GISTs show loss of staining for SDHB, irrespective of which <i>SDHX</i> gene is mutated (or if there is SDHC promoter hypermethylation; see below).^{7,8} SDHB IHC can therefore be used to confirm the diagnosis of SDH-deficient GIST. SDHA loss is only observed in <i>SDHA</i>-mutant GISTs.⁹ Despite the lack of <i>KIT</i> mutations, SDH-deficient GISTs are typically strongly positive for KIT (and DOG1).</p> <p><i>KIT</i> 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).^{10,11} <i>PDGFRA</i> mutations are identified in 10-15% of GISTs, most often in exon 18 (10-12% overall; the most common is p.D842V), rarely in exons 12 or exon 14.^{12,13} Genotype predicts response to tyrosine kinase inhibitor therapy; for example, <i>KIT</i> exon 11-mutant GISTs have the best response to imatinib mesylate, whereas GISTs with <i>PDGFRA</i> D842V mutations show primary imatinib resistance, although such tumours respond to the tyrosine kinase inhibitor avapritinib.^{14,15}</p> <p>SDH-deficient GISTs account for about 5% of GISTs overall, including the majority of gastric GISTs that lack <i>KIT</i> and <i>PDGFRA</i> mutations and most tumours occurring in paediatric patients.¹⁶ SDH-deficient GISTs typically show indolent behaviour with often 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.¹⁷ SDH-deficient GISTs are often associated with germline mutations in <i>SDHA</i>, <i>SDHB</i>, <i>SDHC</i>, or <i>SDHD</i>; these mutations are sometimes associated with Carney-Stratakis syndrome (the dyad of gastric GIST and paraganglioma).¹⁸ SDH-deficient GISTs that lack <i>SDHX</i> mutations usually show hypermethylation of the <i>SDHC</i> promoter; this epigenetic dysregulation is characteristic of Carney triad (SDH-deficient GIST, paraganglioma, and pulmonary chondroma).¹⁹</p> <p>Other genetic alterations in GIST are rare; these include <i>BRAF</i> V600E and <i>EGFR</i> mutations; biallelic <i>NF1</i> inactivation; and tyrosine kinase receptor gene rearrangements.^{20,21}</p> <p>Figure 1 (See the end of document for figure)</p>	

Core/ Non-core	Element name	Values	Commentary	Implementation notes
			<p>References</p> <ol style="list-style-type: none"> Kindblom LG, Remotti HE, Aldenborg F and Meis-Kindblom JM (1998). Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. <i>Am J Pathol</i> 152(5):1259-1269. West RB, Corless CL, Chen X, Rubin BP, Subramanian S, Montgomery K, Zhu S, Ball CA, Nielsen TO, Patel R, Goldblum JR, Brown PO, Heinrich MC and van de Rijn M (2004). The novel marker, DOG1, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of KIT or PDGFRA mutation status. <i>Am J Pathol</i> 165(1):107-113. Miettinen M, Wang ZF and Lasota J (2009). DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors: a study of 1840 cases. <i>Am J Surg Pathol</i> 33(9):1401-1408. Liegl B, Hornick JL, Corless CL and Fletcher CD (2009). Monoclonal antibody DOG1.1 shows higher sensitivity than KIT in the diagnosis of gastrointestinal stromal tumors, including unusual subtypes. <i>Am J Surg Pathol</i> 33(3):437-446. Debiec-Rychter M, Wasag B, Stul M, De Wever I, Van Oosterom A, Hagemeijer A and Sciot R (2004). Gastrointestinal stromal tumours (GISTs) negative for KIT (CD117 antigen) immunoreactivity. <i>J Pathol</i> 202(4):430-438. Medeiros F, Corless CL, Duensing A, Hornick JL, Oliveira AM, Heinrich MC, Fletcher JA and Fletcher CD (2004). KIT-negative gastrointestinal stromal tumors: proof of concept and therapeutic implications. <i>Am J Surg Pathol</i> 28(7):889-894. Gaal J, Stratakis CA, Carney JA, Ball ER, Korpershoek E, Lodish MB, Levy I, Xekouki P, van Nederveen FH, den Bakker MA, O'Sullivan M, Dinjens WN and de Krijger RR (2011). SDHB immunohistochemistry: a useful tool in the diagnosis of Carney-Stratakis and Carney triad gastrointestinal stromal tumors. <i>Mod Pathol</i> 24(1):147-151. Janeway KA, Kim SY, Lodish M, Nosé V, Rustin P, Gaal J, Dahia PL, Liegl B, Ball ER, Raygada M, Lai AH, Kelly L, Hornick JL, O'Sullivan M, de Krijger RR, Dinjens WN, Demetri GD, Antonescu CR, Fletcher JA, Helman L and Stratakis CA (2011). Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking KIT and PDGFRA mutations. <i>Proc Natl Acad Sci U S A</i> 108(1):314-318. Wagner AJ, Remillard SP, Zhang YX, Doyle LA, George S and Hornick JL (2013). Loss of expression of SDHA predicts SDHA mutations in gastrointestinal stromal tumors. <i>Mod Pathol</i> 26(2):289-294. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, Hanada M, Kurata A, Takeda M, Muhammad Tunio G, Matsuzawa Y, Kanakura Y, Shinomura Y and Kitamura Y (1998). Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. <i>Science</i> 279(5350):577-580. Rubin BP, Singer S, Tsao C, Duensing A, Lux ML, Ruiz R, Hibbard MK, Chen CJ, Xiao S, Tuveson DA, Demetri GD, Fletcher CD and Fletcher JA (2001). KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. <i>Cancer Res</i> 61(22):8118-8121. Heinrich MC, Corless CL, Duensing A, McGreevey L, Chen CJ, Joseph N, Singer S, Griffith DJ, Haley A, Town A, Demetri GD, Fletcher CD and Fletcher JA (2003). PDGFRA activating mutations in gastrointestinal stromal tumors. <i>Science</i> 299(5607):708-710. Corless CL, Schroeder A, Griffith D, Town A, McGreevey L, Harrell P, Shiraga S, Bainbridge T, Morich J and Heinrich MC (2005). PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. <i>J Clin Oncol</i> 23(23):5357-5364. Heinrich MC, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, McGreevey LS, Chen CJ, Van den Abbeele AD, Druker BJ, Kiese B, Eisenberg B, Roberts PJ, Singer S, Fletcher CD, Silberman S, Dimitrijevic S and Fletcher JA (2003). Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. <i>J Clin Oncol</i> 21(23):4342-4349. Anonymous (2020). Avapritinib Approved for GIST Subgroup. <i>Cancer Discov</i> 10(3):334. Miettinen M, Wang ZF, Sarlomo-Rikala M, Osuch C, Rutkowski P and Lasota J (2011). Succinate dehydrogenase-deficient GISTs: a clinicopathologic, immunohistochemical, and molecular genetic study of 66 gastric GISTs with predilection to young age. <i>Am J Surg Pathol</i> 35(11):1712-1721. 	

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			<p>17 Mason EF and Hornick JL (2016). Conventional Risk Stratification Fails to Predict Progression of Succinate Dehydrogenase-deficient Gastrointestinal Stromal Tumors: A Clinicopathologic Study of 76 Cases. <i>Am J Surg Pathol</i> 40(12):1616-1621.</p> <p>18 Pasini B, McWhinney SR, Bei T, Matyakhina L, Stergiopoulos S, Muchow M, Boikos SA, Ferrando B, Pacak K, Assie G, Baudin E, Chompret A, Ellison JW, Briere JJ, Rustin P, Gimenez-Roqueplo AP, Eng C, Carney JA and Stratakis CA (2008). 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. <i>Eur J Hum Genet</i> 16(1):79-88.</p> <p>19 Killian JK, Miettinen M, Walker RL, Wang Y, Zhu YJ, Waterfall JJ, Noyes N, Retnakumar P, Yang Z, Smith WI, Jr., Killian MS, Lau CC, Pineda M, Walling J, Stevenson H, Smith C, Wang Z, Lasota J, Kim SY, Boikos SA, Helman LJ and Meltzer PS (2014). Recurrent epimutation of SDHC in gastrointestinal stromal tumors. <i>Sci Transl Med</i> 6(268):268ra177.</p> <p>20 Gasparotto D, Rossi S, Polano M, Tamborini E, Lorenzetto E, Sbaraglia M, Mondello A, Massani M, Lamon S, Bracci R, Mandolesi A, Frate E, Stanzial F, Agaj J, Mazzoleni G, Pilotti S, Gronchi A, Dei Tos AP and Maestro R (2017). Quadruple-Negative GIST Is a Sentinel for Unrecognized Neurofibromatosis Type 1 Syndrome. <i>Clin Cancer Res</i> 23(1):273-282.</p> <p>21 Agaimy A, Terracciano LM, Dirnhofer S, Tornillo L, Foerster A, Hartmann A and Bihl MP (2009). V600E BRAF mutations are alternative early molecular events in a subset of KIT/PDGFRα wild-type gastrointestinal stromal tumours. <i>J Clin Pathol</i> 62(7):613-616.</p>	
Core	HISTOLOGICALLY CONFIRMED METASTASES	<ul style="list-style-type: none"> o Not identified o Present, <i>specify site(s)</i> 	Gastrointestinal stromal tumour (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, longstanding disease.	
Non-core	PATHOLOGICAL STAGING (UICC TNM 8 th edition) ^b	<p>TNM Descriptors (only if applicable)</p> <ul style="list-style-type: none"> <input type="checkbox"/> m - multiple primary tumours <input type="checkbox"/> r - recurrent <input type="checkbox"/> y - post-therapy <p>Primary tumour (pT)</p> <ul style="list-style-type: none"> o Inadequate specimen for assessment o TX Primary tumour cannot be assessed o T0 No evidence for primary tumour o T1 Tumour 2 cm or less o T2 Tumour more than 2 cm but not more than 5 cm o T3 Tumour more than 5 cm but not more than 10 cm o T4 Tumour more than 10 cm in greatest dimension <p>Regional lymph nodes (pN)</p> <ul style="list-style-type: none"> o No nodes submitted or found o NX Regional lymph nodes cannot be assessed^c o N0 No regional lymph node metastasis o N1 Regional lymph node metastasis 	<p>The primary tumour T category in the TNM classification of the Union for International Cancer Control¹ and the American Joint Committee on Cancer² includes the same size cut-offs as the risk assessment system developed by Miettinen and Lasota (2006).³</p> <p>Lymph node metastases are often associated with SDH-deficient GISTs but are rarely seen with <i>KIT</i> or <i>PDGFRA</i>-mutant GISTs.</p> <p>GISTs most often metastasize to the liver and peritoneum. Other distant metastatic sites are rare, other than in patients with longstanding, advanced disease.</p> <p>This staging system should not be applied to syndromic GISTs, which are often multifocal at presentation and usually show indolent behaviour.</p> <p>References</p> <ol style="list-style-type: none"> 1 Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). <i>Union for International Cancer Control. TNM Classification of Malignant Tumours, 8th Edition</i>, Wiley, USA. 2 Amin MB, Edge S, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM and Meyer LR (eds) (2017). <i>AJCC Cancer Staging Manual. 8th ed</i>. Springer, New York. 3 Miettinen M and Lasota J (2006). Gastrointestinal stromal tumors: pathology and prognosis at different sites. <i>Semin Diagn Pathol</i> 23(2):70-83. 	<p>Note that permission to publish the TNM cancer staging tables may be needed in your implementation. It is advisable to check.</p> <p>^b Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley (incorporating any errata published up until 6th October 2020).</p> <p>^c Regional lymph node involvement is rare for GISTs, so that cases in</p>

Core/ Non-core	Element name	Values	Commentary	Implementation notes
				which the nodal status is not assessed clinically or pathologically could be considered N0 instead of NX or pNX.

Figure

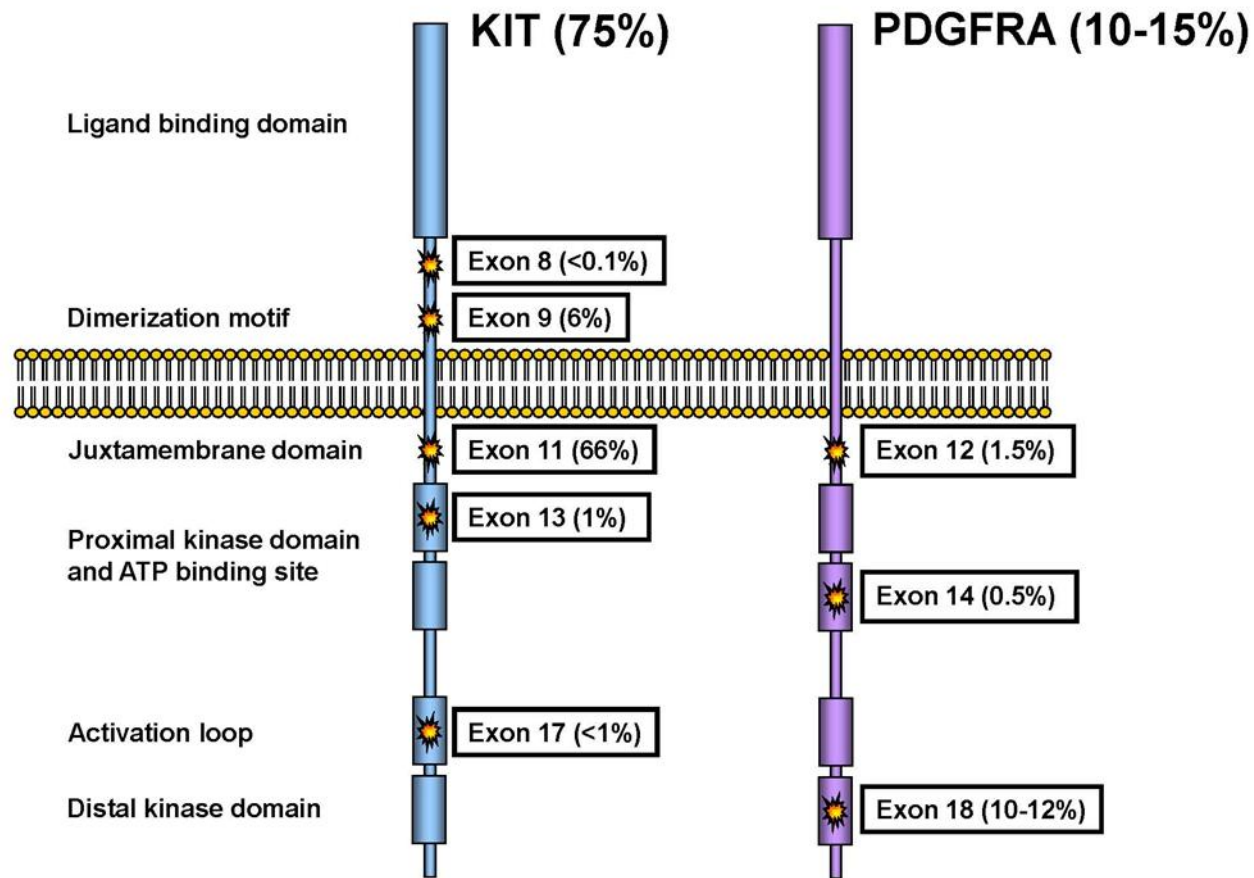


Figure 1: Distribution of KIT and PDGFRA mutations in gastrointestinal stromal tumours. *Permission courtesy of Professor Jason L. Hornick.*

Table

Table 1: 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 - ≤5 cm	Very low (1.9%)	Low (8.3%)	Low (4.3%)	Low (8.5%)
	>5 - ≤10 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 - ≤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%)

^a Defined as metastasis or tumour-related death.

^b Denotes small number of cases.

Modified version reprinted from *Semin Diagn Pathol*, 23(2), Miettinen M and Lasota J, Gastrointestinal stromal tumors: pathology and prognosis at different sites, Pages 70-83 (2006), with permission from Elsevier.³

Reference

3 Miettinen M and Lasota J (2006). Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol* 23(2):70-83.