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Review

Imaging surveillance of gastrointestinal stromal tumour: current recommendation by National Comprehensive Cancer Network and European Society of Medical Oncology-European Reference Network for rare adult solid cancers

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Imaging plays an active role in the surveillance of gastrointestinal stromal tumours (GISTs). Risk stratification schemes, based on size, mitotic count, and anatomical site of origin of the GIST, help in planning preoperative and postoperative imaging strategies especially in determining the frequency and duration of surveillance; however, there is no clear consensus on the optimal imaging strategies in patients with GISTs who are completely cured by surgery and patients who are at risk of recurrence. In addition, current surveillance protocols depend on the resectability of the primary tumour and presence of metastatic disease. The objective of this article is to provide a comprehensive review of the role of the different imaging methods for surveillance of GISTs, focusing on the guidelines recommended by National Comprehensive Cancer Network and European Society of Medical Oncology – European Network for Rare adult solid Cancers, and to propose practical guidelines for surveillance of GISTs for various risk categories.

Introduction

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal system. The last decade has seen dramatic advances in the understanding of pathogenesis and management of GISTs,

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which led to a significant increase in the overall survival of these patients. The biological behaviour of GIST is, however, determined by the interplay of several factors. For routine clinical management, few risk stratification models have been proposed to facilitate optimal patient care.[1–5] A widely used risk stratification model recommended both by National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology - European Reference Network for Rare adult solid cancers (ESMO-EURACAN) classifies GIST into very low-risk, low-risk, intermediate-risk, and high-risk categories based on tumour size ($\leq$2 cm, >2 to $\leq$5 cm, >5 to $\leq$10 cm and >10 cm), mitotic index ($\leq$5 or >5 per 50 high-power fields [hpf]) and anatomical site of origin (stomach, duodenum, jejunum/ileum, and rectum).[6,7] In addition to site, size and mitotic count, factors that determine outcome of GISTs include tumour rupture either at presentation or intra-operatively, male sex, and mutational status.[8] When using the risk estimation schemes, the tumour size and mitotic count should be treated as non-linear continuous variables. A novel prognostic contour mapping was developed by Joensuu *et al.* by nonlinear modelling of tumour size and mitotic count incorporating site and tumour rupture for estimation of individualized outcomes.[8]

Risk stratification schemes help in estimating the recurrence-free survival and in choosing patients who may benefit from adjuvant imatinib therapy, which has been shown to prolong the time for recurrence.[9] Patients with operable GIST (very low and low-risk) are often cured by surgery alone, whereas patients with intermediate- and high-risk GIST benefit from adjuvant imatinib.[8] Risk stratification also helps in planning preoperative and postoperative imaging strategies, especially in determining the frequency and duration of surveillance; however, there is no clear consensus on the optimal imaging strategies in patients with GISTs who are completely cured by surgery and patients who are at risk of recurrence.

The objective of this article is to provide a comprehensive review of the role of imaging in GISTs especially in the setting of long-term surveillance focusing on the guidelines recommended by NCCN and ESMO-EURACAN. Although guidelines are available in public domain, the aim of this article was to bind these guidelines together and propose a simplified practical follow-up protocol for various risk categories based on the existing guidelines. It is important for the radiologist to be aware of the current risk stratification models as radiologists are part of the multidisciplinary team involved in GIST management. Finally, we introduce the key fields of future research in surveillance.

Imaging techniques in GIST

The mainstay for imaging in GISTs is contrast-enhanced computed tomography (CT). CT of the abdomen and pelvis with intravenous contrast medium is often the investigation of choice for initial staging, monitoring response to treatment, and surveillance.[6,7] For initial staging, multiphasic CT in the unenhanced, arterial, and venous phase is recommended for adequate characterization of both the primary tumour and metastasis.[10] For monitoring response and surveillance, contrast-enhanced CT of the abdomen and pelvis in the venous phase is the investigation of choice. Some institutes routinely perform unenhanced CT of the abdomen to detect intra-tumoural haemorrhage. The German GIST Imaging Group recommends multiphasic CT similar to baseline after the end of therapy.[10] Negative oral contrast medium is recommended for initial staging where as positive oral contrast medium is recommended during follow-up to increase detection of peritoneal metastasis.[10] Dynamic perfusion CT is under investigation as a biomarker for response to molecular targeted therapies in metastatic GISTs.[11] Dual-energy CT (DECT) has been shown to be a promising technology for evaluation of liver metastasis in GISTs.[12,13] The use of virtual non-enhanced images generated through DECT can eliminate the need for acquisition of true unenhanced images.[12] Iodine-related attenuation has been shown in a study of 24 patients with liver metastasis from GISTs to be a better indicator of treatment response than Choi criteria.[12]

Chest radiography and chest CT can help to detect pulmonary metastases at initial staging.[10] Surveillance scans are typically limited to the abdomen and pelvis owing to the high incidence of hepatic and peritoneal metastases and infrequent pulmonary metastases in GISTs.[14] In a recent study of 631 patients with GISTs, Shinagare *et al.* concluded that thoracic imaging can be reserved for patients with bulky intra-abdominal disease.[14] In their study, pulmonary metastasis was encountered in 10% patients and was statistically associated only with bulky intra-abdominal metastases.[14] The exclusion of chest imaging helps to decrease surveillance costs and radiation exposure.[14]

Combined positron-emission tomography (PET)/CT can be useful for staging of GISTs, but does not offer an additional advantage over contrast-enhanced CT.[6] The NCCN guidelines suggest that PET is not a substitute for CT, but can be used to characterize ambiguous findings detected on CT or magnetic resonance imaging (MRI), assessing complex metastatic disease prior to surgery, and for staging patients with allergy to iodinated contrast medium (Fig 1).[6] The ESMO-EURACAN guidelines recommend baseline PET/CT to aid in the early assessment of treatment response when targeted therapy is under consideration.[7] There is no role for PET/CT in routine surveillance during and after adjuvant therapy.

MRI provides greater anatomical detail in certain anatomical sites such as the anorectal region and is useful in planning sphincter-saving surgery.[15] During follow-up, MRI of the abdomen and pelvis can be used as an alternative imaging method in young patients on surveillance as CT entails the risk of radiation and also in patients allergic to iodinated intravenous contrast media.[6,7] MRI can also be used as an alternative to CT for monitoring response to treatment. MRI can be used as a problem-solving tool when the response is difficult to interpret on CT due to pseudoprogression occurring in the setting of intra-tumoural haemorrhage, transient increase in lesions size, or the appearance of apparent new lesions that were previously

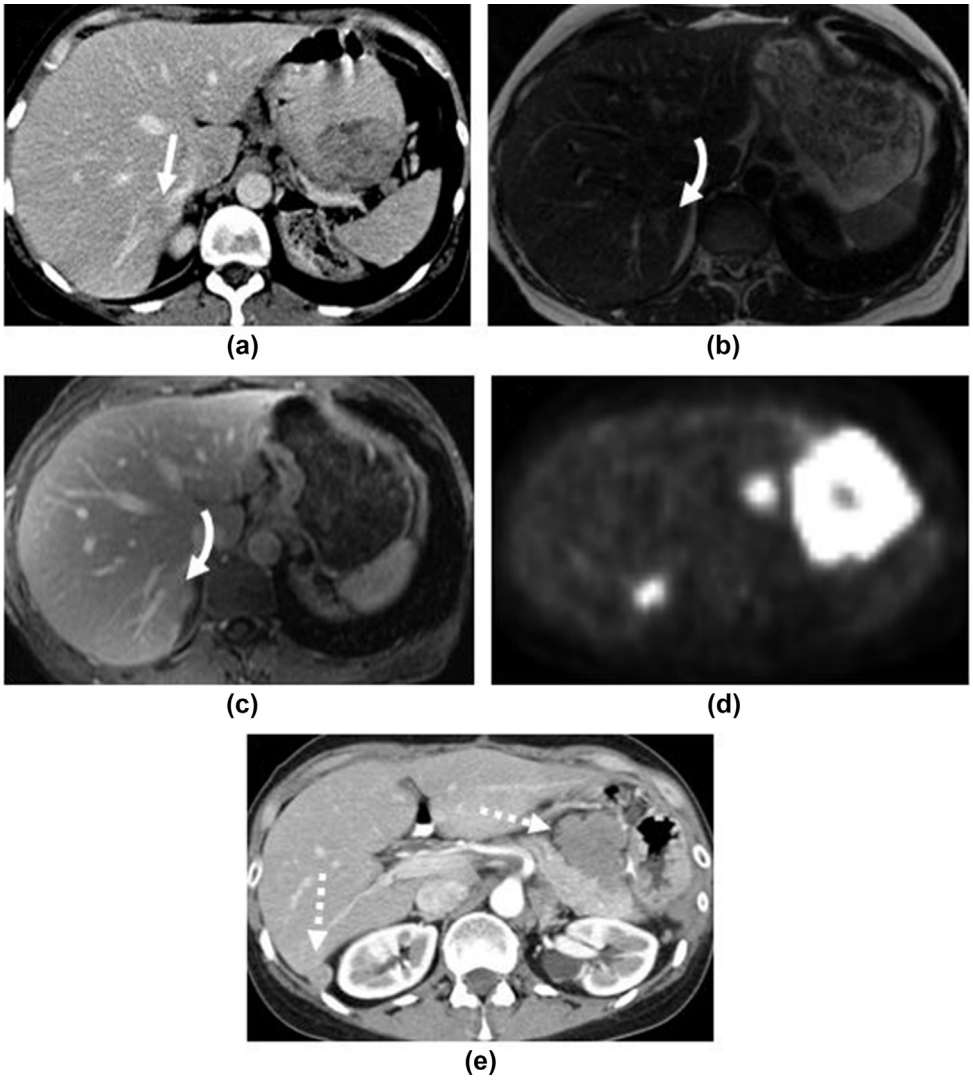

Figure 1 A 49-year-old woman presenting with gastrointestinal bleeding, who was found to have a c-kit-positive high-risk GIST of the stomach fundus. (a) Baseline CT performed for initial staging shows an ill-defined hypodense lesion in liver segment seven (arrow). MRI performed to further characterize the liver lesion shows a corresponding mildly T2-hyperintense lesion (b), with faint homogeneous arterial enhancement (b) (curved arrows), deemed indeterminate. (d) FDG-PET was then performed and showed diffuse FDG uptake of a primary gastric mass, of an adjacent peritoneal lesion, and similar FDG-avid uptake of the liver lesion, which was then characterized as a metastasis from the GIST. The patient underwent neoadjuvant imatinib and subsequently partial gastrectomy, omentectomy, and splenectomy. (e) CT performed for restaging 3 months after debulking surgery showed multiple peritoneal masses (dashed arrows), representing recurrent peritoneal disease.

occult (Fig 2).[6,16,17] New MRI techniques such as diffusion-weighted MRI and dynamic contrast-enhanced MRI enable functional and pharmacokinetic monitoring of anti-angiogenic therapy.[18,19] Their role in the early detection of recurrence warrants further investigation.

Ultrasound can be used for evaluation of liver lesions and guiding biopsy of indeterminate abdominal masses, and suspected liver and peritoneal metastasis. Endoscopic ultrasound with biopsy can be used in the work-up of patients with oesophageal, gastric, duodenal, and rectal GISTs.[20–22] Abdominal ultrasound can be used to follow-up patients in the adjuvant setting, but has several limitations including suboptimal evaluation of extra-hepatic relapses and operator-dependence. Contrast-enhanced ultrasound and contrast-enhanced endoscopic ultrasound enable real-time evaluation of intra-tumoural vasculature in different phases and has been recently shown to detect recurrence and treatment response early in GIST metastasis.[23,24] In a study of 10 patients with GIST metastasis treated with imatinib, De Giorgi *et al.* found that a decrease in tumour vascularity on contrast-enhanced ultrasound occurred before size changes on CT.[25] The potential role of this technique to detect early responses has to be evaluated in prospective studies.

Imaging in GIST

Imaging is used in GISTs for the diagnosis, staging, restaging after commencement of therapy, monitoring

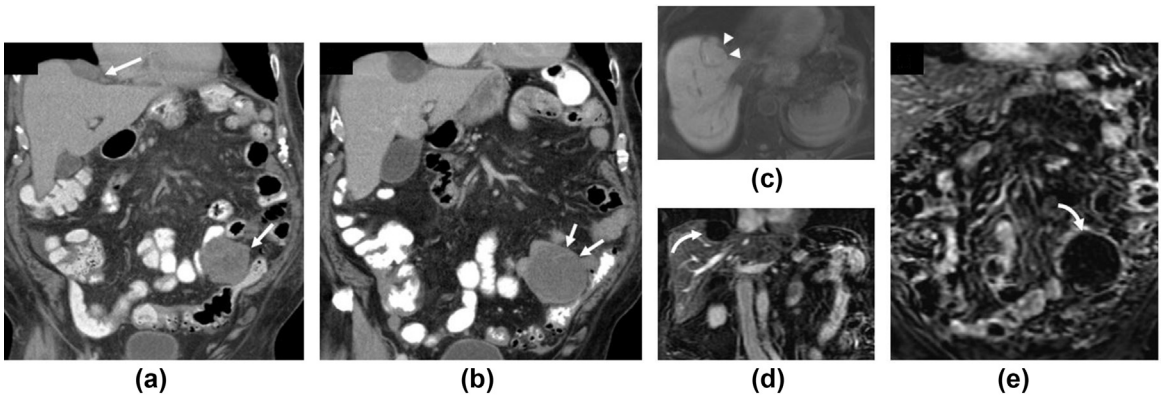

Figure 2 A 81-year-old man with exon 9 mutated high-risk GIST of the small bowel treated with adjuvant high-dose imatinib. (a) Baseline coronal reconstructed CT image of the abdomen and pelvis shows a perihepatic lesion and a peritoneal lesion in the left lower quadrant, demonstrating increased size and new intralesional hypodensity at the 3-month restaging CT (b). Possibility of intralesional haemorrhage was considered and MRI was performed, demonstrating T1 hyperintensity of the perihepatic lesion (c) on T1-weighted non-contrast fat-saturated images, with no enhancement of the perihepatic (d) and left lower quadrant (e) lesions on post-contrast T1 weighted subtracted images, demonstrating internal haemorrhage.

response to therapy, and for surveillance after therapy. The utility and frequency of imaging in the management of GISTs is determined by the presentation and extent of the GIST (Fig 3).

Small GISTs (<2 cm)

Small GISTs (<2 cm) are often incidentally detected on imaging or endoscopy and tend to be homogeneous polypoidal endoluminal lesions.[26] These are often of the low-risk type and can be either followed annually or biopsied/excised depending on the site of origin, patient preference, co-morbidities, and life expectancy.[7] There are no guidelines for optimal surveillance in patients who choose follow-up for small GISTs. The ESMO-EURACAN guidelines suggest an empirical initial short-term follow-up at approximately 3 months, and thereafter, at longer intervals reserving intervention for patients who become symptomatic or show tumour growth.[7] GISTs arising in the rectum, regardless of size are high-risk by definition and are better managed with surgical excision after cross-sectional imaging assessment.[27,28]

GISTs ≥2 cm

GISTs ≥2 cm are heterogeneous hypervascular masses that can display haemorrhage and necrosis. They have an exophytic growth pattern with displacement of adjacent viscera.[26] Spontaneous fistulisation with adjacent bowel loops (tumour–bowel fistula) and rupture with hemoperitoneum seen at the time presentation and portend poor prognosis.[29] Metastasis at the time of presentation can be seen in up to 50% patients with GISTs.[30] The liver and peritoneum are the most common sites of haematogenous metastases. Metastases tend to be heterogeneous and hypervascular with cystic or necrotic changes.[26] Nodal metastasis is uncommon and seen with epithelioid type of GIST especially succinate dehydrogenase (SDH)-deficient GISTs.[31]

GISTs ≥2 cm need surgical resection irrespective of location.[7] Prior to resection, the histopathology can be confirmed by performing biopsy under endoscopic or ultrasound guidance. When encountered with large abdominal masses, which may require multivisceral resection, the ESMO-EURACAN guidelines recommend ultrasound or CT-guided core biopsies of the mass as well as any suspected metastasis to confirm histopathology and guide surgical planning.[7] Preoperative imaging can help in determining patients who may benefit from neoadjuvant and adjuvant imatinib therapy.

Imaging in the adjuvant setting

Although complete surgical resection is feasible in a substantial proportion of GISTs, relapses occurred frequently in the pre-imatinib era, especially in high-risk GISTs. Rutkowski *et al.* in their study of 335 patients with primary resectable GISTs in the pre-imatinib era found that tumours >5 cm had a 5-year disease-free survival of 23–31% compared to 77% for tumours ≤5 cm.[32] Administration of imatinib in the adjuvant setting has been shown to prolong the recurrence-free survival and overall survival. Three-year adjuvant imatinib therapy has been shown in a randomized controlled trial to offer better progression-free survival than 1-year imatinib therapy and recommended by both the NCCN and ESMO-EURACAN.[6,7,9] Surveillance with imaging in these patients can help in timely detection of relapses.

When to image?

The optimal strategy for imaging surveillance is uncertain and can be guided by risk stratification using anatomical site of origin, tumour size, and mitotic count. There are no established guidelines for the frequency of surveillance imaging in GISTs. In patients who have resectable localized GISTs, the NCCN recommends performing CT arbitrarily at

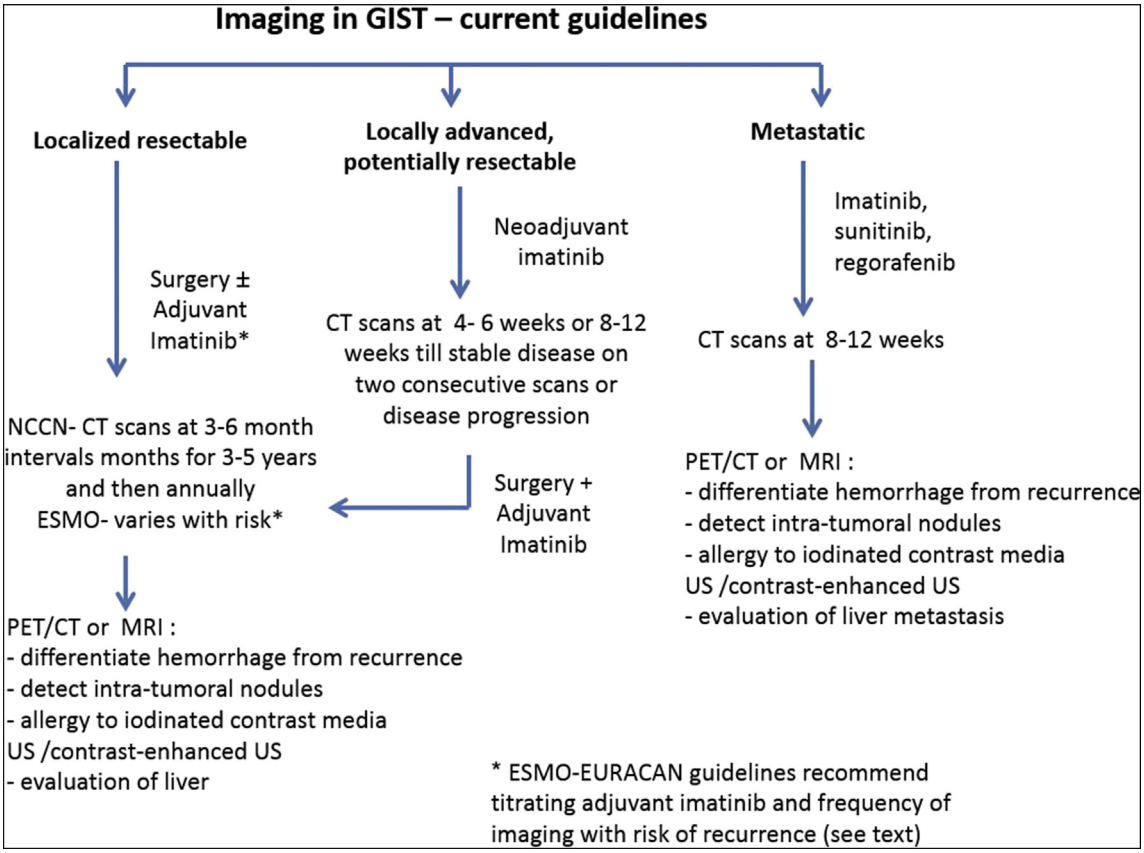

Figure 3 Current guidelines for imaging in gastrointestinal stromal tumour. NCCN, National Comprehensive Cancer Network; ESMO-EURACAN, European Society for Medical Oncology - European Reference Network for Rare Adult Solid Cancers.

intervals of 3–6 months for 3–5 years and then annually in the adjuvant setting after resection of the primary with the aim of detecting local recurrence and distant metastases[6]; however, in a recent study, Joensuu *et al.* found that hazard adjusted follow-up CT recommendations can significantly decrease the number of scans by up to 30% compared to the NCCN recommendations without affecting the efficacy of detecting recurrent tumour.[33] The ESMO-EURACAN guidelines suggest tailoring the follow-up schedules according to risk stratification.[7] GISTs with very low-risk of recurrence are invariably cured by surgery, and therefore, do not need adjuvant imatinib or longitudinal imaging. Whereas GISTs with low-risk (excluding tumours with high mitotic counts) can be followed with sparse imaging for 5 years at 6–12 month intervals, intermediate and high-risk GISTs need denser imaging for at least 13 years (Fig 4).[7] The timing of scans for high-risk GISTs recommended by ESMO-EURACAN includes 3–6 month intervals for the first 3 years during adjuvant imatinib, then every 3 months for 2 years and every 6 months for another 3 years after cessation of imatinib. Annual imaging is recommended for another 5 years.

What to look for?

Early detection of relapse on surveillance scans is of paramount importance and, at the same time, challenging. The most common sites of relapses are the liver and peritoneal cavity. In patients receiving adjuvant therapy with no evidence of disease, relapse can be seen as new metastatic lesions in these sites. In patients with no evidence of disease, but with residual cystic metastases, recurrence is seen as enlargement of existing treated cystic lesions, gradual increase in intra-tumoural density in treated cystic metastases, or development of enhancing intra-tumoural nodules in cystic metastasis referred to as "nodule within mass" pattern of progression.[17,34]

MRI can be useful in the early detection of metastasis and characterizing suspicious lesions seen on CT scan due to better soft-tissue resolution. Recurrence in patients with residual cystic metastases is seen as intra-tumoural nodules that are iso-to hypointense to liver parenchyma on T2-weighted images with intense enhancement after gadolinium administration.[34] Relapses can be detected earlier on PET/CT, which can be seen as new metabolically active metastases or new metabolic activity in treated metastatic lesions.[35] Contrast-enhanced ultrasound and dynamic perfusion CT are under investigation for detecting early relapses.[24]

Surveillance imaging in succinate dehydrogenase-deficient GISTs

In special circumstances, the role of surveillance imaging is to detect metachronous tumours that are either new

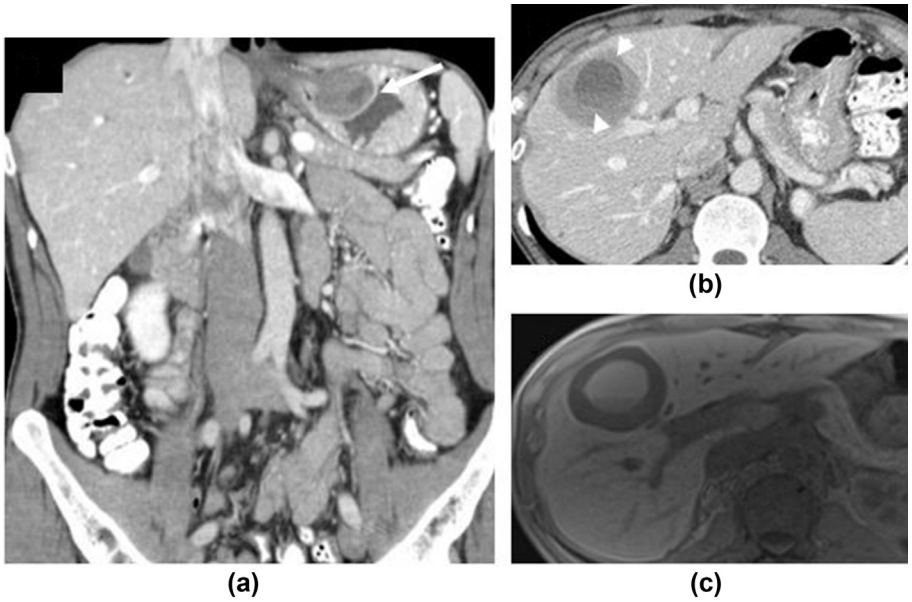

Figure 4 A 43-year-old man with an exon 11 *KIT* mutant GIST of the stomach. Preoperative CT shows a heterogeneous mass at the stomach fundus (arrow), consistent with GIST. The mass was 4.5 cm in size and showed a mitotic index of 86/50, thus categorized as intermediate grade risk. The patient was started on imatinib and underwent follow-up CT every 3–6 months. Follow-up CT performed after 3 years from diagnosis shows a new centrally hypodense liver lesion (b). (c) MRI performed to further characterize the lesion shows a centrally T1 hyperintense lesion with fluid–fluid level representing central haemorrhage, highly suspicious for metastasis from GIST, which was confirmed at tissue biopsy.

GISTs or tumours associated with concurrent syndromes. This is especially true for SDH-deficient GISTs, which are associated with Carney triad and Carney–Stratakis syndrome.[36] Patients with these syndromes are at risk of paragangliomas, which can develop any time during the disease course, sometimes taking decades to develop the full phenotype.[31,36] In addition, SDH-deficient GISTs tend to have an indolent course with a long duration until metastases develop and long survival even after developing metastasis in contrast to aggressive GIST subtypes, especially those with *KIT* exon 9 mutations which have a short disease-free survival (Fig 5).[31] All these factors may necessitate life-long follow-up imaging in these patients. The duration and frequency of longitudinal surveillance in these patients is however uncertain31. SDH-deficient GISTs are often seen in young women and given the need for long duration of follow-up, MRI should be preferred over CT for surveillance to decrease radiation exposure. As paragangliomas can occur anywhere in the body, whole-body PET/CT and whole-body MRI can have a potential role in the surveillance of these patients.

Imaging in the neoadjuvant setting

Although the majority of GISTs are surgically resectable, surgery can be challenging due to size and location of locally advanced resectable GISTs. Administration of imatinib in the neoadjuvant setting has been shown to decrease tumour size and enable less morbid, organ-preserving surgeries, as well as decreasing the risk of postoperative recurrence when combined with adjuvant imatinib.[28,37,38] CT is often performed in such patients at 4–6 week, or in some institutes at 8–12 week, intervals after the start of therapy to determine response and the possibility of resectability.[6,7] The duration of follow-up CT in these patients prior to surgical resection is uncertain. Empirical imaging guidelines suggested by NCCN for determining the timing of surgery include stable disease (plateau response) on two consecutive examinations or the development of progressive disease on follow-up.[6] In a retrospective study of 20 patients, it was shown that the maximum response to neoadjuvant imatinib occurs at 28 weeks after start of therapy and plateaus at 34 weeks.[39] In a phase II study of 53 resected large GISTs of the stomach treated with neoadjuvant imatinib for 24–36 weeks, the R0 resection rate was 91%.[40]

Imaging in the metastatic setting

In patients with metastatic GISTs, imatinib is the first-line treatment. Serial contrast-enhanced CT is used to monitor the response to imatinib and to determine whether cytoreductive surgery is feasible in selected patients. The response to imatinib on CT is different from conventional chemotherapy. The heterogeneous metastasis shows decrease in density with little or no shrinkage in size.[41] In addition, some lesions can increase in size with decrease in density or occult lesions can become apparent mimicking new lesions, a phenomenon referred to as pseudoprogression.[16] The decrease in density correlates at histopathology with cellular depletion and myxoid degeneration with no necrosis or inflammation.[42] Responding lesions can have near cystic attenuation on CT. The density changes are not captured by the Response Evaluation Criteria In Solid

Figure 5 A 38-year-old man with SDH-deficient gastric GIST. The patient underwent partial gastrectomy and adjuvant imatinib for 1 year. (a) CT performed after 6 years from diagnosis, shows enlarged gastrohepatic nodes, suspicious for metastasis (arrows). Therapy with high-dose imatinib was initiated. (b) Restaging CT performed 3 years after re-initiation of imatinib shows increased size of the gastrohepatic nodes, which were subsequently resected. (c) Follow-up CT performed 6 years after debulking surgery and 15 years after initial diagnosis, shows small soft-tissue nodules adjacent to the gastric remnant, suspicious for recurrent disease (curved arrow).

Tumours (RECIST), which are based on unidimensional size changes.[43] The Choi criteria, which incorporate subjective changes in the density for response evaluation, have therefore been proposed for assessing response to imatinib in metastatic GISTs.[43] In one of the earlier studies evaluating the response patterns in metastatic GISTs treated with imatinib, Choi criteria had higher sensitivity (97%) for detecting metabolic response on PET/CT compared to RECIST (52%).[43]

On MRI, response to treatment is seen as an increase in signal on T2-weighted images with decrease in enhancement. Occasionally intratumoural haemorrhage can result in an increase in intra-tumoural density on CT masking the treatment response, especially in metastasis treated with sunitinib.[17] MRI can be helpful in such cases as haemorrhage can be confidently characterized and differentiated from viable tumour tissue on MRI.[17] Diffusion-weighted imaging with apparent diffusion coefficient (ADC) maps can help to detect the treatment response as early as 1 week after therapy.[18,19] Metastatic lesions responding to treatment typically show an increase in ADC value after treatment.

PET can detect response to therapy earlier than anatomical imaging. A drop in the metabolic activity on PET/CT occurs as early as 24 hours after the start of imatinib therapy.[44,45] The degree of decrease in metabolic activity on PET after initiation of therapy has been shown to correlate with prognosis.[45] An increase in metastatic lesion size and appearance of apparent new lesions due to treatment effect on CT can be differentiated from progression by lack of metabolic activity on PET/CT.[6,17]

Resistance to treatment

Patients with metastatic GISTs treated with molecular targeted therapies are regularly monitored with imaging to ensure treatment response and detect early signs of resistance. Resistance to treatment with imatinib can be primary or secondary. Primary resistance to imatinib occurs in the first 6 months of therapy and encountered in GISTs with *KIT* exon 9, PDGFRA exon 18, SDH-deficient and wild-type GISTs.[46] Primary resistance to treatment is suspected on imaging when there are no typical density changes or decline in metabolic activity on the first restaging CT or PET/CT. Primary resistance is managed with escalation of imatinib dose followed by switching to sunitinib for most GISTs except for some wild-type GISTs.[7]

Secondary resistance to imatinib refers to disease progression after an initial response for at least 6 months and often occurs due to secondary mutations in *KIT* exon 11.[47] Secondary resistance is seen on imaging as growth of pre-existing lesions or new lesions. Atypical patterns of secondary resistance include increase in intra-tumoural density and new intratumoural enhancing nodules described as the “nodule within mass” pattern of progression.[34]

Proposed follow-up and imaging schedules

We propose a simplified imaging-based follow-up protocol partially based on existing recommendations.[48,49] The follow-up for patients with surgically resected GISTs should be based on size and risk (Fig 6). Adjuvant imatinib therapy is not recommended for very-low and low-risk GISTs except for tumours with high mitotic counts. For very low risk and tumours $\leq$2 cm that are resected, a single follow-up at 12-month intervals is sufficient to ensure complete cure. For tumours $>$2 cm and $\leq$5 cm and low risk, CT examinations at 6-month intervals for 5 years is a reasonable follow-up strategy. Patients with tumours $>$5 cm and tumours of intermediate or high-risk need adjuvant imatinib for at least 3 years according to the existing evidence. The imaging frequency should be 3 monthly for the first year and 6 months for the next 2 years for both intermediate- and high-risk GISTs. After the end of adjuvant imatinib, intermediate-risk GISTs should be followed annually for 10 years where as high-risk GISTs need more frequent follow-up at 6-month intervals for 10 years.

Although mutational status determines the outcome of GISTs, the mutation profile is not an established risk factor and not included in the current risk stratification models. There are as no such mutation-specific follow-up protocol recommendations; however, indolent GISTs such as SDH-deficient GISTs and GISTs associated with syndromes need longer, though less frequent (annual) follow-up imaging.

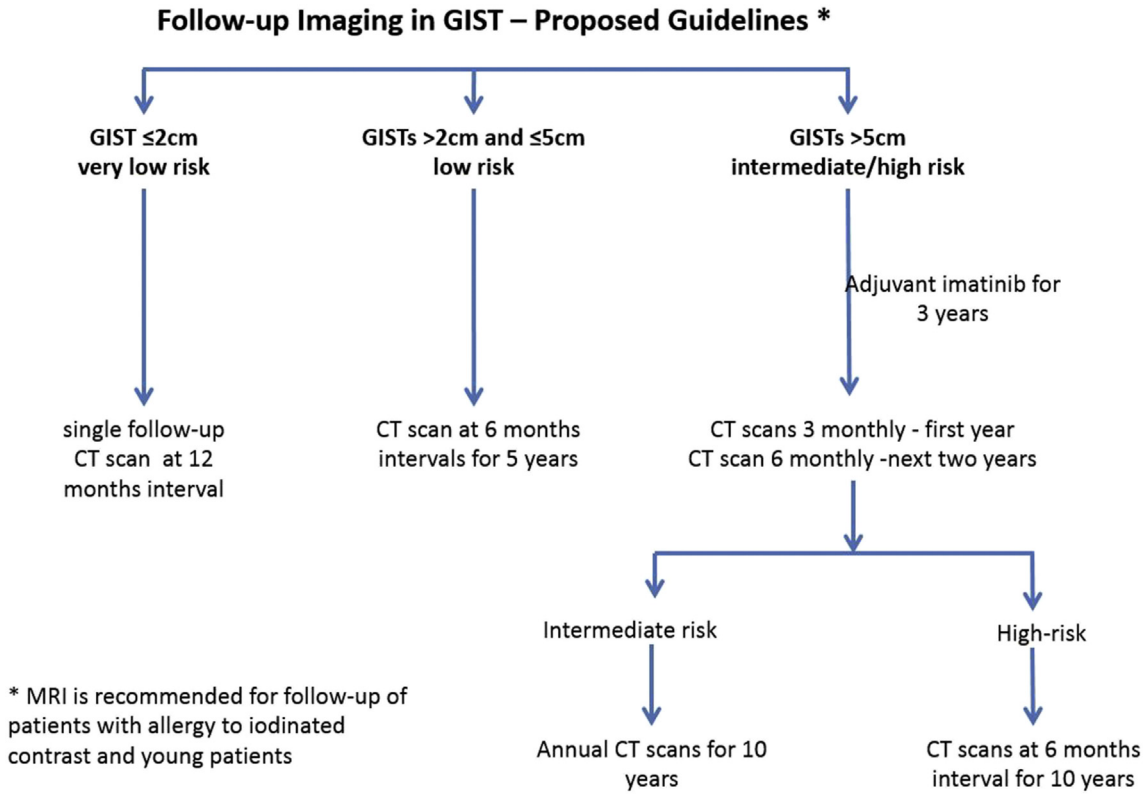

Figure 6 Proposed guidelines for follow-up imaging after surgical resection in patients with GIST.

Key fields for future research

Advances of next-generation sequencing techniques have expanded significantly the amount of data potentially available for GIST diagnosis and stratification. Circulating tumour DNA (ctDNA) are small fragments of DNA derived from cancerous cells.[50] In GISTs, ctDNA tumour mutation types represent potentially independent prognostic factors, with rare tumour mutations identified only on ctDNA.[51] MicroRNAs (miRNAs) are small non-coding RNAs regulating gene expression, and various studies have demonstrated their carcinogenic effect in different types of cancer.[52] Several miRNAs have been identified as potential prognostic biomarkers for GISTs. Various miRNAs correlated with shorter disease-free survival time and aggressive disease behaviour including tumour size, mitotic counts, and risk grade.[53–56]

In the future, high-quality data derived from genomic sequencing could be used to optimize risk stratification and improve surveillance protocols.

Conclusion

Surveillance protocols for GISTs depend on the resectability of the primary tumour and on the presence of metastatic disease as per NCCN and ESMO-EURACAN guidelines. An optimal surveillance protocol for follow-up imaging after surgical resection in patients with GISTs should be tailored according to the risk of recurrence.

Conflict of interest

The authors declare no conflict of interest.

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