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POSITION PAPER

Indian Council of Medical Research consensus document for the management of gastrointestinal stromal tumors

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EXECUTIVE SUMMARY

- This consensus statement was produced along with the gastric cancer discussions as stomach is the most common site for gastrointestinal stromal tumor (GIST). The recommendations apply to treatment of GIST.
- Evaluation of a patient with newly diagnosed GIST should include essential tests: A standard white light endoscopy with 6-8 biopsies (c-KIT testing on immunohistochemistry) from the tumor for confirmation of the diagnosis, a computed tomography (CT) scan (multi-detector or helical) of the abdomen and pelvis for staging with a CT chest or chest X-ray, and complete blood counts, renal function tests and liver function tests. Endoscopic ultrasonography (EUS)/ magnetic resonance imaging (MRI)/positron emission tomography (PET)-CT are not recommended for all patients.
- For localized and resectable disease, surgery is recommended. The need for adjuvant treatment with imatinib would be guided by the risk stratification on the histopathological analysis of the resected specimen.
- For localized but borderline resectable tumors, upfront surgery may be considered only if complications due to the tumor are present such as major bleeding or gastric outlet obstruction. In all other patients, neoadjuvant imatinib should be considered to downstage the disease followed by surgery (with a curative intent, if feasible) in those with stable or partial response. This may be followed by adjuvant imatinib. In those patients with a poor response, further imatinib with dose escalation or sunitinib may be considered.
- Patients with metastatic disease must be assessed for treatment with imatinib as first-line therapy followed by sunitinib as second-line therapy versus best supportive care on an individual basis.

Key words: *Diagnosis, GIST, guidelines, ICMR, treatment*

INCIDENCE

Gastrointestinal stromal tumors are uncommon mesenchymal smooth muscle tumors that may arise in any part of the GI tract. They account for <1% of all GI tract cancers[1]. Among all the sites in the GI tract, gastric GISTs are the most common [1-3]. In one of the largest retrospective series of gastric GISTs[4], it was noted that these tumors occurred in patients above the age of 40 years, a finding confirmed by Indian studies[2,3]. These tumors present with a median diameter of 6 cm[4]. Gastric GISTs may present as part of the Carney triad syndrome (other lesions including paragangliomas and parachondromas). The incidence of GIST in India is unknown. Data regarding management strategies are largely derived from studies in Caucasian patients.

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PURPOSE

Several International Consensus Guidelines are available for the management of GISTs[5,6]. It is essential to analyze the evidence pertaining to GISTs from India and the rest of the world with an aim to formulate reliable, evidence-based guidelines that could be applicable to Indian patients bearing in mind the socio-cultural diversity, the distribution of resources and the availability and accessibility to health-care. Taking into consideration peripheral oncology centers, regional cancer centers and tertiary cancer centers in major cities, the set of recommendations includes two categories, *viz*:

- Desirable/Ideal: Tests and treatments that may not be available at all centers but the centers should aspire to have them in the near future; and
- Essential: Bare minimum that should be offered to all the patients by all the centers treating cancer patients.

DIAGNOSIS AND STAGING

Evaluation of a patient presenting with a gastric GIST should be aimed at pathological confirmation of the diagnosis and an accurate staging of the disease.

Essential tests which need to be done in all patients include:

- Standard white light endoscopy with 6-8 biopsies from the tumor for confirmation of the diagnosis (c-kit/DOG-1 testing on immunohistochemistry)[7].
- CT scan (multi-detector or helical) of the abdomen and pelvis which consists of a nonenhanced phase, an arterial phase, and a portal venous phase. Patients may receive a negative/water-equivalent oral contrast agent for the detection of GI tract wall lesions. If the patient is allergic to contrast media, then an MRI of the abdomen is recommended along with a noncontrast CT thorax.
- CT Thorax or X-ray for staging of the chest, and
- Routine blood investigations-complete blood counts, renal function tests, and liver function tests.

Desirable investigations (when indicated) include:

- 2-[^{18}F] fluoro 2-deoxyD-glucose-PET or PET-CT-if metastatic disease is suspected.
- EUS may be used for gastric GISTs to stage and accurately identify subjects with an early GIST in whom endoscopic therapy could be planned.

RISK ASSESSMENT

The TNM classification is not able to risk stratify patients with GIST, hence, its routine use is not recommended. Over the years, the key prognostic criteria for GIST are the size of primary tumor, mitotic rate, the location of primary (gastric GIST have a better prognosis than small bowel or rectal GISTs), and rupture at the time of surgery. After curative resections, patients with a mitotic rate of ≥10/50 high-power fields (HPFs) have a poorer survival rate as compared to smaller lesions[8]. Fletcher *et al.*[9] stratified the risk of aggressive or malignant behavior in GISTs, based on size and mitotic rate, and this is widely followed:

- Very low risk <2 cm and <5/50 HPFs.
- Low risk 2-5 cm and <5/50 HPFs.
- Intermediate risk either[1] <5 cm and 6-10/50 HPFs or[2] 5-10 cm and <5/50 HPFs.
- High risk includes[1] >5 cm and >5/50 HPFs,[2] >10 cm and any mitotic rate, or[3] any size and >10/50 HPFs.

Table 1 shows the evolution of risk criteria over the years. Patients with gastric GISTs do significantly better compared to others. Recently, heat and contour maps give added information and may be used routinely in the future.

TREATMENT PLAN

All patients should be discussed at the multidisciplinary team (MDT) or tumor board meetings, and a care plan advised. The MDT should comprise of surgical, medical, and radiation oncologists; gastroenterologists; pathologists; radiologists (including interventional and nuclear medicine radiologists); nurse specialists; and palliative care physicians. Treatment decisions are based on the extent of disease. The intent of treatment is "curative" for patients with localized resectable disease and "palliative" for patients with metastatic disease. In patients with locally advanced disease, surgical resection may be undertaken following neoadjuvant imatinib[14].

Table 1: Risk stratification criteria for GIST over the years

Author (reference)	Year	Risk stratification criteria for GIST
DeMatteo *et al.*[10]	2000	Mitoses
Fletcher *et al.*, NIH[9]	2002	Mitoses + size of the tumor
Miettinen and Lasota, AFIP[4]	2006	Mitoses + size of tumor + site of tumor
Joensuu Modified NIH[11]	2008	Mitoses + size of tumor + site of tumor + presence of rupture
Joensuu *et al.*, Prenen *et al.*[12,13]	2006, 2012	Mitoses + size of tumour + site of tumor + presence of rupture + mutation + heat contour maps

GIST — Gastrointestinal stromal tumors

Nonmetastatic, resectable gastric cancer (including loco-regionally advanced disease)

Role of surgery

The ideal treatment for a nonmetastatic GIST ≥2 cm [4] or even tumors <2 cm but symptomatic, is complete surgical resection (R0) without injury to the pseudocapsule wherever technically feasible without undue risk to the patient[10]. In patients with tumors that are ≥10 cm or that have ruptured (where there is a high-risk of cells being shed), every attempt must be made to resect all visible tumor. Such tumors that have been removed with a microscopically positive margin (R1) recurrence-free survival at a median of 4 years was found to be not different from those patients who underwent an R0 resection[15]. Gastric GISTs generally arise from the wall and grow outward. As a result, rather than standard resections, often a wedge resection with negative margins may be adequate. In the case of advanced GISTs that have invaded surrounding structures, *en bloc* resections of the involved organs, is recommended.

Lymphadenectomy is not indicated as part of surgery for GISTs as they seldom metastasize to lymph nodes[16]. However, enlarged lymph nodes that appear suspicious of malignant invasion may be sampled at the time of surgery.

For localized but borderline resectable GIST, upfront surgery may be considered only if complications due to the tumor are present such as major bleeding or gastric outlet obstruction. In all other patients, neoadjuvant imatinib should be considered to downstage the disease followed by surgery in those with stable or partial response[14,17].

SYSTEMIC THERAPY IN NONMETASTATIC GASTROINTESTINAL STROMAL TUMOURS

Neoadjuvant imatinib

Neoadjuvant imatinib for treating a localized GIST is a matter of surgical and medical discretion and should be made on an individual basis. Preoperative imatinib may be used in the following settings: If an R0 resection is unlikely, very large localized, but potentially resectable GIST that may bleed or rupture, poorly located small GISTs that are difficult to resect, nonmetastatic, but localized, GISTs deemed unresectable.

In unresectable or locally advanced GISTs, preoperative imatinib could be useful to improve resectability and reduce surgical morbidity[17]. The optimal duration of preoperative therapy is unknown; hence, imatinib may be continued until maximal response. Early response assessment after 8 weeks of initiation of therapy should be done. Each new cross-sectional imaging should prompt multidisciplinary reappraisal of the surgery timing or continuation of preoperative imatinib. If the progression is confirmed with CT scan, surgery is recommended after discontinuing imatinib.

Adjuvant imatinib

Standard care for primary resectable localized gastric GISTs is surgery followed by postoperative radiologic surveillance for recurrence. However, because many patients develop recurrence after resection, imatinib is indicated in the postoperative setting to reduce recurrence. Adjuvant imatinib 400 mg daily for resectable GIST should be considered in high-risk disease (tumor size >10 cm and any mitotic index; any tumor size and mitotic index >10, tumor size 5 cm and mitotic index >5, tumor size ≤5 cm and mitotic index >5 (nongastric site), tumor size 5.1-10 cm and mitotic index ≤5 (nongastric site), any tumor size and any mitotic index in the presence of tumor rupture). Prospective randomized evidence shows that this treatment must be continued for 3 years in patients with c-kit/CD-117 positive GIST[18]. Ideally, *PDGFRA D-842V* mutation testing should also be considered as these patients do not respond to imatinib and patients with exon 9 *kit* mutation need higher doses of imatinib (800 mg)[19].

Metastatic gastrointestinal stromal tumors

Role of surgery

Palliative resections may need to be undertaken in patients who have uncontrolled bleeding or gastric outlet obstruction who are otherwise well with a projected longer life expectancy. A gastrojejunostomy may be helpful in patients with distally obstructing tumors with distant metastases. In those patients with short-life expectancy, endoscopic stenting or an endoscopically-placed nasojejunal tube for feeding may be useful for palliation. In patients with recurrent or metastatic GIST, cytoreductive surgery may need to be considered in the following settings-stable disease or disease responsive to imatinib therapy when complete gross resection is possible, progression of isolated clones on therapy after initial response (indicative of secondary drug resistance), while other disease sites remain stable (limited disease progression) and in case of emergencies, including hemorrhage, perforation, obstruction, or abscess formation. Surgery should also be considered for patients with impending emergencies, including those with significant cystic degeneration who are at potential risk for perforation. Complete excision of residual metastatic disease has been associated with a good prognosis, but there are no randomized data to support this. Hence, each decision should be individualized within an MDT setting[20].

Role of biological therapy

For recurrent or metastatic GIST, the current standard of care is imatinib 400 mg for the patient who is c-kit positive [21,22]. Patients with kit exon nine mutations do better on the higher dose of imatinib 800 mg (19). The treatment in metastatic patients has to be continued indefinitely. It is important to discuss compliance and drug interactions with the patient at the time of commencing therapy. Tumor response should be assessed at 3 monthly intervals to begin with and then 6 monthly if response is ongoing. If patients demonstrate progressive disease on imatinib, the standard approach is to increase the dose from 400 mg to 800 mg daily[22].

In the case of progression or intolerance on imatinib, second-line treatment with sunitinib can be considered. Sunitinib at the dose of 50 mg has been shown to be effective in terms of progression-free survival using a '4 weeks on-2 weeks off' regimen though nonrandomized data has shown that continuous dosing at 37.5 mg is better tolerated and equally effective[23]. After failing on sunitinib, patients with metastatic GIST can be considered for third-line treatment with regorafenib or be considered for participation in a clinical trial[24].

FOLLOW-UP

There are no data on optimal follow-up for patients with GIST. The aim of follow-up is to detect recurrences early as well as to assess any complication due to surgery/radiotherapy. Follow-up can be risk stratified, and patients with high-risk disease should be followed-up every 3-4 months for the first 2 years and then 6 monthly. Patients with low-risk disease may be followed-up 6 monthly. A repeat endoscopy after 6 months to a year postsurgery is advised. CT scans can be done at annual intervals or sooner if the patient develops symptoms suspicious of recurrent disease. Further research should focus on epidemiologic and genetic markers in Indian patients as there is some suggestion that the biology may be different in Indian patients.[25]

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