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POSITION PAPER

Indian Council of Medical Research consensus document for the management of gastric cancer

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EXECUTIVE SUMMARY

- The document is based on consensus among the experts and best available evidence pertaining to Indian population and is meant for practice in India.
- Evaluation of a patient with newly diagnosed gastric cancer should include essential tests: A standard white light endoscopy with multiple biopsies 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 and liver function tests. Endoscopic ultrasonography/magnetic resonance imaging/positron emission tomography-CT is not recommended for all patients.
- For early stage disease (IA/B, N0), surgery alone is recommended. The need for adjuvant treatment would be guided by the histopathological analysis of the resected specimen.
- For locally advanced stage (IB, N^+ to IIIC), neoadjuvant chemotherapy may be considered to downstage the disease followed by surgery. This may be followed by adjuvant chemotherapy (as part of the peri-operative chemotherapy regimen)
- Patients with stage IV/metastatic disease must be assessed for chemotherapy versus best supportive care on an individual basis.
- Clinical examination including history and physical examination are recommended at each follow-up visit, with a yearly CT scan of the chest, abdomen, and pelvis.
- HER2 testing should be considered in patients with metastatic disease.
- 5-FU may be replaced with capecitabine if patients do not have gastric outlet obstruction. Cisplatin may be replaced with oxaliplatin in the regimens.

Key words: *Diagnosis, gastric cancer, guidelines, Indian Council of Medical Research, treatment*

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INCIDENCE

Gastric cancer is the second most common cause of cancer-related deaths among Indian men and women.[1] It ranks among the five most common cancers among young Indian men and women (aged 15-44 years) based on a study from Karnataka.[2] It has been estimated that the number of new gastric cancers is about 34,000 (with a male predominance ratio of 1:2) with a progressive

increase postulated such that by the year 2020, there would be approximately 50,000 new gastric cancer cases annually in India. The 5-year survival rate for surgically resected patients was reported to be just 27% in 1992.[3]

The National Cancer Registry Program listed the incidence of gastric cancer to be the highest in the north-east parts of the country-in Aizawl, Mizoram state, the age-adjusted incidence rate in males is 57.3 and 33.6 among females per 100,000.[4]

PURPOSE

Though International Consensus Guidelines are available for the management of gastric cancer, it is not entirely feasible to apply these guidelines to the Indian population owing to differences in incidence of the disease in different parts of India, socioeconomic factors, and availability of resources.[5,6] Therefore, it is essential to analyze the evidence pertaining to gastric cancer from India and the rest of the world with an aim to formulate evidence-based guidelines that could be applicable to Indian patients. 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

In India, due to the lack of screening programs for gastric cancer, clinicians must be aware of the clinical symptoms and signs of gastric cancer such as anorexia, unexplained weight loss, sudden onset of dyspepsia after the age of 40 years, and malaena. These should prompt the clinician to prescribe investigations that would confirm or rule out gastric cancer. Evaluation of a patient presenting with a gastric cancer should be aimed at pathological confirmation of the diagnosis and an accurate staging of the disease.

Diagnosis of gastric cancer

Upper gastrointestinal standard white light endoscopy with multiple biopsies from the tumor is regarded as an essential test for the confirmation of the diagnosis of gastric cancer. The endoscopy report should mention the type of tumor (proliferative/ulcerated/linitis plastica), the longitudinal and circumferential extent of the tumor, and a comment on the involvement of the gastro-esophageal junction (GOJ) or the antrum where applicable. The histology should be reported as per the World Health Organization criteria. Endoscopic ultrasonography (EUS) is desirable in patients with early gastric cancer (EGC) in whom endoscopic therapy is planned.

Tumor markers such as serum carcinoembryonic antigen and carbohydrate antigen 19-9 (CA 19-9) are not recommended in the routine management of gastric cancer but they may serve a useful purpose in patient follow-up if they are raised at the time of initial diagnosis.

Staging of gastric cancer

Routine investigations to be performed include complete blood counts, renal and liver function tests. A computed tomography (CT) scan (multi-detector/MD or helical) of the abdomen and pelvis for staging with a CT chest or chest X-ray is regarded as essential for the appropriate staging of gastric cancer. Endoscopic ultrasound and magnetic resonance imaging (MRI) are other equivalent investigations for T staging and serosal involvement. EUS is more accurate in proximal EGCs and essential prior to planning endoscopic resections to confirm T1/T2 N0 status as more advanced cancers may require neoadjuvant therapy.[5]

Optional investigations available, but not routinely recommended except in specific clinical scenarios, include a trans-abdominal ultrasound in patients suspected of having metastatic disease as it will allow confirmation of the metastases, especially to the liver and permit a fine needle aspiration to confirm the diagnosis thereby avoiding extensive, costly investigations. MDCT, MRI and 2-[^{18}F] fluoro 2-deoxyD-glucose positron emission tomography (FDG-PET-CT) have high (and equivalent) sensitivity and specificity for hepatic metastases, but with poor sensitivity for peritoneal metastases.[7] Hence, staging laparoscopy may be of use in patients with T3/4 (bulky) disease prior to commencing neoadjuvant therapy as it may help detect occult which may change the intent of treatment for the patient. While FDG-PET or PET-CT is not routinely recommended and is not of use in mucinous or signet ring tumors, it may be used in patients with suspected extra-abdominal metastases from proximal gastric cancers.[8]

In patients with metastatic disease, testing for Her2 receptor overexpression is regarded as essential only if trastuzumab is available for the patient.[9]

Staging should be performed as per the American Joint Committee on Cancer staging manual (7th edition, updated in 2010), and patients should be assigned a TNM stage.[10]

TREATMENT PLAN

Treatment of each patient should ideally be undertaken by a multidisciplinary team. The intent of treatment is "curative" for patients with stage I-IIIC and "palliative" for patients with stage IV disease. In patients with locally advanced disease, surgical resection should be undertaken following neoadjuvant chemotherapy only if a complete/R0 (microscopically negative margins) resection is feasible (based on the assessment of response to chemotherapy).

Early gastric cancer

EGC is defined as a cancer in which the depth of invasion is limited to the submucosal layer of the stomach on histological examination, irrespective of lymph node metastasis.[11]

In the absence of high-quality evidence to support the routine recommendation of endoscopic submucosal dissection/endoscopic mucosal resection for EGC, in the Indian scenario, these may be offered as an option if all of the following criteria are met:

- Staging indicates — early gastric tumor (≤T1) with no lymph node metastases
- Tumor can be completely excised with negative margins (depth and circumferential)
- Experienced surgeons in gastric cancer are available as back-up.

If the histological assessment confirms complete excision, no further treatment is required. However, if the histology review indicates a more advanced lesion as evidenced by failure to achieve an en bloc resection, size >2 cm, histologically of undifferentiated-type, >pT1a, positive horizontal and/or vertical margins and lymphovascular infiltration, the patient must then be treated as having a lesion other than EGC and a gastric resection must be performed.[12] For all other EGCs, surgery should be considered as a treatment of choice.

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

The standard surgical resections for gastric cancer include:

a. Total gastrectomy for lesions in the upper third of the stomach or those originating and mainly located in the middle third of the stomach
b. Proximal gastrectomy is an oncologically acceptable alternative to total gastrectomy for tumors in the upper third of the stomach although they are associated with a higher risk of reflux esophagitis and anastomotic stenosis as compared to total gastrectomy[13]
c. Distal subtotal gastrectomy is the preferred operation for tumors arising from, or involving, the distal third of the stomach.
d. A D2 lymphadenectomy must be performed.[14] In patients with tumors determined to be T1a on investigation, a D1 gastrectomy would be adequate.
e. Laparoscopic resection may be attempted by experienced laparoscopic surgeons if distal gastrectomy is being considered for EGC. There is no evidence for other surgeries.[15]
f. Desirable: Intra-operative frozen section analysis of the margins should be performed, if the facilities are available, for two main reasons, viz. because gross palpation of margins often leads to underestimation of tumor involvement and also because positive resection margins are associated with a poorer outcome.[16]
g. Splenectomy should be performed as part of radical gastrectomy only in T3/4 tumors of the greater curvature of the body of the stomach or direct invasion of the splenic hilum.

Role of chemotherapy in nonmetastatic gastric cancer

The role of peri-operative chemotherapy has been established by the MAGIC trial, which showed a 13% improvement in 5-year survival from 23% to 36% with peri-operative epirubicin-cisplatin-5-fluorouracil (ECF) compared to surgery alone in early stomach and GOJ tumors.[17] Hence, peri-operative chemotherapy may be considered in patients with locally advanced (T3/4, N^+), gastric cancers unless surgical resection is warranted owing to complications secondary to the tumor such as gastric outlet obstruction or bleeding requiring repeated transfusions or deeply penetrating ulcers at risk of perforation. In these patients, adjuvant therapy is guided by the histology. In patients receiving neoadjuvant chemotherapy, surgery must be undertaken 4-6 weeks after completion of the planned cycles.[14,17] 5-fluorouracil (FU) may be replaced with capecitabine for better quality-of-life for patients as it avoids the need for insertion of a central venous device while cisplatin may be replaced with oxaliplatin to avoid less time spent by patients in day-care.[18] Owing to the higher toxicities and also difficulties in the need for central venous access encountered when administering the ECF regimen as per the MAGIC trial, Sirohi *et al.* compared the efficacy and safety profile of EOX in the Indian scenario.[19] In patients with resectable GO adenocarcinoma, it is possible to deliver the MAGIC-type peri-operative chemotherapy with EOX with better compliance, toxicity, and efficacy rates.

Alternatively, in those patients in whom an upfront resection has been undertaken, the use of adjuvant capecitabine-oxaliplatin adds survival benefit and should be considered in patients with stage II-IIIB gastric cancer.[20]

Role of radiotherapy in nonmetastatic gastric cancer

The role of radiotherapy in resectable gastric cancer is in those patients who undergo upfront surgery with D1

lymphadenectomy. The Intergroup-0116 study showed that chemoradiotherapy (5 days cycle of 5-FU and leucovorin followed by 45 Gy in 25 fractions of radiation given concurrently with 5-FU and leucovorin, followed by two additional cycles of 5-FU and leucovorin at 1-month intervals) led to an increased survival (median 27-36 months), which remained at 10 years of follow-up.[21] Radiotherapy has also been indicated in patients undergoing R1 resections.[22] Radiotherapy, along with chemotherapy, may be considered in the radical setting as a definitive treatment for unresectable, nonmetastatic cancer or resectable disease in a patient not suitable for surgery owing to preexisting medical conditions. Although adjuvant chemoradiotherapy is largely considered as the standard treatment after curative surgery in gastric cancer, there are very limited data for its benefit after D2 nodal dissection as majority of patients in the Intergroup-0116 trial had undergone D1 nodal dissection.

Metastatic gastric cancer

Role of surgery

While surgery is not indicated in the presence of distant metastatic disease, palliative resections may need to be undertaken in patients who have uncontrolled bleeding or gastric outlet obstruction who are otherwise well-preserved with a projected longer life expectancy.[23] A gastrojejunostomy may be helpful in patients with distally obstructing tumors with features of gastric outlet obstruction but distant metastases. In those patients with short-life expectancy, endoscopic stenting or an endoscopically-placed nasojejunal tube for feeding may be useful in patients with obstructing tumors.

Role of chemotherapy in recurrent/metastatic gastric cancer

The management of recurrent/metastatic gastric cancer depends on the patient's performance status (PS), co-morbidities and end-organ function. Patients with a poor PS may only be offered best supportive care. The 5-year survival for metastatic gastric cancer is less than 10%, and median overall survival remains less than 1-year. The backbone of chemotherapy for patients with advanced gastric cancer is fluoropyrimidine and platinum. With respect to chemotherapy, there is no standard across the world for metastatic gastric cancer though most regimens used are cisplatin-based. In Europe, ECF or EOX (epirubicin, oxaliplatin, capecitabine), in the United States, cisplatin-fluoropyrimidine, while in Japan, cisplatin-S1 are considered standard chemotherapy regimens. A meta-analysis of first-line chemotherapy studies in metastatic gastric cancer has shown that the best survival results are achieved with three-drug regimens containing anthracycline, 5-FU, and cisplatin.[24] The REAL-2 Study showed that capecitabine and oxaliplatin are as effective as 5-FU and cisplatin, respectively.[18] Docetaxel is the preferred agent for use in combination with cisplatin, 5-FU.[25] The ECF regimen is associated with response rates in excess of 70% and is considered by many as reference regimen in first-line therapy of advanced gastric cancer. Data from India show that the overall response rates and progression-free survival in our population of 40%/6 months is similar to those seen in the western population which ranges from 35-48%/5-6 months with combination regimens respectively.[26] The use of taxanes was an important factor for overall survival. Indian patients present with a poorer PS and aggressive histology but if they go on to receive second-line regimens, the outcomes are similar to those reported from the west.

Her2 positivity has been reported in approximately 15-20% of gastroesophageal cancers.[9] The trastuzumab for gastric cancer (ToGA) trial proved the efficacy of trastuzumab in combination with chemotherapy for patients with Her2 positive gastric cancers. The median overall survival was significantly prolonged in the trastuzumab-containing arm (13.8 vs. 11.1 months; hazard ratio 0.74; $P = 0.0046$).

Almost all patients with advanced gastric cancer will develop progressive disease after first-line therapy. Second-line therapy in patients who have progressed after first-line will depend on PS and disease-free interval on first-line therapy. For patients with good PS, various options are irinotecan, docetaxel, and paclitaxel, though there is no standard approach.[27,28] The use of targeted therapy except trastuzumab in Her2 positive patients is not indicated though search for new targets continues.[29] Re-treatment with standard therapy if a long disease-free interval is attained after first-line chemotherapy also remains an option.

FOLLOW-UP AND REHABILITATION

Patients should be encouraged to maintain lead a healthy lifestyle and abstain from tobacco and alcohol. The aim of follow-up is to detect recurrences early as well as to assess any complication due to surgery/radiotherapy. Postsurgery, the follow-up is done every 3-4 months for the 1st year with each visit comprised of clinical examination (including history and physical examination). The follow-up in years 2-3 is every 6 months and annually, thereafter till year 5. At the end of each of the first 3 years, a CT scan of the chest, abdomen, and pelvis is recommended. For patients with advanced gastric cancer, the scans are symptom-driven or for response assessment.

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