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CONSENSUS DOCUMENT FOR MANAGEMENT OF GASTRIC CANCER

Prepared as an outcome of ICMR Subcommittee on Gastric Cancer

Indian Council of Medical Research
2014

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Prepared as an outcome of ICMR Subcommittee on Gastric Cancer

Coordinated by

Division of Non Communicable Diseases

Indian Council of Medical Research,
Ansari Nagar, New Delhi – 110029
2014

Disclaimer

This consensus document represents the current thinking of experts on the topic based on available evidence. This has been developed by national experts in the field and does not in any way bind a clinician to follow this guideline. One can use an alternate mode of therapy based on discussions with the patient and institution, national or international guidelines. The mention of pharmaceutical drugs for therapy does not constitute endorsement or recommendation for use but will act only as a guidance for clinicians in complex decision-making.

Dr. V.M. Katoch
Secretary,
Department of Health Research
and Director General, ICMR

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Foreword

I am glad to write this foreword for Consensus Document for Management of Gastric Cancer. The ICMR had constituted sub-committees to prepare this document for management of various cancer sites. This document is the result of the hard work of various experts across the country working in the area of oncology.

This Consensus Document on Management of Gastric Cancers summarizes the modalities of treatment including the site-specific anti-cancer therapies, supportive and palliative care and molecular markers and research questions. It also interweaves clinical, biochemical and epidemiological studies.

The various subcommittees constituted under Task Force project on Review of Cancer Management Guidelines worked tirelessly in drafting cancer site-specific guidelines. Each member of the subcommittee's contribution towards drafting of these guidelines deserves appreciation and acknowledgement for their dedicated research, experience and effort for successful completion. We hope that this document would provide guidance to practicing doctors and researchers for the management of Gastric Cancer patients and also focusing their research efforts in Indian context.

It is understood that this document represents the current thinking of national experts on this topic based on available evidence and will have to be revised as we move. Mention of drugs and clinical tests for therapy do not imply endorsement or recommendation for their use, these are examples to guide clinicians in complex decision making. We are confident that this first edition of these guidelines will serve the desired purpose.

(Dr.V.M.Katoch)
Secretary, Department of Health Research &
Director General, ICMR

Message

I take this opportunity to thank Indian Council of Medical Research and all the expert members of the subcommittees for having faith and considering me as Chairperson of ICMR Task Force project on Guidelines for Management of Cancer.

The Task Force on Management of Cancers has been constituted to plan various research projects. Two sub-committees were constituted initially to review the literature on management practices. Subsequently, it was expanded to include more sub-committees to review the literature related to guidelines for management of various sites of cancer. The selected cancer sites are lung, breast, oesophagus, cervix, uterus, stomach, gall bladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukemia, acute lymphoblastic leukemia, CLL, Non Hodgkin's Lymphoma-high grade, Non Hodgkin's Lymphoma-low grade, Hodgkin's Disease, Multiple Myeloma, Myelodysplastic Syndrome and paediatric lymphoma. All aspects related to management were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects. The published literature till December 2012 was reviewed while formulating consensus document and accordingly recommendations are made.

Now, that I have spent over a quarter of a century devoting my career to the fight against cancer, I have witnessed how this disease drastically alters the lives of patients and their families. The theme behind designing of the consensus document for management of cancers associated with various sites of body is to encourage all the eminent scientists and clinicians to actively participate in the diagnosis and treatment of cancers and provide educational information and support services to the patients and researchers. The assessment of the public-health importance of the disease has been hampered by the lack of common methods to investigate the overall; worldwide burden. ICMR's National Cancer Registry Programme (NCRP) routinely collects data on cancer incidence, mortality and morbidity in India through its co-ordinating activities across the country since 1982 by Population Based and Hospital Based Cancer Registries and witnessed the rise in cancer cases. Based upon NCRP's three year report of PBCR's (2009-2011) and Time Trends on Cancer Incidence rates report, the burden of cancer in the country has increased many fold.

In summary, the Consensus Document for management of various cancer sites integrates diagnostic and prognostic criteria with supportive and palliative care that serve our three-part mission of clinical service, education and research. Widespread use of the consensus documents will further help us to improve the document in future and thus overall optimizing the outcome of patients. I, thank all the eminent faculties and scientists for the excellent work and urge all the practicing oncologists to use the document and give us valuable inputs.

(Dr. G.K. Rath)
Chairperson
ICMR Task Force Project

Preface

Cancer is rapidly increasing in epidemic proportions in the Indian subcontinent. A recent landmark publication has observed that stomach (gastric) cancer ranks amongst the top 10 cancers in India. This requires a multipronged approach to tackle it effectively. While progress has been made in screening and preventive aspects, definitive treatment currently holds the only chance of cure for this disease which can often carry a dismal prognosis.

The plethora of information available on gastric cancer is a reflection of the vast ongoing research on gastric cancer. However, this information explosion can often leave the clinician and other care givers confused when it comes to translating this information into day to day practice.

The Indian Council for Medical Research (ICMR), in a wonderful initiative in the right direction, set up a task force to develop consensus statement for management of Gastric Cancer in India. The task of this renowned expert group from all corners of our country was to glean and analyse the available literature, collate the highest available evidence and develop practical and sound guidelines that can be actually implemented in day to day practice in the current Indian scenario. The onus remains on us to generate Indian data, hence the research questions generated by the group will help us to take this further.

We take this opportunity to thank each and every member of the group who took time out from their busy schedules and remained committed to their assigned tasks in a time bound manner. We would also like to thank Dr. Rath and Dr. Tanvir Kaur for their tireless efforts to make us stick to timelines.

These guidelines would be updated from time to time and we would look forward to your feedback that would help us to ultimately treat our patients better than ever before.

Shailesh V. Shrikhande
Chairman
Subcommittee on Gastric Cancer

Preface

Cancer is a leading cause of disease worldwide. Globally cancer of various types effect millions of population and leads to loss of lives. According to the available data through our comprehensive nationwide registries on cancer incidence, prevalence and mortality in India among males; cancers of lung, mouth, oesophagus and stomach are leading sites of cancer and among females cancer of breast, cervix are leading sites. Literature on management and treatment of various cancers in west is widely available but data in Indian context is sparse. Cancer of gall bladder and oesophagus followed by cancer of breast marks as leading site in North-Eastern states. Therefore, cancer research and management practices become one of the crucial tasks of importance for effective management and clinical care for patient in any country. Hence, the need to develop a nationwide consensus for clinical management and treatment for various cancers was felt.

The consensus document is based on review of available evidence about effective management and treatment of cancers in Indian setting by an expert multidisciplinary team of oncologists whose endless efforts, comments, reviews and discussions helped in shaping this document to its current form. This document also represents as first leading step towards development of guidelines for various other cancer specific sites in future ahead. Development of these guidelines will ensure significant contribution in successful management and treatment of cancer and best care made available to patients.

I hope this document would help practicing doctors, clinicians, researchers and patients in complex decision making process in management of the disease. However, constant revision of the document forms another crucial task in future. With this, I would like to acknowledge the valuable contributions of all members of the Expert Committee in formulating, drafting and finalizing these national comprehensive guidelines which would bring uniformity in management and treatment of disease across the length and breadth of our country.

(Dr.D.K.Shukla)
Head, NCD Division

Acknowledgement

The Consensus Document on Management of Cancer is a concerted outcome of effort made by experts of varied disciplines of oncology across the nation. The Indian Council of Medical Research has constituted various sub committees to formulate the document for management of different cancer sites. The Task Force on Management of Cancers has been constituted to formulate the guidelines for management of cancer sites. The sub-committees were constituted to review to review the literature related to management and treatment practices being adopted nationally and internationally of different cancer sites. The selected cancer sites are that of lung, breast, oesophagus, cervix, uterus, stomach, gall bladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukaemia, ALL, CLL, NHL-high grade, NHL-low grade, HD, MM, MDS, and paediatric lymphoma. All aspects related to treatment were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects.

This document represents a joint effort of large effort of large number of individuals and it is my pleasure to acknowledge the dedication and determination of each member who worked tirelessly in completion of the document.

I would like to take this opportunity to thank Dr. GK Rath, chairperson, ICMR Task Force on Guidelines for Management of Cancer for his constant guidance and review in drafting the consensus document especially perseverance behind each subcommittee in formulating these documents. The chairperson of subcommittee is specially acknowledged in getting the members together, organizing the meetings and drafting the document.

I would like to express gratitude to Dr. VM Katoch, Secretary, Department of Health Research and Director General, Indian Council of Medical Research, for taking his special interest and understanding the need of formulating the guidelines which are expected to help cancer patients.

I would like to acknowledge here the initiative undertaken with the able guidance of Dr. Bela Shah. I would like to thank Dr. DK Shukla for his support and coordination in finalizing this document. I would also like to acknowledge the assistance provided by administrative staff. This document is the result of the deliberations by subcommittees constituted for this purpose. The guidelines were further ratified by circulation to extended group of researchers and practitioners drawn from all over the country. It is hoped that these guidelines will help the practicing doctors to treat cancer patients effectively and thus help them to lead a normal and healthy life.

The ICMR appreciatively acknowledges the valuable contribution of the members for extending their support in formulating these guidelines. The data inputs provided by National Cancer Registry Programme are gratefully acknowledged.

(Dr.Tanvir Kaur)
Programme Officer & Coordinator

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CHAPTER

1 INTRODUCTION

Gastric cancer is the fourth leading cancer in the world and the second most common cause of death due to malignancy, accounting for 736,000 deaths (9.7% of the total)[1]. Nearly 1 million new cases of gastric cancer and 0.7 million gastric cancer deaths are reported every year. Age-standardized incidence rates are approximately twice as high in men as in women, ranging from 3.9 in Northern Africa to 42.4 in Eastern Asia for men and from 2.2 in Southern Africa to 18.3 in Eastern Asia for women[1]. Currently, gastric cancer is more common in Asia than in the United State of America (USA) or Europe. Notably, 42% of cases occur in China alone.

In India, the incidence rate of gastric is very low compared to that in western countries, and the number of new gastric cancer cases is approximately 34,000, with a male predominance (male-to-female ratio, 2:1). It is estimated that by the year 2020, approximately 50,000 new gastric cancer cases will be reported annually in India. The recent nationally representative survey of cancer mortality in India indicated that gastric carcinoma was the second most common cause of cancer-related deaths amongst men and women[2]. The 5-year survival rate for patients undergoing surgical resection was reported to be only 27% in 1992[3]. According to a study conducted in Karnataka, gastric cancer ranks amongst the 5 most common cancers, even amongst young Indian men and women (aged 15–44 years)[4].

The incidence of gastric cancer has been relatively high in southern India, namely in Chennai; however, recent data indicate that the incidence rates are the highest in the north-eastern region[5]. In Aizawl, in the state of Mizoram, the incidence rate is 57.3 in men and 33.6 in women; however, these data need to be interpreted with caution because the north-eastern registries are relatively new registries, and in the initial years, there may be many prevalent cancer cases that contribute to the incidence rate.

As per the latest reports available from the National Cancer Registry Programme[6], among the older registries, the incidence rate for gastric cancer was Aizawl (64.2) and Nagaland (26.2) for men and among the older PBCRs, Chennai had the highest AAR (12.2). For women, the AAR was 31.2 in Aizawl followed by Nagaland (12.5). Bangalore had the highest AAR among women (5.5) among the older PBCRs. In Mumbai, the rates are as low as 4.2 per 100,000[6] . Gastric cancer is the most common cancer among men and women in Aizawl district of Mizoram[6].

Age-adjusted incidence rates (AARs) per 10,000 as recorded in population-based cancer registries in India

	AAR	
Registry	Men	Women
Mumbai (2009–2011)	4.2	2.4
Bangalore (2009–2011)	9.1	5.5
Chennai (2009–2011)	12.2	5.2
Thiruvananthapuram (2009-2011)	4.8	1.9
Delhi (2009–2011)	3.4	1.6
Aurangabad (2009–2011)	1.7	0.8
Source: National Cancer Registry Programme (2013)		

Over the years, from 1982 to 2005, the incidence of gastric cancer has remained more or less stable (although increases/decreases have been noted in some years) both in Chennai and in Bangalore, whereas, in Mumbai, the incidence has shown a decline from 7.1 to 4.9 per 100,000 during the same period[7].

GIST

GISTs are the most common mesenchymal tumours of the gastrointestinal tract and constitute less than 1% of all digestive tract tumours[8]. They may be benign or malignant (30%), and can occur in any part of the gastrointestinal tract; however, the stomach is the most common site[9]. They develop with the same prevalence in men and in women, usually above the age of 50 years, and the peak incidence is observed between the fifth and the sixth decades of life[10]. Currently, there are very few known risk factors for GISTs. These include being older[10] and the presence of genetic syndromes (most GISTs are sporadic and not inherited, and there is no clear cause. In rare cases though, GISTs have been found in several members of the same family who inherited a gene mutation such as neurofibromatosis type 1 (or von Recklinghausen disease) or Carney-Stratakis syndrome as well as nerve tumours called paragangliomas[11]. The incidence of GIST is not known for all populations; most data are representative of Caucasian populations.

Risk factors for gastric cancer

Risk factors may differ for proximal and distal gastric cancers. The important risk factors include gastric adenomas or dysplasia and chronic atrophic gastritis. Previous gastric surgery also increases the risk of gastric cancer. Incidence rates across the world indicate that gastric cancer is more common among men, irrespective of the geographical region[1].

The incidence of gastric cancer shows a sharp increase after the age of 50 years. Most individuals are diagnosed with gastric cancer between their late 60s and 80s [1] .

H. pylori infection is considered one of the most important risk factors for non-cardia gastric cancer[12]. In 1994, an expert working group convened by the International Agency for Research on Cancer classified *H. pylori* as carcinogenic to humans [13] on the basis of epidemiological evidence. Seroepidemiological studies from India indicate a prevalence of *H. pylori* infection of 22–57% in children under the age of 5, which increases to 80–90% in adulthood [14-16]. Gastric cancer is reported to develop in 0.1–3% of patients with *H. pylori* infection[17]. Prospective studies from western countries suggest that gastric cancer is 2–3 times more common in individuals with chronic *H. pylori* infection. High intake of pickled, smoked, salted, or preserved foods and a low intake of fruits and vegetables increase the risk of gastric cancer[18-19]. The role of tobacco in the development of gastric (cardia) cancer has been studied by many researchers worldwide. The frequency as well as the duration of smoking is an important factor in increasing an individual's risk of gastric cancer[20]. Smoking cessation decreases the risk of gastric cancer only after 1 to

2 decades[20]. A specific association between alcohol consumption and cancers of the gastric cardia has been suggested by studies conducted in the USA[21], Italy[19] and Spain[22]. A meta-analysis of cohort studies indicated that overweight status and obesity are associated with an increased risk of gastric cancer. The strength of the association increases with an increase in the body mass index (BMI)[23] . A family history of gastric cancer is observed in up to 10–15% of cases[24] . A history of gastric cancer in siblings or parents is associated with an at least 2 times increased risk of gastric cancer[25-26]. Gastric cancer can also be a part of inherited syndromes such as hereditary nonpolyposis colon cancer and hereditary diffuse gastric cancer. A definite subgroup of gastric cancers has been found to be associated with Epstein-Barr virus infection, and these cases account for 7% to 18% of all cases[27-29].

According to the Population-Based Cancer Registry of Sikkim, the age-adjusted incidence rates for stomach cancer are 12.6 and 4.7 times higher in the Bhutia group than in other ethnic groups in men and women, respectively[30]. Other risk factors include socioeconomic status, stomach lymphoma, geographical region, Menetrier disease (hypertrophic gastropathy), pernicious anaemia, and blood group A.

Appendix A provides details on the prevention of gastric cancer.

CHAPTER

2 DIAGNOSIS CRITERIA AND INITIAL WORKUP

2.1 History

The symptoms of gastric cancer are generally non-specific. Anorexia, unexplained weight loss, sudden onset of dyspepsia after the age of 40 years and melaena are some of the symptoms and signs that may alert a person to undergo an examination.

2.2 Physical examination

Abdominal examination is usually not contributory owing to the fact that the upper half of the stomach is situated under the rib cage. For advanced, large distal stomach tumours, a mass may be palpable in the epigastrium. Should GOO exist in such patients, visible peristalsis may be noted in the left hypochondrium moving from the left to the right side of the abdomen.

2.3 Blood tests

These include a complete blood count and liver and kidney function tests.

2.4 Tumour markers

Most studies evaluating tumour markers are retrospective and heterogeneous, and the data available are conflicting. Tumour markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) have been evaluated in gastric cancer, but presently there is insufficient evidence to recommend the use of any tumour marker in the screening, diagnosis, prognostication, or surveillance of gastric cancer[31]. Evaluation of tumour markers is currently neither recommended by any of the standard guidelines for gastric cancer nor mentioned in any recommendations on the use of tumour markers[32].

Recommendation: Tumour markers are not recommended in the routine management of gastric cancer, (Level 3B) but they may serve a useful purpose in patient follow-up if their levels are elevated at the time of initial diagnosis (Level 5B).

2.5 Endoscopy in gastric cancer

Standard white light endoscopy (esophagogastroduodenoscopy) with multiple (6–8 pieces) biopsies from the tumour is essential for confirmation of diagnosis. The endoscopy report should mention the type of tumour (proliferative/ulcerated/linitis plastica) and the longitudinal and circumferential extent of the tumour, with a comment on the involvement of the gastro-oesophageal junction or the antrum where applicable. The histology should be reported as per the World Health Organization (WHO) criteria.

Endoscopic ultrasonography (EUS): The most important indication for EUS is staging and accurate identification of patients with early gastric cancer for whom endotherapy can be planned. EUS may also be helpful in locoregional (tumour and nodal) staging; however, its utility lies mainly in the staging of proximal gastric tumours. It is of limited use for distal tumours. Fine needle aspiration cytology can

be combined with EUS for the diagnosis of submucosal tumours or for sampling suspicious nodes. Widespread use of EUS is limited by its availability (desirable).

2.6 Histopathology

Histological confirmation of the primary neoplasm is preferable, but if this is not feasible, histological confirmation of the metastatic site is mandatory before definitive therapy (essential).

2.7 Staging laparoscopy

Staging laparoscopy can upstage up to 30% of tumours and can be considered for cT3/4 tumours. However, there is no evidence from randomized clinical trials in this regard[33]. Peritoneal washings can be collected for cytology evaluation during laparoscopy, and a positive result is considered a poor prognostic factor (desirable).

2.8 Imaging

Various imaging modalities and their roles[34-41] (See **Appendix B** for computed tomography [CT] staging of tumours and the CT reporting template)

Imaging is primarily used for staging in gastric cancer, but also for response assessment following NACT.

Staging

- *Multi-detector computed tomography (MDCT, 16-row and higher) of the chest, abdomen and pelvis is the preferred initial method for staging.* This method is superior to helical CT for T staging because of its higher resolution and multiplanar reformations.
- However, helical CT can be used if MDCT is not available.
- EUS and magnetic resonance imaging (MRI) are as accurate as MDCT for T staging and detecting serosal involvement, but may not be widely available.
- *MDCT has the advantage of complete staging with nodal and metastatic workup.*
- EUS may have a role in proximal tumours to confirm T1–T2, N0 status, in cases where upfront surgery is contemplated, because T3–T4, N+ tumours will require neoadjuvant therapy prior to restaging.
- MRI can be a problem solving modality for liver metastases.
- Positron emission tomography (PET)-CT findings can be negative in one-third of gastric cancer cases, including mucinous and diffuse tumours. Hence, PET-CT has a limited role in gastric cancers.

For post-neoadjuvant therapy response assessment, CT of the chest, abdomen and pelvis is the preferred modality, and not EUS.

Summary

Essential investigation (minimum optimal)

- Helical CT of the abdomen and pelvis plus chest radiography/computed tomography
  Ideal method (optimal with highest evidence)
- MDCT of the chest, abdomen, and pelvis

- EUS in select cases to distinguish T1–T2, N0 status from T3–T4, N+ status
- MRI of the liver—only for problem solving

Staging laparoscopy

The proposed advantages of staging laparoscopy over conventional imaging (CT) are a more accurate assessment of local disease, especially in the lesser sac, and detection of sub-radiologic/radiologically occult metastatic disease. A recent systematic review on the accuracy and indications of diagnostic laparoscopy for gastric cancer included 21 articles (12 prospective and 9 retrospective; no randomised controlled trials). With the final histopathological diagnosis as reference, the overall accuracy of diagnostic laparoscopy for TNM staging was as follows:

T-stage: 84.4–97.7%

N stage: 64.3–98.9%

M stage: 85–100%

Moreover, the use of staging laparoscopy altered management in 8.5–59.6% of cases, with laparotomy being avoided in 8.5–43.8% of cases.

Indications for staging laparoscopy[42-48]

1. T3/T4 tumours as assessed by CT, with or without lymph node metastases—prior to the commencement of NACT to determine treatment intent (Level 3)
2. Receipt of neoadjuvant therapy—prior to or at the time of surgical exploration for definitive resection (Level 3)

GIST

In 85% of cases, KIT mutations are present in GIST. Gain of function mutations have been identified in exon 11, exon 9, and exon 17. These mutations lead to uncontrolled, ligand-independent activity of the KIT receptor[49]. In addition, 10% of GIST patients show mutational activation of platelet derived growth factor receptor A (PDGFRA) receptor kinase and BRAF kinase mutations are present in very rare cases. Approximately 5% of GIST cases will have no detectable kinase mutations; however, they may have mutations in Krebs cycle enzymes[50-51]. On immunohistochemistry, GIST cells are positive for CD117 and CD34. CD117-negative GIST is identified by DOG-1 positivity[52] .

Radiology (for baseline staging): Triphasic CT of the abdomen, consisting of a non-enhanced phase, an arterial phase, and a portal venous phase of the liver, should be performed. Patients should receive a negative/water-equivalent oral contrast agent for the detection of gastrointestinal (GI) tract wall lesions. CT of the thorax is performed at baseline to complete the staging workup. In case the patient is allergic to the contrast medium, MRI of the abdomen is performed along with non-contrast CT of the thorax.

Follow-up scan: CT of the abdomen is recommended as a follow-up evaluation; this should be biphasic and positive oral contrast should be used along with CT. Because the incidence of pulmonary metastasis is less than 2%, routine CT of the thorax is not performed as a follow-up evaluation, unless progression is noted[53].

Response assessment: For GIST, response assessment is based on changes in lesion size, changes in lesion density, and the appearance of new lesions. The assessment of lesion density is important, as therapy response is reflected by a decrease in lesion density due to myxoid degeneration; however, lesion

size remains unchanged or may increase. To quantitatively assess response, there should be at least a 15% decrease in attenuation on CT images[54].

PET: PET is not routinely recommended for staging or follow-up. However, it is used for early response assessment to targeted therapy. A decrease in the maximum standardised uptake value indicates tumour response. A metastatic GIST lesion in the omentum can be subtle and, hence, easily missed on CT; however, this could be detected on PET because neither the bowel wall nor the omentum takes up the fluorodeoxyglucose glucose (FDG) tracer with avidity.

CHAPTER

3 STAGING AND PROGNOSTIC CRITERIA

Tumours are staged according to the American Joint Committee on Cancer staging for gastric cancer, seventh edition, updated in 2010[55]. As per this consensus document, for all intents and purposes, the TNM staging system should be used for gastric cancer staging (Level 1A).

Seventh edition of the American Joint Committee on Cancer Staging of Gastric Cancer[55]

Primary tumour (T)			
TX	The primary tumour cannot be assessed		
T0	No evidence of the primary tumour		
Tis	Carcinoma *in situ*: intraepithelial tumour without invasion of the lamina propria		
T1	The tumour invades the lamina propria, muscularis mucosae, or submucosa		
T1a	The tumour invades the lamina propria or muscularis mucosae		
TIb	The tumour invades the submucosa		
T2	The tumour invades the muscularis propria		
T3	The tumour penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures. T3 tumours also include those extending into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures		
T4	The tumour invades the serosa (visceral peritoneum) or adjacent structures		
T4a	The tumour invades the serosa (visceral peritoneum)		
T4b	The tumour invades adjacent structures such as the spleen, transverse colon, liver diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum		
Regional lymph nodes (N)			
NX	The regional lymph node(s) cannot be assessed		
N0	No regional lymph nodal metastasis		
N1	Metastasis in 1–2 regional lymph nodes		
N2	Metastasis in 3–6 regional lymph nodes		
N3	Metastasis in 7 or more regional lymph nodes		
Distant metastases (M)			
M0	No distant metastases		
M1	Distant metastases		
Anatomic stage			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0

Stage IIB	T4a T3 T2 T1	N0 N1 N2 N3	M0 M0 M0 M0
Stage IIIA	T4a T3 T2	N1 N2 N3	M0 M0 M0
Stage IIIB	T4b T4a T3	N0/N1 N2 N3	M0 M0 M0
Stage IIIC	T4b T4a	N2/N3 N3	M0 M0
Stage IV	Any T	Any N	M1

Pathological staging of gastric cancer should include the following:

Type (sub-classification as the intestinal or diffuse type, because this may have implications on therapy)
Grade
Depth of tumour invasion
Vascular invasion
Status of deep and mucosal margins
Location of the tumour in relationship to the oesophagogastric junction [OGJ] (whether the tumour crosses the OGJ)
Lymph node status and the number of lymph nodes removed (retrieval of at least 15 lymph nodes is recommended to avoid stage migration)
Tumour regression grade (to assess tumour response to neoadjuvant therapy)
HER2 testing by immunohistochemistry can be considered in all patients with advanced disease.

Hereditary diffuse gastric cancer is a rare type of gastric cancer that is attributable to a mutation in the E-cadherin (CDH1) gene. It is inherited in an autosomal dominant pattern. Patients with this genetic mutation have a lifetime risk of diffuse gastric cancer of 60–80%. The mean age at onset is 37 years. Hereditary genetic predisposition can have implications on management. Prophylactic gastrectomy is recommended for relatives who are identified as having the CDH-1 mutation. Referral to genetics centres for the testing of patients and their families should be considered for patients who have a family history of 2 cases of diffuse gastric cancer of which 1 is noted in a patient aged <50 years. Genetics testing can also be considered in families with a single case of gastric cancer in a patient aged <40 years.

GIST

The 3 most important prognostic factors for GIST are the primary tumour size, mitotic activity, and the location of primary disease. After curative resection, patients with a mitotic rate of 10/50 high-power fields (HPFs) had a median survival rate of 18 months, compared with an 8-year disease-free survival rate of 80% in patients with a mitotic rate of <10/50 HPFs[56]. Patients with gastric GIST tend to fare better than do those with extragastric GIST.

Fletcher et al have stratified the risk of aggressive or malignant behaviour in GIST on the basis of tumour size and mitotic rate[57]:

Very low risk : tumour size < 2 cm and mitotic rate < 5/50 HPFs

Low risk : tumour size, 2–5 cm and mitotic rate < 5/50 HPFs

Intermediate risk: (1) tumour size < 5 cm and mitotic rate, 6–10/50 HPFs or (2) tumour size, 5–10 cm and mitotic rate < 5/50 HPFs

High risk: (1) tumour size > 5 cm and mitotic rate > 5/50 HPFs, (2) tumour size > 10 cm and any mitotic rate, or (3) any tumour size and mitotic rate > 10/50 HPFs

Recent data suggest that not all mutations in exon 11 are equivalent. A deletion at this locus confers a poor prognosis and PDGFRA mutation is associated with a favourable outcome, with a low risk of recurrence[58-59].

CHAPTER

4 MULTIDISCIPLINARY TREATMENT FOR EARLY DISEASE

Multidisciplinary care remains at the core of treating gastric cancer—such treatment relies upon an effective multidisciplinary network including surgical, medical, and radiation oncologists; gastroenterologists; pathologists; radiologists (for interventional and nuclear medicine); nurse specialists, and palliative care physicians.

All new cases should be discussed at the tumour board or in multidisciplinary team meetings, and the treatment strategy should be confirmed. In most patients with localised disease, resection will be the treatment of choice, and adjuvant chemotherapy or CRT following resection will be considered on the basis of the histopathology. More commonly, in India, patients present with locally advanced disease (evident on imaging). In these cases, the use of pre-operative chemotherapy should be considered.

Recommendation:

- **Operable disease (T1N0M0) : surgery alone (Level 1A)**
- **Operable disease (>T1N0) : Surgery with perioperative chemotherapy (ECX or ECF, 3 cycles before and after surgery) (Level 1A)**

4.1 Treatment of the primary tumour

Extent of resection

Early gastric cancer—defined as cancer in which the depth of invasion is limited to the submucosal layer of the stomach on histological examination[60] , irrespective of lymph node metastasis[61-62] .

Endoscopy

- Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESMD) are 2 minimally invasive, endoscopic techniques used in the treatment of early gastric cancer. EMR is indicated for removing sessile or flat neoplasms, <2 cm, confined to the superficial layers (mucosa and submucosa) of the GI tract[63] .
- ESMD is performed for en bloc removal of large (usually >2 cm), flat lesions.
- EUS should be performed prior to EMR/ESMD to rule out involvement of the deeper layers and the presence of lymph node metastases.
- En bloc and complete resection rates are significantly lower in patients undergoing EMR than in those undergoing ESD (en bloc resection: 53.8% vs. 94.3%; complete resection: 37.5% vs. 92.6%)[64]. The overall 5-year recurrence-free rate is also lower in the EMR group (82.5% vs. 100%).
- EMR seems to be comparable to ESD for lesions in the millimetre range.
- The common complications are bleeding and perforation, the rates of both of which are higher after ESMD than after EMR.

- Both these procedures require considerable expertise and should not be attempted by untrained endoscopists.
- Chromoendoscopy and narrow band imaging emphasize the mucosal vasculature and help identify and delineate gastric intestinal metaplasia or early gastric cancer[65]. These techniques require training and expertise as well as availability of specialized equipment. (desirable)
- In India, as early gastric cancer is very rarely diagnosed, the above modalities have limited applicability.
- Although 5-year survival rates have been compared between EMR and surgical resection on the basis of retrospective series[66-67], a Cochrane review noted the lack of randomised controlled trials[68] (Level 1).
- Nasojejunal feeding tubes can also be placed endoscopically for nutritional support in patients with GOO for whom neoadjuvant therapy has been planned.

Recommendation

In the absence of high-quality evidence to support the routine recommendation of EMR for early gastric cancer, in the Indian scenario, EMR may be offered as an option for the treatment of early gastric cancer if all of the following criteria are met:

- Adequate staging procedures indicate early gastric tumour (≤T1) with no lymph node metastases
- The tumour can be completely excised with negative margins (depth and circumferential)
- Adequately experienced surgeons in gastric cancer are available if required

If histological assessment confirms the complete excision of early gastric cancer (as per the definition above), no further treatment is required. However, if the histological review indicates a more advanced lesion, the patient must be treated as having a lesion other than early gastric cancer (please see below).

4.2 Surgery

Anatomically, the stomach is divided into the upper, middle, and lower thirds[69] . Three surgeries have been defined oncologically, namely subtotal (distal), proximal, and total gastrectomy.

Principles of surgery

- Figure indicates the optimal choice of surgery according to the location of the tumour.[70-72] (Level 1A). For lesions in the upper third, although there was no significant difference in overall survival between the 2 procedures (sub-total vs. total gastrectomy), the recurrence rates as well as the incidence of reflux oesophagitis and anastomotic stenosis were lower in patients who underwent total gastrectomy[73].
- In general, surgery should be performed 4–6 weeks after completion of NACT (Level 2A) .
- For gastric cancer: The basic aim of gastric cancer surgery should be to achieve complete removal of the tumour with histologically confirmed tumour-free (R0) surgical margins. The affected part of the stomach with preferably 5 cm of grossly normal stomach on either side should be resected. For distal and cardia lesions, this may not be possible for distal and proximal margins, respectively. In such cases, a negative margin of at least 1 cm confirmed by intraoperative frozen section analysis is deemed acceptable.

- Gastrectomy with D2 lymphadenectomy is the current standard of care for non-metastatic, resectable T3/T4 gastric cancer (**Appendix C** lists the lymph node stations according to the location of the tumour in the stomach)[74] (Level 1B).
- Type of anastomotic technique: The outcomes of stapled and sutured anastomoses do not differ for distal lesions. However, for proximal lesions, stapled anastomosis may be associated with a lower anastomotic leakage rate[75] (Level 2A).
- Intraoperative frozen section analysis of the margins is encouraged, because gross palpation of the margins may be erroneous in terms of underestimating tumour involvement. It has been well documented that positive resection margins are associated with a poorer outcome[76].
- Laparoscopy may be performed in patients with early gastric cancer only because no long-term evidence exists to confirm the comparative oncological adequacy of laparoscopy to open surgery for lesions other than early gastric cancer.
- In case of GISTs, the ideal treatment for a non-metastatic GIST ≥ 2 cm[77] or symptomatic tumours < 2 cm is complete surgical resection (R0)[78] (Level 3A) without injury to the pseudocapsule, wherever technically feasible without undue risk to the patient.
- Lymphadenectomy is not indicated as part of surgery for GISTs, as they seldom metastasize to the lymph nodes[79] (Level 3A). However, enlarged lymph nodes suspicious of malignant invasion may be sampled at the time of surgery.
- Laparoscopic resection of gastric GISTs is feasible[80-85] (Level 3B). However, in the absence of high levels of evidence, should laparoscopic resections be performed, they should be restricted to the resection of GISTs < 5 cm.

Appendix D provides a post-surgery pathology reporting template.

4.3 Nutritional support

The nutritional status of gastric cancer patients should be assessed at presentation, before and after surgery, and at regular intervals thereafter, and appropriate nutritional interventions should be initiated as required. The enteral route is preferred for feeding wherever feasible[86] (Level 1A). Venting gastrostomy may be useful in select patients with GOO.

Recommendations

- Patients with a severe nutritional risk can be given nutritional support for 10–14 days prior to surgery [86] (Level 1A). Severe nutritional risk is defined by the presence of at least one of the following: weight loss > 10–15% within 6 months, BMI < 18.5 kg/m^2, Subjective Global Assessment Grade C, and serum albumin concentration < 3.0 g% with no evidence of hepatic or renal dysfunction.
- In patients undergoing surgery, preoperative enteral nutrition, preferably with immune modulating substrates (arginine, omega-3 fatty acids, and nucleotides), is recommended for 5–7 days, independent of their nutritional status[86] (Level 1A).

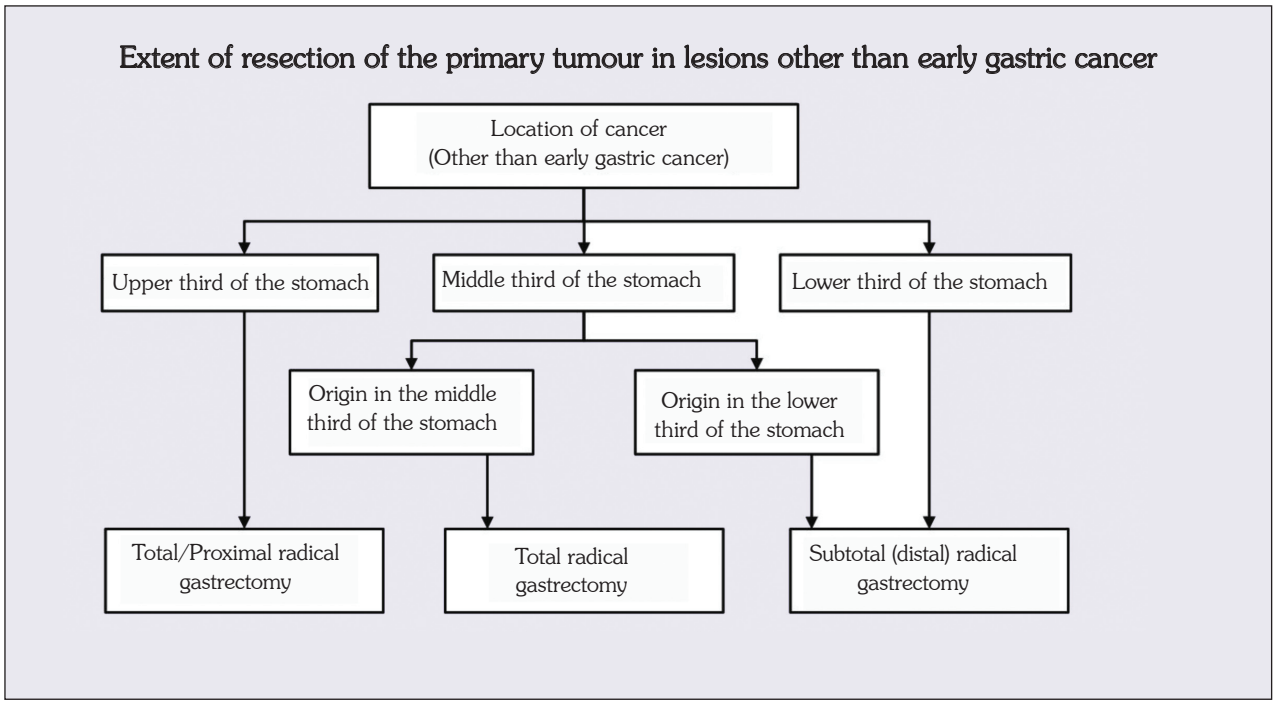
4.3.1 Postoperative nutritional support

Gastric resection can result in weight loss ranging from 10% to 30%[87-88]. This weight loss can be multifactorial resulting from post-gastrectomy syndrome, inadequate intake, malabsorption, and bacterial overgrowth. Post-gastrectomy dietary counselling and follow up is therefore extremely important. Deficiencies of iron, vitamin B_{12} and folic acid are common after gastrectomy, and their adequate supplementation is equally

important. Monitoring and treatment of metabolic bone disease may be indicated in long-term survivors of gastric cancer (Level 3B).

Summary of the Surgical Recommendations

Gastric Adenocarcinoma			
		Desirable/Ideal	**Essential**
Extent of resection of the primary tumour	Early gastric cancer	EMR (please see the text above, laparoscopic gastrectomy	Open gastrectomy
	Lesions other than early gastric cancer	Open radical gastrectomy with intraoperative frozen section analysis of the margins	Open radical gastrectomy
Extent of lymphadenectomy	Early gastric cancer	No lymphadenectomy	No lymphadenectomy
	Lesions other than early gastric cancer (>T1 tumours)	D2 lymphadenectomy	D1 lymphadenectomy
Gastric GIST			
Extent of resection		Complete surgical resection with no gross residual disease (R0), amounting to multivisceral resection if required, so long as R0 surgery is possible without added morbidity or the risk of mortality. This may also be achieved with wedge gastric resection.	Complete surgical wedge resection of the tumour
Extent of lymphadenectomy		No lymphadenectomy unless grossly positive lymph nodes are present	No lymphadenectomy unless grossly positive lymph nodes are present



4.4 Splenectomy

Splenectomy may have to be performed in some cases of splenic hilar node involvement. Prior to consideration of splenectomy, the following should be considered:

1. Vaccinations
    a. Polyvalent pneumococcal vaccine: Pneumovax accounts for 85% to 90% of pneumococcal types and should be administered at least 2 to 3 weeks preoperatively to all patients older than 2 years. The vaccine should be administered again 5 years after splenectomy.
    b. Meningococcal vaccine can be administered as a one-time vaccination to patients older than 2 years. Some physicians reserve meningococcal vaccination for the paediatric age group.
    c. The *Haemophilus influenza* type B conjugate vaccine should be considered if the patient did not receive the vaccine during infancy.
    d. Influenza vaccination should be considered.
2. Preoperative imaging

Right upper quadrant ultrasonography is indicated preoperatively for patients who are at a high risk for developing gallstones (those with haemolytic anaemia and sickle cell anaemia), so that cholecystectomy may be concomitantly performed.

3. Other considerations

If the patient has been receiving steroids during the preoperative period, stress dose steroids should be administered. Antibiotic prophylaxis, which may be lifelong in some cases, should be discussed with the patient.

4.5 Management of complications arising from gastric cancer

Patients with gastric cancer may present for the first time with complications such as bleeding, perforation, or GOO. Decision making for these patients relies heavily on whether the disease is localised or metastatic. The use of palliative gastrectomy for GOO has reduced in the modern era of endoscopic stenting.

Table lists the options for managing the 3 most common complications depending on the intent of the surgery[89]. In case of GOO, management of patients with metastatic disease depends on life expectancy[90].

Management of complications of gastric cancer

Complication	Disease (cancer) state	Option	Additional therapy
Bleeding	Localised disease	Radical gastrectomy + D2 lymphadenectomy	Adjuvant chemotherapy (if indicated)
	Metastatic disease	Haemostatic external beam radiotherapy	Palliative chemotherapy if the patient's functional status permits; otherwise, palliative care
Perforation	**Localised disease** Haemodynamically stable intraoperatively	Radical gastrectomy + D2 lymphadenectomy or palliative resection with negative margins	Adjuvant chemotherapy
	Haemodynamically unstable intraoperatively	Two-stage procedure Emergent setting: peritoneal lavage with drain insertion and attempt at omental patch closure of the perforation Second stage: attempt at palliative resection	May consider palliative chemotherapy
	Metastatic disease Good functional status	Interventional radiology – insertion of drains	Palliative chemotherapy (if the patient's performance status permits)
	Poor functional status	Best supportive care	
GOO	**Localised disease** Endoscopic nasojejunal tube insertion (feasible) + nasogastric tube: partial GOO	Nutritional build up via nasojejunal tube + NACT followed by radical gastrectomy + D2 lymphadenectomy	Adjuvant chemotherapy
	Endoscopic NJT insertion (not feasible) – complete GOO	Upfront radical gastrectomy + D2 lymphadenectomy	Adjuvant chemotherapy ± radiotherapy (if indicated)
	Metastatic disease Short life expectancy vs. Prolonged life expectancy	Endoscopic stenting vs. surgical gastro-jejunostomy	Palliative chemotherapy (depending on the patient's performance status)

Appendix E provides algorithms for managing the more common surgical complications following gastric surgery.

4.6 Role of Radiotherapy

Radiotherapy is indicated for gastric cancers in the following situations:

1) In the postoperative setting for node positive and/or T3/T4 disease and/or patients with microscopically positive margins (R1)/grossly positive resection margins (R2)

2) In the radical setting as definitive treatment with chemotherapy for unresectable, non-metastatic cancer or for resectable disease in a patient not suitable for surgery because of medical conditions

3) Emerging role in the preoperative setting as a part of preoperative CRT (although this indication is still largely investigational)

4.6.1 Adjuvant CRT

In patients who undergo curative surgery for node-positive T3/T4 disease of the stomach, the available evidence from the literature is sufficient to conclude the following:

(1) Radiotherapy alone or combined with adjuvant chemotherapy significantly reduces the 3-year and 5-year mortality rates compared to surgery alone;

(2) The largest reduction in the 5-year overall mortality rate was noted in studies on postoperative CRT;

(3) Treatment-related mortality during the postoperative follow-up period was not significantly increased by CRT, despite the higher rate of side effects; and

Although adjuvant CRT is largely considered the standard treatment after curative surgery for gastric cancer, there is very limited data to support its benefit after D2 nodal dissection (Level 2A).

Recommendation[91-93]:

- pT3, pT4, N+ disease with <D2 nodal dissection or R+ resection: 45 Gray (Gy) radiotherapy with 5-FU-based chemotherapy (Level IA).
- pT3, pT4, N+ disease with D2 nodal dissection: 45 Gy radiotherapy with 5-FU-based chemotherapy (Level IIIB).
- In all cases of gastric cancer, wherever radiation is indicated, 3-dimensional conformal radiotherapy or intensity-modulated radiation therapy is preferable to reduce the dose to the small bowel, liver, and kidneys and improve target coverage (Level III A).

4.6.2 Preoperative CRT

Preoperative CRT is not yet a standard treatment modality for resectable gastric cancer because of the lack of a major randomized controlled trial, although this is a promising strategy and is the subject of on-going multicentric phase III trials.

4.7 Adjuvant chemotherapy

(Details of regimens with dose modification are presented in **Appendix G)**

The role of preoperative chemotherapy was established by the MAGIC trial[94], which demonstrated a 13% increase (23% to 36%) in the 5-year survival rate with perioperative ECF compared to surgery alone for stomach and oesophagogastric junction (OGJ) tumours. The MAGIC and the French trials have shown that chemotherapy in the perioperative setting is associated with a survival benefit. The addition of pre/peri/post-surgery chemotherapy has consistently demonstrated a benefit versus surgery alone[94-95].

Meta-analyses have shown a small survival benefit for adjuvant chemotherapy, with an apparently greater benefit noted in the 5 studies from Asia (relative risk [RR] 0.74, 95% confidence interval [CI] 0.64–0.85) compared with the 14 studies conducted outside Asia (RR 0.90, 95% CI 0.85–0.96)[96] (Level 1A).

A review of the other guidelines and current recommendations are shown below:

Setting	European Society for Medical Oncology	National Comprehensive Cancer Network	Japanese guidelines	ICMR consensus
Preoperative	IIIC	Trials	No	Trials
Perioperative	IA	2A	No	IA
Postoperative	IA	2A	Yes[97]	IA[98]
Replace 5-FU with capecitabine [99]	IVC	2A	NA	IIA
Replace cisplatin with oxaliplatin[100]	IA (advanced)	2A	NA	IVB

Recommendation

Patients should be considered for perioperative chemotherapy with 3 cycles of ECF or ECX (Level 1A). 5-FU may be replaced with capecitabine for better patient quality of life in order to avoid the placement of a central venous access device (Level 2 A). Cisplatin may also be replaced with oxaliplatin to reduce the time spent by patients in day-care (Level 4A).

Eight cycles of capecitabine and oxaliplatin (CAPOX) after R0 resection may also be recommended, on the basis of the CLASSIC trial[98] (Level 2A).

4.8 Adjuvant therapy for GIST

Complete surgical resection is the standard of care. Despite R0 surgical resection, some patients still relapse. The 5-year recurrence-free survival rate is 49%. Radiation and chemotherapy do not have a role. Prospective data support the clinical benefits of imatinib therapy in adjuvant settings in patients with primary localized, fully resected GIST who are at risk of relapse.

The efficacy of imatinib in GIST was first demonstrated in a landmark pilot study of a single patient with rapidly progressive GIST that was resistant to chemotherapy. This eventually led to phase II and phase III clinical trials that confirmed the efficacy of imatinib in an advanced/metastatic disease setting, improving the overall survival time from approximately 12 months in the pre-imatinib era to over 60 months. This ultimately led to trials investigating the efficacy of imatinib in the adjuvant setting among patients who had operable GIST[101-110].

For how long should patients with high-risk GIST receive adjuvant imatinib? This question was answered by the SSG trial (Scandinavian Sarcoma Group study SSG XVIII/AIO) that randomized 400 patients with high-risk disease (as defined by the National Institutes of Health consensus criteria) or those with evidence of tumour rupture to either 12 months or 36 months of imatinib at a dose of 400 mg/day[106]. At a median follow-up period of 54 months, the investigators observed a significant improvement in the primary end points of recurrence-free survival (hazard ratio 0.46, 95% CI 0.32–0.65, $p < 0.0001$) and overall survival (hazard ratio 0.45, 95% CI 0.22–0.89, $p = 0.02$) among patients who received 3 years of imatinib compared to those who received 1 year of imatinib. The 5-year recurrence-free survival rate was 65.6% among patients receiving 3 years of imatinib and 47.9% among those receiving 1 year of imatinib therapy. Further to these results, the Food and Drugs Administration has recently approved the use of 3 years of adjuvant imatinib[106].

Postoperative adjuvant Imatinib: The standard care for primary resectable localized GIST 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 in patients with high-risk disease (tumour size >10 cm and any mitotic index, any tumour size and mitotic index > 10, tumour size 5 cm and mitotic index > 5, tumour size ≤5 cm and mitotic index > 5 [non-gastric site], tumour size 5.1–10 cm and mitotic index ≤ 5 [non-gastric site], any tumour size and any mitotic index in the presence of tumour rupture). Many studies have established that adjuvant imatinib reduces recurrence in intermediate- to high-risk patients. The current duration of such adjuvant therapy is 3 years [58, 106,107,111].

Preoperative Imatinib

Preoperative imatinib for treating localized GIST is a matter of surgical and medical discretion. In many patients, treatment of very large localized GISTs with imatinib as the first-line therapy for tumour downstaging is possible. Preoperative imatinib may be used for both large tumours and small GISTs in difficult locations that are difficult to resect. Patients with primary localized GIST whose tumours are deemed unresectable should also receive imatinib. Currently, the decision to use preoperative therapy for patients with resectable primary or locally advanced GIST should be made on an individual basis (Level 4A). For unresectable or locally advanced GISTs, preoperative imatinib could be useful for improving resectability and reducing surgical morbidity[112]. Because the optimal duration of preoperative therapy remains unknown, imatinib may be continued until maximal response is noted in patients. Maximal response is defined as no further improvement as assessed by 2 successive CT scans, which can take as long as 6 to 12 months. It is not always necessary to wait for a maximal response in order to perform surgery. Each new cross-sectional imaging scan should prompt multidisciplinary reappraisal of the timing of surgery or continuation of preoperative imatinib. If progression is confirmed on CT, surgery is recommended after discontinuing imatinib (Level 4A).

CHAPTER

5 MULTIDISCIPLINARY TREATMENT FOR ADVANCED (METASTATIC) DISEASE

General approach

Unfortunately, most patients will present with metastatic disease not amenable to resection. In these cases, curative treatment is not possible, but many patients will benefit in terms of both quality of life and survival from the use of systemic chemotherapy and supportive measures. Evidence suggests that greater benefit is achieved if patients are treated early, before becoming symptomatic. The survival of patients with gastric cancers varies widely and is dependent on disease bulk, the general clinical state, tumour biology, and response to treatment. Accordingly, it is often better to avoid providing definite time periods when questioned about prognosis. Many patients, irrespective of receiving chemotherapy or supportive care, will benefit from palliative care alone. Palliative care referrals should only be made at an appropriate time, after discussion with the patient.

A recent change in treatment for patients with advanced gastric cancer has been the addition of the targeted therapeutic agent trastuzumab to chemotherapy for patients whose tumours show HER2 overexpression. HER2 is a growth factor receptor and a driver of tumourigenesis. The phase III ToGA study[113] proved that patients with overexpression of HER2 in metastatic gastric or OGJ tumours (immunohistochemistry score of 3+ or 2+ and positive fluorescent in situ hybridization results: 22.1% in this study) benefit from trastuzumab in addition to chemotherapy (cisplatin and capecitabine or 5-FU) in terms of significantly improved overall survival (13.8 vs. 11.1 months).

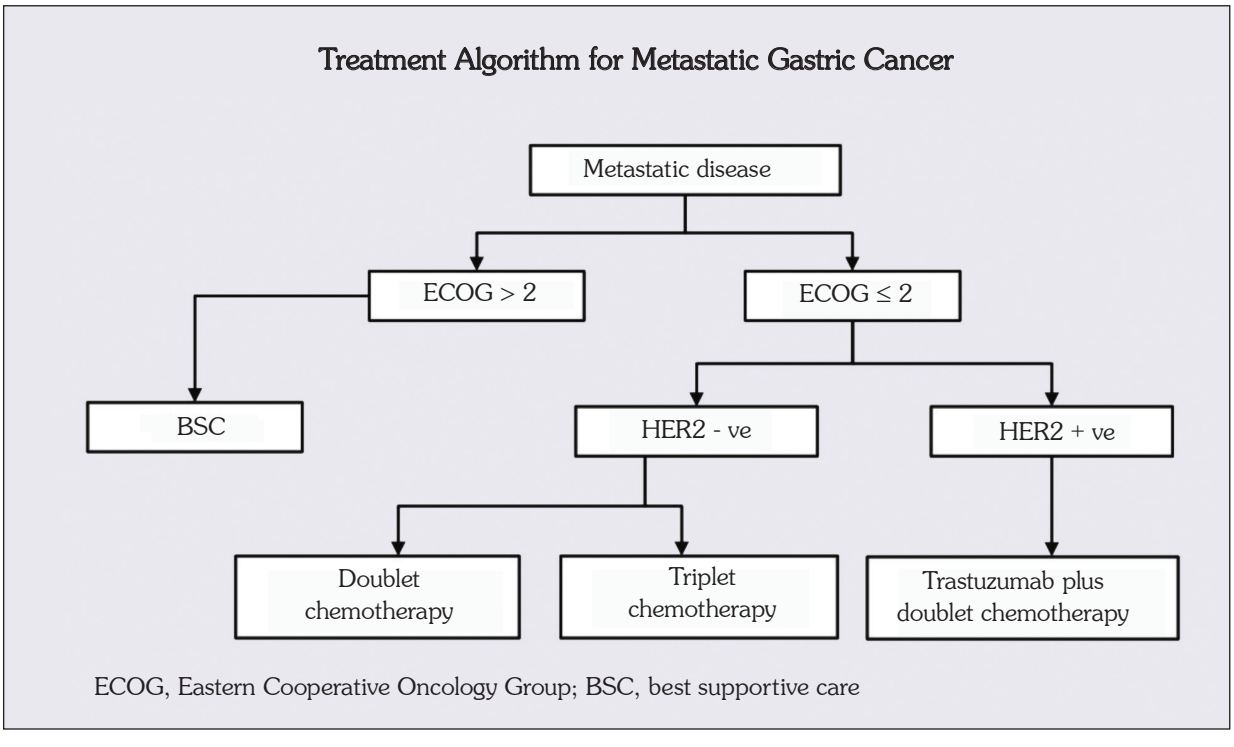
Chemotherapy agents that have modest activity in gastric cancer

Drug	Response rate (%)
Fluorinated pyrimidines	
5- FU	21
UFT (tegafur and uracil)	28
S-1 (tegafur and 2 modulators)	49
Capecitabine	26
Antibiotics	
Doxorubicin	17
Epirubicin	19
Heavy metals	
Cisplatin	19
Taxanes	
Paclitaxel	17
Docetaxel	19
Camptothecins	
Irinotecan	23

The backbone of chemotherapy for patients with advanced gastric cancer is fluoropyrimidine and platinum. Wagner et al conducted a systematic review and meta-analysis of randomized phase II and III clinical trials on first-line chemotherapy in advanced gastric cancer and concluded that the best survival results are achieved with 3-drug regimens containing 5-FU, an anthracycline, and cisplatin (Level 1).

The REAL-2 Phase 3 Trial was conducted to study whether capecitabine could be substituted for 5-FU and/or oxaliplatin could be substituted for cisplatin[114] .The study included 4 arms: ECF, EOF, ECX, and EOX. The median overall survival and 1-year overall survival rate did not differ between the arms. The median survival times in the ECF, ECX, EOF, and EOX groups were 9.9, 9.9, 9.3, and 11.2 months, respectively, and the survival rates at 1 year were 37.7%, 40.8%, 40.4%, and 46.8%, respectively. In the secondary analysis, overall survival was longer with EOX than with ECF. Progression-free survival and response rates did not differ significantly between the regimens. Toxicity profiles were similar for capecitabine and 5-FU. Oxaliplatin was associated with lower incidences of grade 3/4 neutropenia, alopecia, renal toxicity, and thromboembolism but slightly higher incidences of grade 3/4 diarrhoea and neuropathy than cisplatin. Thus, capecitabine and oxaliplatin are as effective as 5-FU and cisplatin, respectively, in patients with previously untreated advanced oesophagogastric cancer and can be used to replace these drugs even in perioperative chemotherapy regimens [114] (Level 3).

Docetaxel is the preferred agent for use in combination with cisplatin and 5-FU. In the V325 trial, the DCF regimen (docetaxel, cisplatin, and 5-FU) was compared to the cisplatin and 5-FU (CF) regimen, and DCF resulted in a significant overall survival (23% risk reduction) advantage and better time to tumour progression (32% risk reduction), with doubling of the 2-year survival rate. The DCF regimen was however associated with excessive toxicity, particularly myelosuppression (Level 3). Various modified DCF regimens are being used (e.g. DOX). These regimens have comparable efficacy with reduced toxicity (Level 3). The addition of an anthracycline to the CF regimen significantly improves survival. The ECF regimen is associated with response rates of more than 70% (Level 2). This regimen is considered by many as a reference regimen for the first-line treatment of advanced gastric cancer[99,100,115-117] .



ECOG, Eastern Cooperative Oncology Group; BSC, best supportive care

Chemotherapy showed a significant survival advantage over single-agent chemotherapy in a meta-analysis of 11 studies (hazard ratio, 0.82; 95% CI, 0.74–0.90). A secondary analysis of the response rate and time to progression also favoured combination chemotherapy. Overall, treatment-associated toxicity was higher with combination chemotherapy; however, treatment-related mortality was not significantly different between the 2 arms[114,116-118].

Recommendation

The regimen should be chosen according to the HER2 status, if applicable, the performance status, co-morbidities, and the toxicity profile of the drugs.

First-line systemic therapy

HER2-negative tumours: palliative chemotherapy (EOX as standard therapy, EOF if the patient is unable to tolerate capecitabine, or carboplatin plus 5-FU/capecitabine if the patient is an unsuitable candidate for oxaliplatin; ECX and ECF are alternative options) (Level 1A).

HER2-positive tumours (immunohistochemistry score of 3+): trastuzumab in combination with chemotherapy (cisplatin and either 5-FU or capecitabine) for 6 cycles, followed by continued monotherapy with trastuzumab until disease progression (trastuzumab is not administered in combination with anthracyclines because of the risk of cardiotoxicity).

Second-line systemic therapy

Trastuzumab plus chemotherapy (for HER2-positive tumours if trastuzumab was not used in first-line treatment), irinotecan-cisplatin, irinotecan-fluoropyrimidine, FOLFIRI (leucovorin, 5-FU, and irinotecan), irinotecan, docetaxel, or paclitaxel

Clinical trials:

Single-agent docetaxel[119] (Level 2B)

Single-agent irinotecan[120] (Level 2B)

Retreatment with standard therapy (in cases of a long treatment-free interval after first-line chemotherapy) (Level 4C).

GIST: The current standard treatment for recurrent or metastatic GIST is imatinib[101,104,121-123] (Level 1A).

Before the era of imatinib, the median time to recurrence after the resection of primary GIST was approximately 2 years. Several studies have evaluated the impact of cytoreductive surgery on survival in patients with advanced GIST after treatment with imatinib. The first large study to report survival rates in patients who underwent resection of advanced GIST after medical therapy found that outcomes of surgery and survival rates correlated with response to tyrosine kinase inhibitor therapy.

The indications for considering cytoreductive surgery in cases of recurrent or metastatic GIST are as follows: 1) stable disease or disease responsive to tyrosine kinase inhibitor therapy when complete gross resection is possible; 2) progression of isolated clones on tyrosine kinase inhibitor therapy after initial response (indicative of secondary drug resistance), while other disease sites remain stable (limited disease progression); and 3) emergencies, including haemorrhaging, 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.

Radiofrequency ablation and hepatic artery embolization are other alternative options for treating liver metastases. Radiofrequency ablation or cryoablation in conjunction with liver resection may be required to completely treat or eradicate liver parenchymal disease. Percutaneous ablation of liver lesions smaller than 5 cm may also be considered. Hepatic artery embolization should be considered for bulky disease and progressive liver disease in imatinib-resistant patients who are not suitable candidates for sunitinib as a second-line therapy. Radiofrequency ablation is usually reserved for unresectable tumours.

When patients show disease progression with imatinib, the standard approach is to increase the dose from 400 mg to 800 mg daily, (Level 3B) except in the case of insensitive mutations. Dose escalation may be useful in cases of GIST with a KIT exon 9 mutation[121-124].

In the case of progression with or intolerance to imatinib, the second-line standard treatment is sunitinib (Level 2B). This drug was shown to be effective in terms of progression-free survival on using a '4 weeks on–2 weeks off' regimen. Data show that a continuously dosed daily oral regimen with a lower daily dose may be effective and well tolerated; although no formal comparison has been performed in a randomized clinical trial setting. After sunitinib failure, patients with metastatic GIST should be considered for participation in a clinical trial of new therapies or new combinations[125].

CHAPTER

6 SUPPORTIVE CARE

Supportive care involves providing support at all stages of a person's experience with cancer. The primary aim of treatment is to bring about symptomatic benefit and improvement in the quality of life of patients with incurable malignancies and support patients while receiving chemotherapy. Common problems that may occur in patients with gastric cancer include the following:

- Pain
- Nausea and vomiting
- Poor appetite
- Bowel obstruction
- Anxiety, emotional distress, or depression
- Chemotherapy-related toxicities
- Nutritional depletion

The optimal control of these symptoms often requires input from specialist teams, including palliative care, surgical, and psychological support teams. Where symptom control is problematic, many patients will benefit from early palliative care.

6.1 Fertility

Chemotherapy (and radiotherapy) has the potential to adversely affect fertility. The risk of infertility varies between chemotherapy drugs. Examples of chemotherapy drugs used in the treatment of gastric cancer that are associated with the risk of infertility are as follows:

- Oxaliplatin
- Doxorubicin
- Cisplatin

Other commonly used chemotherapy agents may be associated with a lesser risk, but all chemotherapy drugs should be considered to have the potential to have a negative effect on fertility. Pelvic irradiation is also gonadotoxic and places patients at risk of infertility. All men and premenopausal women undergoing treatment placing them at risk of infertility should have these risks discussed with them and should be offered the option of considering fertility-preserving strategies (such as sperm banking for men and *in vitro* fertilization or embryo freezing for women) before commencing chemotherapy, especially in the adjuvant chemotherapy setting. Men should be made aware that they need to undergo hepatitis B and C virus and human immunodeficiency virus testing prior to sperm banking. Barrier contraception should be discussed with all patients during chemotherapy and for up to 2 years thereafter.

6.2 Bowel obstruction

Any intra-abdominal malignancy may cause bowel obstruction, especially in the case of peritoneal disease. This diagnosis must be borne in mind for any patient who presents with colicky abdominal pains, nausea, and vomiting. Patients who have protracted vomiting or whose pain is poorly controlled should be admitted. They should be kept nil by mouth and intravenous (IV) fluid administration should be commenced. Subcutaneous infusion of morphine (and cyclizine) can be effective for analgesia, and steroids can be administered intravenously. These measures are often sufficient to improve symptoms, but if vomiting persists, use of a naso-gastric tube may be necessary. In severe cases, octreotide can be considered, as this can be helpful in reducing GI secretions. In select cases, the opinion of a surgeon should also be considered, especially if the obstruction is thought to be localised to a particular area. Possible surgical interventions include palliative bypass procedures, defunctioning stoma, and stenting.

Algorithm for bowel obstruction

For single lesions, surgical resection can be performed to relieve obstruction

For multiple lesions, surgery is not an option; symptomatic medical management should be considered:

- **Sub-acute and potentially reversible: bowel sounds hyperactive**
- **Minimal hydration via the SC route or sips of fluid and ice or pineapple chunks**

Dexamethasone, 16 mg/day SC/IV (rarely) to reduce tumour oedema
Metoclopramide, 10–30 mg q6h SC/IV for vomiting may be considered in some situations
Octreotide to reduce secretions
Hyoscine butyl bromide 20 mg q6h/SC or dicyclomine 10–20 mg q6-8h SC for colicky pain

- **Complete and irreversible: bowel sounds absent (terminal care)**

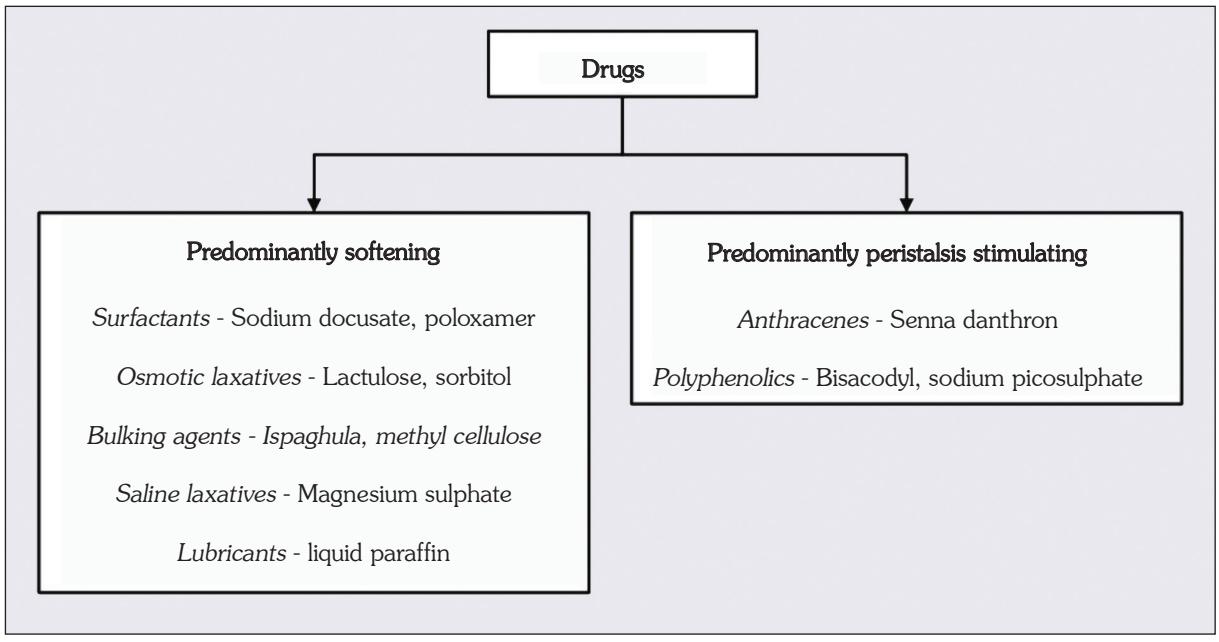
Morphine, 10 mg q4h, SC injection or rarely IV (helps to further relax the bowel)
Haloperidol, 1–2 mg SC/24 h (controls vomiting)
Hyoscine butyl bromide 20mg q6h/SC or Octreotide (reduce secretions)

6.3 Constipation

This is commonly due to drugs, reduced oral intake, vomiting, and/or lack of exercise. Anti-emetics can also lead to constipation.

General measures

- Good general symptom control
- Encourage activity
- Maintain adequate oral fluid intake
- Maximize fibre content in the diet
- Anticipate constipating effects of drugs
- Alter treatment or start prophylactic administration of a laxative



In general, combinations are found to be more effective, e.g. Cremaffin Plus (liquid paraffin + milk of magnesia + sodium picosulphate)

6.4 Liver pain

Patients with metastatic liver disease may report sharp pain in the right hypochondrium, which may be worse on deep inspiration (referred shoulder tip pain may also be a feature). This pain is thought to be due to 'stretching' of the liver capsule by the tumour. A short reducing course of steroids (with proton pump inhibitor [PPI] cover) is usually an effective treatment for this, but longer-term analgesia may also be necessary. Non-steroidal anti-inflammatory drugs with PPI cover can also be helpful.

Pain

WHO analgesic ladder

Step 1 Non-opioid ± adjuvant	**Step 2** "Mild opioid" for mild–moderate pain ± non-opioid ± adjuvant	**Step 3** "Strong opioid" for severe pain ± non-opioid ± adjuvant
General/neurosurgery/orthopaedic surgery Interventional anaesthetic techniques TENS/acupuncture/complementary therapy		
Disease-modifying treatment Chemotherapy/radiotherapy/radiopharmaceuticals/steroids/bisphosphonates		
Address psychological, emotional, spiritual, social, financial distress		

Mild opioid: Tramadol (100 mg 4 times a day [QDS] = 20 mg QDS of morphine), codeine, dihydrocodeine

Stronger opioid: Morphine diamorphine, fentanyl, buprenorphine, oxycodone, hydromorphone

Paracentesis

a) The puncture site needs to be away from scars, tumour masses, distended bowels, the liver and bladder, and other organs; the right or left lower quadrant is usually safe. Ultrasonography should be performed to so that the radiologist can mark a suitable site.

b) In patients who have undergone multiple paracentesis procedures, the ascites may become loculated. Ultrasonography is mandatory in these patients to locate the point of maximum fluid.

The role of palliative surgery has been described above.

Symptomatic treatment of toxicities related to chemotherapy

Although chemotherapy agents have individual toxicity profiles, the severity of side effects encountered varies widely from patient to patient. The recording of treatment-related toxicity is standardised according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE). Two versions are in use, version 3.0 and version 4.0 (applicable from 10.01.2009). Both versions are available on the intranet link 'NCIC common toxicity criteria' under the 'clinical' section or on the internet website http://ctep.cancer.gov/reporting/ctc.html. This terminology provides criteria to grade treatment-related toxicities on a scale of 1 to 5. Guidance on the dose reductions required for patients receiving off-study/ trial treatment can be found in this handbook. Below is a general guide:

Grade (general definitions)

0 = No adverse event or laboratory values within normal limits

1 = Mild adverse event

2 = Moderate adverse event

3 = Severe and undesirable adverse event

4 = Life-threatening or disabling adverse event

5 = Death related to adverse event

Diarrhoea

The cause of diarrhoea should be established so that the most appropriate treatment can be recommended. Rectal examination and plain radiography should enable the exclusion of organic pathologies. Recent antibiotic therapy may suggest *Clostridium difficile* diarrhoea, and a stool sample should be sent for examination before commencing treatment with oral metronidazole. Loperamide should not be administered to patients with proven *C. difficile* diarrhoea because of the risk of toxic megacolon.

For 5-FU-related diarrhoea, consider the following:

I.	**Evaluate**
	1. Onset and duration of diarrhoea: for a duration of >12 hours, collect a stool sample
	2. Number of stools and stool composition (watery, blood)
	3. Assessment for fever, neutropenia, abdominal pain, dizziness, and weakness
	4. Medication profile (diarrhoeatic e.g. bulk agents, softeners, prokinetics)
II.	**Management**
	1. Consider oral rehydration solution as part of fluid intake
	2. Drink 8–10 large glasses of clear fluids per day (water, clear soup, non-carbonated soft drinks)
	3. Eat frequent small meals as tolerated
	4. Administer antibiotics as appropriate (fluoroquinolones)
	5. Admit neutropenic patients with grade 3 diarrhoea or worse
III.	**Treatment**
	1. Initially, loperamide 4 mg followed by 2 mg after every loose stool up to 16 mg daily or codeine phosphate 30–60 mg QDS
	2. Reassessment after 12 h

After 12–24 hours

Diarrhoea resolved:

1. Stop loperamide after a 12-h diarrhoea-free interval
2. Check that the patient is eating small frequent meals

Persistent diarrhoea: Grade 1-2

1. Continue with loperamide 2 mg every 2 h up to 16 mg/24 h
2. Administer antibiotics as appropriate

Grade 3–4: Admit the patient

Tab budesonide 9 mg per oral (PO) once a day (OD) until diarrhoea resolves (all patients with an improvement in diarrhoea post-budesonide should receive prophylactic treatment during chemotherapy with subsequent courses of budesonide 9 mg PO OD for 3–5 days).

IV fluids and antibiotics should be administered as appropriate.

Diarrhoea unresolved:

Octreotide 100–150 mcg SC thrice a day (TDS) for 5 days; this dose should be increased by 50 mcg up to 200 mcg TDS if necessary.

Irinotecan-associated late-onset diarrhoea

This may occur approximately 1 week after treatment (and may therefore coincide with neutropenia). Patients should follow specific instructions, which should be provided on an information sheet to all patients receiving irinotecan.

These include the following:

Take loperamide 4 mg once after the first liquid stool then 2 mg every 2 h. Continue this regimen for 12 h after the last liquid stool (do not continue beyond 48 h).

If diarrhoea has not resolved within 24 h, start ciprofloxacin 250 mg PO BD for 7 days.

Patients should contact the hospital for advice as soon as diarrhoea is experienced.

If diarrhoea is severe; continues for more than 48 h; or is associated with nausea, vomiting, or fever, the patient needs to be admitted to a hospital.

On admission

Stool culture, microscopy
Patients should be closely monitored: daily urea and electrolytes, abdomen radiography, urine output monitoring.
Ciprofloxacin should be continued for a total of 7, unless pyrexia develops, in which case, appropriate IV antibiotics should commence.
Loperamide should continue at 16 mg daily.
If diarrhoea persists, consider octreotide and other possible causes.

Chest pain whilst receiving fluoropyrimidines

Fluoropyrimidine (capecitabine/5-FU) agents are known to rarely cause a syndrome of angina-like chest pain, which is thought to relate to coronary artery spasm. If patients develop angina-like pain whilst receiving 5-FU or capecitabine, treatment should be discontinued immediately. Echocardiography must be

performed to exclude myocardial infarction, and cardiac enzyme levels and troponin should be measured. Patients should be admitted overnight if they have experienced significant pain within the previous 24 h. If echocardiography or blood abnormalities are noted or the patient redevelops chest pain whilst off chemotherapy, referral for a cardiology opinion should be considered.

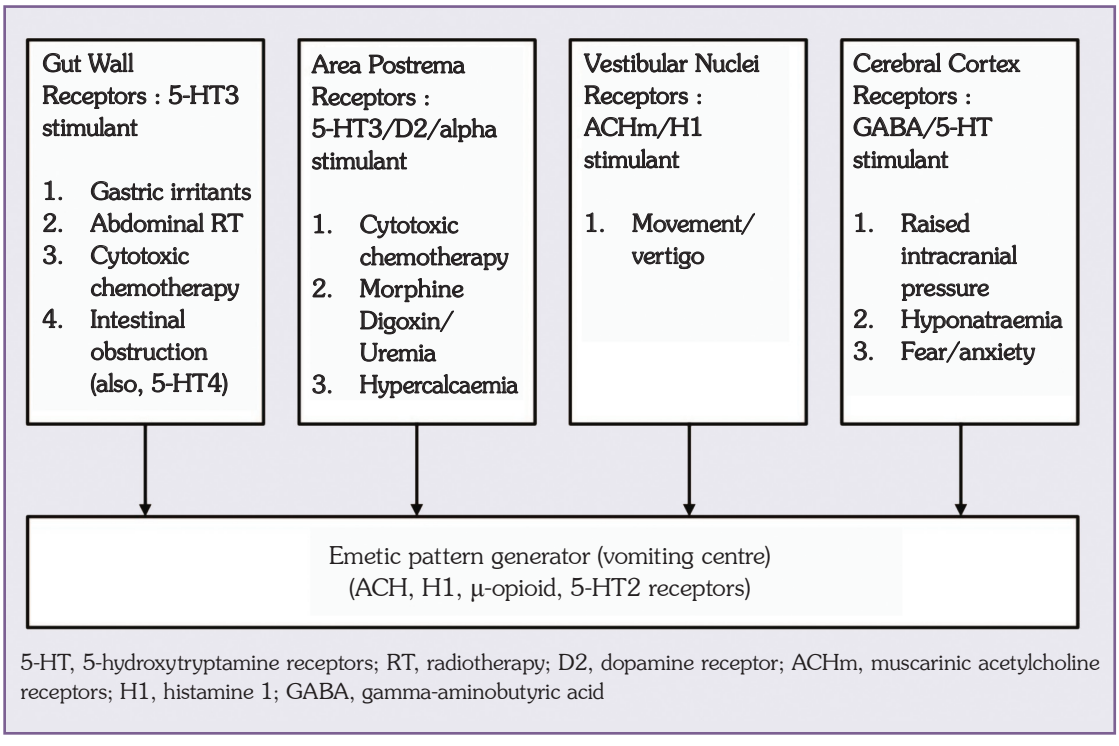
Patients should not recommence treatment, but their case should be discussed and consideration should be given to alternative chemotherapy (oral uracil-tegafur). In some cases, in discussion with a cardiologist, fluoropyrimidines may be recommenced with anti-anginal cover (Ca++ channel antagonist and nitrate).

Nausea and vomiting:

It is important to assess the cause of vomiting in order to be able to treat it correctly

- Comprehensive history and physical examination
- Minimum investigations: Consider 'holistic' assessment.

The receptors shown below are stimulated to induce vomiting. Drugs are chosen for specific receptors.



5-HT, 5-hydroxytryptamine receptors; RT, radiotherapy; D2, dopamine receptor; ACHm, muscarinic acetylcholine receptors; H1, histamine 1; GABA, gamma-aminobutyric acid

Commonly used drugs acting on specific receptors

Drug	Dosage	D2	H1	ACHm	5-HT2	5-HT3	5-HT4
Metoclopramide	10–20 mg q4-6 h PO/SC/IV	++	0	0	0	+	++
Domperidone	10–20 mg q4-8 h PO	++	0	0	0	0	0
Haloperidol	0.5–2 mg q6-12 h PO/SC/IV	+++	0	0	0	0	0
Ondansetron	4–8 mg Q8-12	0	0	0	0	+++	0
Chlorpromazine	25–50 mg q6-8 h PO/IV	++	++	+	0	0	0
Diphenhydramine	50–100 mg q4-6 h PO/IV	0	++	++	0	0	0
Prochlorperazine	10–20 mg q6 h PO/IV or 25 mg q6 h PR	++	+	0	0	0	0
Olanzapine	1.25–2.5 mg PO OD	+	++	++	++	+	0
Dexamethasone	4–20 mg q AM PO/IV/SC	0	0	0	0	?	0

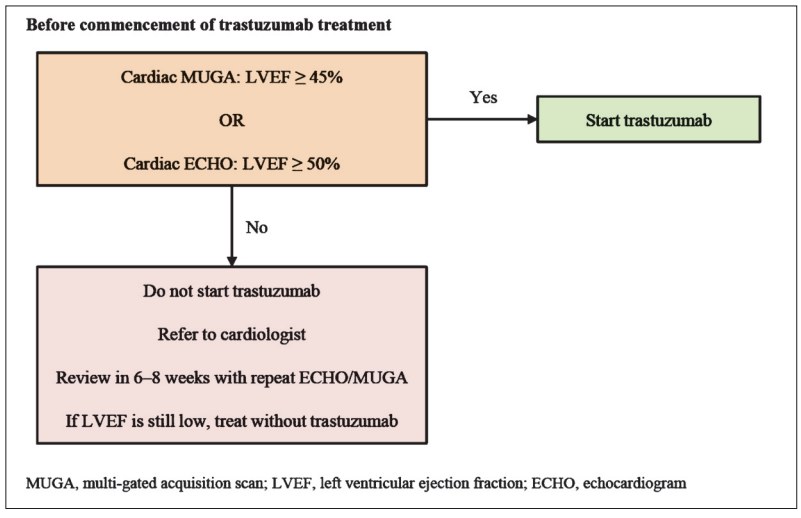
Measures other than medication include consuming small tasty meals, a variety of foods, or cold food; a break from cooking; and home ventilation.

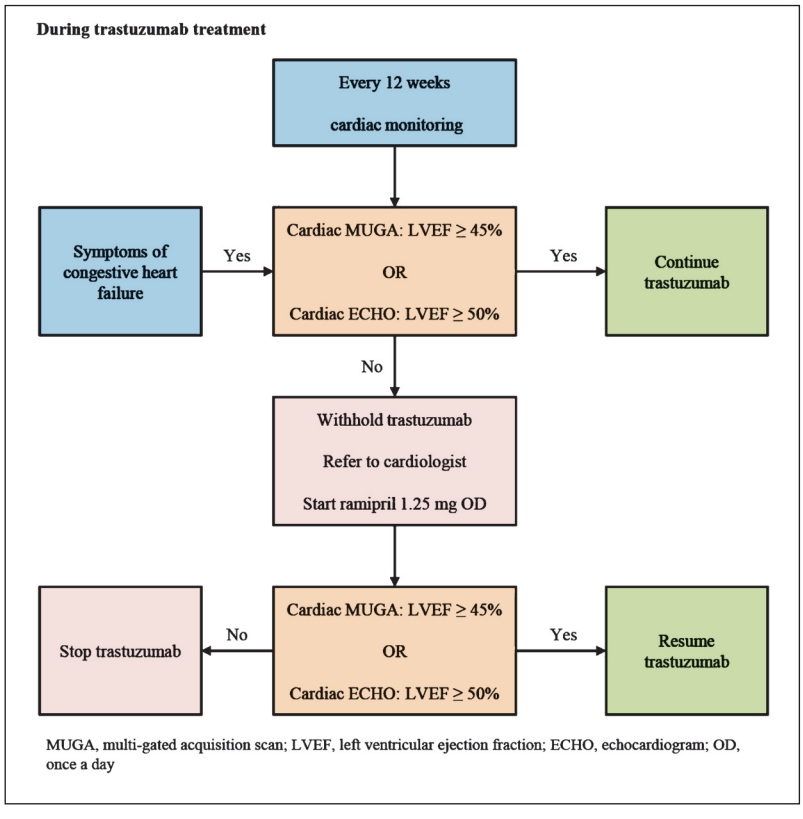
Before the administration of oxaliplatin, dexamethasone and ondansetron is recommended.

For the prevention of delayed nausea and vomiting, use corticosteroids and metoclopramide (and ondansetron, if required).

Trastuzumab monitoring:

A pre-treatment cardiac multi-gated acquisition scan (MUGA) scan or 2-dimensional echocardiogram is required for all patients, and this is acquired again every 12 weeks after treatment to monitor left ventricular ejection fraction.





CHAPTER

7 FOLLOW UP AND SURVIVORSHIP

Gastric cancer

Follow-up schedule after adjuvant chemotherapy or NACT

Year	Time from start of chemotherapy (months)	Clinical examination	Elevated tumour marker levels, CEA or CA 19-9, at diagnosis	CT CAP	Discharge
0	0	✓	✓	✓	
1	3	✓	✓		
	6	✓	✓		
	9	✓	✓		
	12	✓	✓	✓	
2	18	✓	✓		
	24	✓	✓	✓	
3	30	✓	✓		
	36	✓	✓	✓	
4	48	✓	✓		
5	60	✓	✓		✓

GIST

Follow-up schedule after adjuvant chemotherapy or NACT

Year	Time from diagnosis	Clinical examination and blood tests (for patients on imatinib)	CECT abdomen/PET-CT	Discharge
0	0	✓	✓	
1	3	✓		
	6	✓	✓	
	9	✓		
	12	✓	✓	
2	15	✓		
	18	✓		
	21	✓		
	24	✓	✓	
3	30	✓		
	36	✓		
4	48	✓		
5	60	✓		✓

Advanced disease: Gastric cancer

- Following completion of chemotherapy, review every 3 months (may be extended if the patient is stable)
- Measure the CEA/CA 19-9 level (whichever is elevated at diagnosis) at each clinic visit
- No routine imaging is indicated, unless symptom driven
- Consider CT if signs/symptoms suggest disease progression or increasing tumour marker levels
- Ensure that all patients receive palliative care support if possible (desirable)
- If no further treatment can be offered following evidence of disease progression, the patient should be discharged from the clinic with adequate psychological/palliative support, if possible.

CHAPTER

8 PALLIATIVE CARE

Palliative care is aimed at providing comfort to the patient in all possible scenarios. Patients should receive physical, psychological, spiritual, and social support, if feasible. Quality of life should be the main focus of care. Care should be offered for each type of suffering by a multidisciplinary professional team in the hospital, home, or hospice, depending on the choice of the patient and family in concurrence with the treating physician.

8.1 Palliative therapeutic endoscopy in advanced disease

Endotherapy for pyloric stenosis

- Self-expanding metal stents (SEMS) can be used for the palliation of GOO caused by distal tumours.
- Technical success rates are generally more than 90%, and 60–80% of patients are able to eat at least soft diets [126].
- Early complications include perforation and bleeding and are seen in less than 1% of the procedures.
- Delayed complications include stent migration and restenosis.
- Nasojejunal feeding tubes can be placed endoscopically for nutritional support in cases of GOO in patients with advanced gastric cancer who are unable to afford SEMS placement.

8.2 Palliative radiotherapy

Palliative radiotherapy is indicated for locally advanced or metastatic gastric cancer to control bleeding or to relieve obstruction or pain. In a study by Tey et al [127], palliative radiotherapy with or without palliative chemotherapy yielded a median survival time of 145 days. In that study, palliative radiotherapy elicited a response in 55% of patients with bleeding, with response duration of 140 days; in 25% of patients with obstructive symptoms, with a median response duration of 102 days; and in 25% of patients with pain, with a substantial response duration. Various dosage and fractionation schemes ranging from a single fraction up to 20 fractions can be used.

Recommendation

- Palliative radiotherapy (with variable dosage) should be used to relieve obstruction and pain and to stop bleeding (Level 2A).

Appendix F provides details on the techniques of radiotherapy planning

CHAPTER

9 RESEARCH ISSUES

- Epidemiology of gastric cancer
- Non invasive /invasive screening in high prevalence areas
- Molecular pathology and outcomes
- Role of chemotherapy in various settings
- Role of radiotherapy in various settings
- Role of extent of surgery in gastric cancer
- Training and credentialing of surgeons, pathologists, radiologists, medical oncologists, and radiation oncologists in site-specific areas
- Role of new techniques for diagnosis and management like PET-CT and IMRT
- Role of targeted therapies

CHAPTER

10 APPENDICES

Appendix A

10.1 Prevention of gastric cancer

Primary prevention of gastric cancer focuses on the modifiable risk factors for gastric cancer. Strategies that have been evaluated include eradication of *H. pylori* infection and dietary/lifestyle interventions.

Eradication of *H. pylori* prevents the development of pre-neoplastic changes of the gastric mucosa (Level 1B, recommendation grade A) and has the potential to reduce the risk of gastric cancer development (Level 1C, recommendation grade B [12] . A population 'test and treat' strategy for *H. pylori* infection in communities with a high incidence of gastric cancer can be considered for gastric cancer prevention (Level 2A, recommendation grade B) [128].

Improvement of public health, community sanitation, and hygiene can also be a preventive strategy to reduce the burden of *H. pylori* in the population [18,128]. Dietary interventions include increased intake of fresh fruits and vegetables, which can ensure adequate vitamin C and dietary fibre, and avoidance of increased salt intake. Tobacco and alcohol consumption are other risk factors that can be targeted by lifestyle modifications.

Secondary prevention mainly involves screening of high-risk populations using endoscopy with targeted biopsies. Serological tests such as pepsinogen level measurement or *H. pylori* antibody tests can indicate field cancerisation by identifying patients with atrophic gastritis and *H. pylori* infection who would be at a high risk for gastric cancer [17,129]. These tests cannot however provide information on already established focal precancerous/cancerous lesions. Serological tests have been used to identify subjects who may benefit from screening.

10.2 Screening for gastric cancer

Screening targets individuals who do not have any symptoms of cancer in order to identify cancer at an early stage, when treatment is most likely to be effective.

Population screening for gastric cancer is practiced in Japan, Korea, and some areas of Taiwan, areas with a high incidence of gastric cancer (the age-standardised rates for gastric cancer in Japan are 46.8 and 20.5 per 100,000 population for men and women, respectively) [1,17]. The investigations used are double-contrast barium examination, endoscopy with multiple targeted biopsies, and a serum pepsinogen level assay. Other countries do not have formal programs. Endoscopy and pathology expertise is required for endoscopy-based screening programmes.

India has a low incidence of gastric cancer[1]. Thus, screening would not be cost effective, as a large number of people are required to be screened to detect 1 case of gastric cancer. Hence, a screening strategy for the general population is not economically viable in India. Screening may be cost effective in moderate- to high-risk populations where endoscopic screening and subsequent surveillance could be recommended for those with definite risk factors.

10.3 Diagnosis and eradication of H. Pylori infection

Since many patients with *H. pylori* infection do not have any related clinical disease, routine testing is not advised [12]. Serological tests or endoscopy and biopsy can be used to diagnose *H. pylori* infection. In populations at a low risk for gastric cancer, screening for *H. pylori* is not recommended [130]. *H. pylori* testing and eradication is recommended for duodenal or gastric ulcers (Level 1A), for mucosa associated lymphoid tissue lymphoma (Level 1A), for atrophic gastritis (Level 3B), after gastric cancer resection (Level 3B), in first-degree relatives of patients with gastric cancer (Level 3B), and if the patient so desires (Level 5A) [12].

Treatment of *H. pylori* infection: Combination therapy using a PPI with 2 antibiotics (clarithromycin, amoxicillin, or metronidazole) is recommended for cases in which resistance to clarithromycin is less than 15–20%. Metronidazole is preferred over amoxicillin for cases in which resistance to metronidazole is less than 40%. Bismuth-containing quadruple treatments are alternative first- or second-choice treatments, if available[12] . Treatment is recommended for 7–14 days and should be selected taking into account the prevailing antibiotic resistance rates and patterns. A 10-day sequential therapy using a PPI plus amoxicillin for 5 days followed by a PPI, clarithromycin, and tinidazole for 5 days can also be an alternative[131]. Treatment should achieve an eradication rate of 80%. Indian studies show high prevalence of antibiotic resistance (metronidazole: 77.9–85%, clarithromycin: 44.7%, amoxicillin: 32.8%, and tetracycline: 7.5%) [132-133]. Indian studies show that *H. pylori* eradication rates vary from 31% to 96%[134-136].

Appendix B

CT staging of gastric cancers

T1 tumours: Focal thickening of the inner layer with a visible outer layer of gastric wall and a clear fat plane around the tumour

T2 tumours: Focal/diffuse thickening of the gastric wall and smooth outer border of the wall or only a few small linear soft tissue strands extending into the fat plane, accounting for less than one-third of the tumour.

T3 tumours: Transmural tumours with obvious blurring of at least one-third of the tumour or wide reticular strands surrounding the outer border of the tumour

T4 tumours: Obliteration of the fat plane between the gastric tumour and an adjacent organ or invasion of an adjacent organ.

CT reporting template

Localized/generalized gastric wall thickening/exophytic mass

Location: gastroesophageal junction, fundus, body, antrum, extension to the duodenum

Length of the segment

Thickness of the wall

Perigastric fat plane: clear/stranding present.

If stranding is present, specify whether less than one-third or more than one-third of the length of the gastric lesion.

Adjacent organs: a) loss of the fat plane with the liver/pancreas/any other structures b) Invasion of adjacent structures—liver/pancreas/any other organ or aorta

Nodes: perigastric/gastrohepatic/celiac/paraaortic

Number of abnormal nodes, tumour size, necrosis

Metastases: liver, lungs, bones, peritoneum, ovaries, ascites, any other region

Appendix C

Definition of lymphadenectomy as per the subsite of the stomach[69]

			Middle third		
		Upper third	Upper	Lower	Lower third
D1	Removal the first group of lymph nodes	1, 2, 3, 4sa, 4sb	1, 2, 3, 4, 5, 6	1, 3, 4sb, 4d, 5, 6	3, 4d, 5, 6
D2	Removal of the second group of lymph nodes	**D1** + 4d, 7, 8a, 9, 10, 11	**D1** + 7, 8a, 9, 10, 11, 12a	**D1** + 7, 8a, 9, 11p, 12a	**D1** + 1, 7, 8a, 9, 11p, 12a, 14v

Appendix D

Pathology

Assessment of tumour response

Tumour regression grade	Description
0 (complete response)	No cancer cells
1 (moderate response)	Single cancer cell or a small group of cancer cells
2 (minimal response)	Residual cancer outgrown by fibrosis
3 (poor response)	Minimum or no treatment effect; extensive residual disease present

HER2 testing[112]: Immunohistochemical criteria for scoring HER2-neu expression in gastric and esophagogastric carcinomas

	Surgical specimen expression pattern, immunohistochemistry	Biopsy specimen expression pattern, immunohistochemistry	Assessment of HER2-neu overexpression
0	No reactivity or membranous reactivity in <10% of cancer cells	No reactivity or no membranous reactivity in any cancer cell	Negative
1+	Faint or barely perceptible membranous reactivity in >10% of cancer cells; cells are reactive only in parts of the membrane	Cancer cell cluster with a faint or barely perceptible membranous reactivity, irrespective of the percentage of positive cancer cells	Negative
2+	Weak to moderate complete, basolateral or lateral membranous reactivity in >10% of cancer cells	Cancer cell cluster with weak to moderate complete, basolateral, or lateral membranous reactivity, irrespective of the percentage of positive cancer cells	Equivocal
3+	Strong complete, basolateral or lateral membranous reactivity in >10% of cancer cells	Cluster of 5 or more cancer cells with a strong complete, basolateral, or lateral membranous reactivity, irrespective of the percentage of positive cancer cells	Positive

Synoptic reporting template for pathology:

GROSS DESCRIPTION

Received a specimen of _____ measuring _____ cm along the lesser curve and _____ cm along the greater curve. The oesophagus is _____ cm in length. The omentum is attached to the greater curvature and measures _____ cm. On opening the specimen, a _____ is seen involving the _____. The tumour measures _____ cm. On gross examination, the tumour is seen invading the stomach wall up to the level of the _____. The tumour is _____ cm from the proximal margin and _____ cm from the distal margin. Doughnuts are received separately measuring _____ cm.

D1/D2 lymphadenectomy has been performed. _____ lymph nodes are dissected from the lesser curve and _____ lymph nodes are dissected from the greater curve. The nodes are soft, grey/firm, white on gross examination. The largest lymph node measures _____ cm.

Other groups of lymph nodes: _____

Grossed by: _____

HISTOLOGY

Oesophago-gastrectomy/distal gastrectomy/total gastrectomy/wedge resection (post chemotherapy/radiotherapy):

_____ differentiated adenocarcinoma of the stomach/gastro-oesophageal junction/lower oesophagus.

Tumour invades the _____ (T).

Lymphovascular tumour emboli are seen/not seen.

Proximal and mucosal resection is _____

The distal mucosal margin is _____

Doughnuts are _____

The adjacent stomach mucosa shows _____

The gastroesophageal junction is _____

Lymph nodes along the lesser curve: _____

Lymph nodes along the greater curve: _____

Other group of lymph nodes: _____

IMPRESSION: Oesophago-gastrectomy/distal gastrectomy/total gastrectomy/local resection of gastric tumour (post chemotherapy/radiotherapy):

Adenocarcinoma: Completely resected (R0)/R1/R2

TNM (Union for International Cancer Control TNM, seventh edition): T N/y Ty N

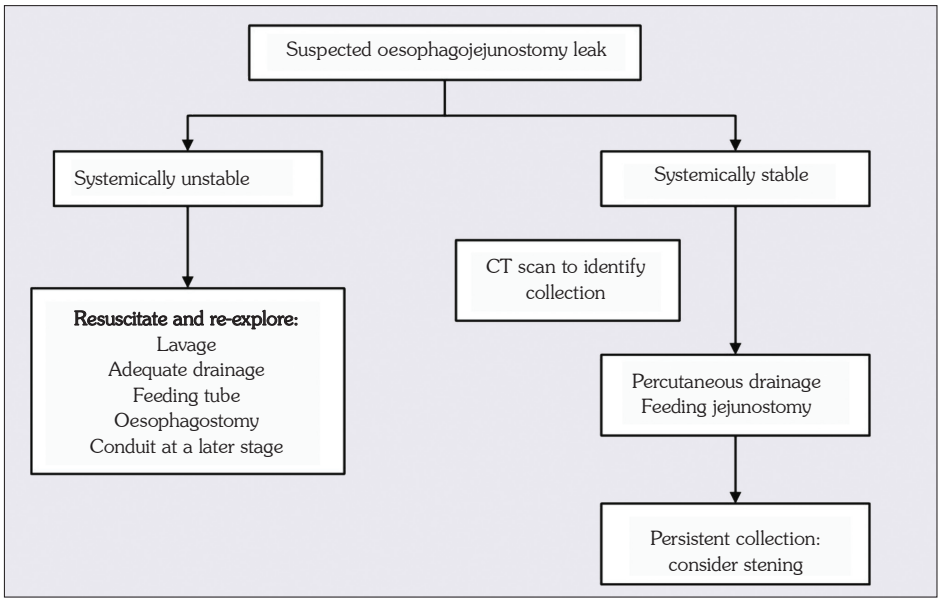
Appendix E

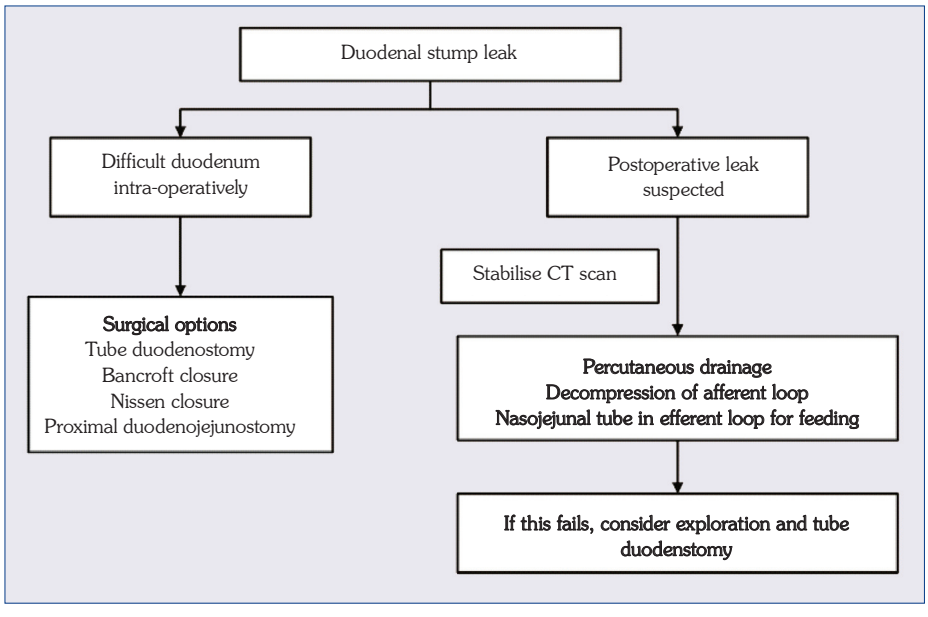
Surgical complications and their management

The 3 most important complications of gastric cancer surgery are as follows:

- Anastomotic leakage
- Duodenal stump leakage
- Delayed gastric emptying (DGE)

Figures provide useful algorithms for managing an oesophagojejunostomy leakage (after total gastrectomy) or a duodenal stump leakage[137] .





A consensus definition to aid the identification and management of DGE has been recently provided by the International Study Group for Pancreatic Surgery [138] . Put simply, there are 3 grades of DGE, which have been defined in Table. The management of grade A DGE is conservative, whereas patients with grade B DGE will benefit from prokinetic agents. Patients with grade C DGE, too, are best managed by the use of prokinetics and nutritional support. Very rarely, repeat surgery is warranted, and this has a low success rate and hence needs to be reserved as a last resort [137] .

DGE post gastric surgery

	Nasogastric drainage requirement
DGE grade A	up to postoperative day 4–7
DGE grade B	postoperative day 7–14
DGE grade C	beyond postoperative day 14

Appendix F

Techniques of radiation therapy planning

Role of advanced radiotherapy techniques

The majority of protocols used for the treatment of gastric cancer (including INT0116) have primarily employed parallel-opposed anteroposterior-posteroanterior (AP-PA) field arrangements, which are associated with significant acute normal tissue toxicity. Current modern techniques of radiation delivery employ multiple radiation fields that conform more accurately to the high-risk volume, with the potential to produce superior dose distributions and reduce normal tissue toxicity. In their study, Leong et al [139] reported that 3DCRT results in superior dose distributions and reduces radiation doses to the kidneys and spinal cord compared to techniques employing AP-PA field arrangements, with the potential to reduce treatment toxicity. A study from PMH [140] showed that, for patients treated with 3DCRT with same the dose and fractionation schedule as in the INT0116 trial, the rate of acute grade 3 toxicity was 25% compared to 41% reported in the INT0116 trial. Intensity-modulated radiation therapy (IMRT) further improves the conformity between the target volume and normal tissues achieved by the process of inverse planning. A German study of 60 patients by Heggemann et al [141] showed that with a median follow-up period of 67 months, the 2-year overall survival rate was 37% in patients treated with 3DCRT compared to 67% in patients treated with IMRT. Dosimetrically, the renal doses were significantly reduced with IMRT, especially in the high-dose region, compared to 3DCRT.

Despite several studies showing that IMRT may yield better dosimetric outcomes than 3DCRT, its role is still investigational and this technique should be used cautiously as there are several complexities involved in implementing IMRT for this site. Because the stomach is an abdominal organ, immobilization and an accurate understanding of the internal motion of the residual stomach and nodal groups is essential. Translation and deformation resulting from the variable filling of hollow organs and the effects of respiration on target position are better understood with image guidance.

With regard to surgery, the radiotherapy plans developed at high-volume centres could be better than those developed at low-volume centres, as shown in a study from UCSF [142]. This study concluded that although IMRT improved the dosimetric outcomes with respect to the planning target volume (PTV) and liver doses, experienced centres can yield superior IMRT plans.

Summary: In all cases of gastric cancer for which radiation therapy is indicated, conformal techniques are preferable to reduce the dose to the small bowel, liver, and kidneys and to improve target coverage (Level 3A). Although IMRT appears to be dosimetrically superior, it should be used cautiously, especially in low-volume centres. Organ motion must be accounted for when determining the PTV when the conformal or IMRT technique is used.

Pre-planning

It is important to review the preoperative radiological findings, especially the preoperative CT scan, which will help determine the extent of disease, the involvement of regional lymph nodes, and spread if any to adjacent organs. The preoperative tumour extent will form the basis for the radiotherapy treatment volume of the tumour bed. It is also important to note the intra-operative and histopathological findings. The nutritional status is of importance in these patients as they are likely to be nutritionally deprived after the radical nature of the surgery. Patients undergoing total gastrectomy require more aggressive nutrition supplementation than those undergoing partial gastrectomy and a proportion of these patients will

require a feeding tube to tolerate CRT toxicity.

Simulation

CT simulation and three-dimensional treatment planning is strongly recommended.

- **Empty stomach**
- **Supine position with arms overhead**
- **Immobilization device (thermoplastic mould or a full body vacloc and a knee rest)**
- **IV/oral contrast (for better target delineation in order to document the position of the stomach, distal oesophagus, duodenum, and lymph nodes).**
- **CT slices are taken at 5-mm intervals from the top of the heart superiorly to the L4–L5 interspace inferiorly, with 3 alignment fiducials for patient setup.**

Contouring guidelines

The radiation oncologists planning three-dimensional radiotherapy should be well versed with the recommendations published by the International Commission of Radiation Units.

The clinical target volume (CTV) includes the entire residual stomach, anastomotic site, and lymph node groups. The structures to be included in the CTV are outlined below according to site:

A. Primary tumours in the proximal one-third/cardia/gastro-oesophageal junction

A 3–5-cm margin of the distal oesophagus, medial left hemidiaphragm, and adjacent pancreatic body should be included. The nodal areas at risk include the para-oesophageal, perigastric, celiac, and suprapancreatic lymph nodes.

B. Primary tumours in the middle one-third/body

The body of the pancreas is included. The nodal areas at risk include the perigastric, celiac, splenic hilar, porta hepatic, suprapancreatic, and pancreaticoduodenal lymph nodes.

C. Primary tumours in the distal one-third/antrum/pylorus

The head of the pancreas and a 3–5-cm margin of the duodenal stump should be included. The nodal areas at risk include the perigastric, celiac, porta hepatic, suprapancreatic, and pancreaticoduodenal lymph nodes.

Typical constraints used for planning are given below:

- No more than 5% of the spinal cord within the fields may receive more than 4500 cGy and no portion of the spinal cord may receive more than 5000 cGy.
- No more than 60% of the liver may receive more than 3000 cGy.
- If possible, both kidneys should be shielded such that no more than 33% of each kidney receives more than 2250 cGy. If this is not possible, it is recommended that a renal scan be performed to determine the functioning of both kidneys. It is then permissible for 1 kidney to receive up to 4500 cGy but no more than 33% of the second kidney to receive more than 2250 cGy.
- No more than 30% of the heart may receive more than 4000 cGy. The maximum field size is 400 cm^2 but every attempt should be made to use shielding to reduce the actual volume to less than 225 cm^2 (15 × 15 cm).

Adequate margins are added to the CTV to obtain the planning target volume. Radiation will typically be given using 5 to 7 fields. A multileaf collimator will be used for shielding, and wedges will be used to improve dose homogeneity. Lung corrections will be used when a significant amount of lung tissue is within the treatment field.

Central axis isodose distributions and dose volume histograms will be used to determine the dose to the planning target volume and critical structures. The dose will be prescribed to the isocentre. Treatment will be delivered using high-energy photons, typically of mixed energy 6MV/18MV photon beams. The beams eye view technique will be used to confirm set-up during conventional simulation. Electronic portal images will be acquired at the time of radiation delivery to confirm setup errors.

The radiation dose prescribed is 45–50 Gy in 25–28 fractions over 5–5.5 weeks.

Appendix G

Chemotherapy regimens used in gastric cancer: Doses and dose modifications

ECF regimen

Epirubicin : 50 mg/m^2 every 3 weeks

Cisplatin* : 60 mg/m^2 every 3 weeks

5-FU : 200 mg $m^{-2}day^{-1}$ by continuous infusion via a portacath/peripherally inserted central catheter line

*Carboplatin (area under the curve 5) should be considered for patients with poor renal function or impaired hearing. Alternatively, EOX/F may be administered for locally advanced disease that is inoperable at presentation, but potentially operable if downsizing is achieved with chemotherapy. If epirubicin-carboplatin-5-F is given perioperatively with a curative intent, prophylactic granulocyte-colony stimulating factor treatment should be considered.

Requirements:

Absolute neutrophil count ≥1.0 cisplatin (≥ 1.5 carboplatin), Platelet count ≥ 75 (≥ 100 carboplatin), Stable renal function (CrCl > 60 mL/min), Bilirubin ≤ 26 (see dose modifications if greater)

ECX regimen

Epirubicin : 50 mg/m^2 every 3 weeks

Cisplatin* : 60 mg/m^2 every 3 weeks

Capecitabine : 1250 mg $m^{-2}day^{-1}$ in 2 divided doses for 21 days

Cisplatin and capecitabine (CX) plus trastuzumab regimen (21-day cycle)

Trastuzumab : Day 1: 8 mg/kg IV loading dose, followed by 6 mg/kg for subsequent cycles

Cisplatin* : Day 2: 80 mg/m^2 for Cycle 1 (Day 1 for subsequent cycles)

Capecitabine : Days 2–15: 2000 mg $m^{-2}day^{-1}$ in 2 divided doses for Cycle 1 (Days 1–14 for subsequent cycles)

CF plus trastuzumab regimen (21-day cycle)

Trastuzumab : Day 1: 8 mg/kg IV loading dose, followed by 6 mg/kg for subsequent cycles

Cisplatin* : Day 2: 80 mg/m^2 for Cycle 1 (Day 1 for subsequent cycles)

5-FU : Days 2–6: 800 mg $m^{-2}day^{-1}$ continuous infusion over 5 days for Cycle 1 (Days 1–5 for subsequent cycles)

*Carboplatin (area under the curve 5) should be considered instead of cisplatin for patients with poor renal function (<40 mL/min) or impaired hearing.

Trastuzumab monotherapy

Trastuzumab : 6 mg/kg IV 3 weekly (if treatment is delayed for 8 days or more, as per proforma, reload with 8 mg/kg IV, followed by 6 mg/kg IV for subsequent cycles)

Docetaxel

Docetaxel : 75 mg/m^2 in a 21-day cycle

Dose modifications

Peripheral neuropathy: The oxaliplatin dose can be adapted according to the table below:

	Duration of the toxicity		
Toxicity	**≤7 days**	**>7 days and <14 days**	**Persistent between cycles**
Paraesthesia/dysaesthesia without functional impairment (grade 1 NCI)	No change	No change	No change
Paraesthesia/dysaesthesia with functional impairment without impeding the activities of the daily living (grade 2 NCI)	No change	No change	65 mg/m^2
Paraesthesia/dysaesthesia with pain or functional impairment, impeding the activities of daily living (grade 3 NCI)	65 mg/m^2	65 mg/m^2	Stop oxaliplatin
Persistent disabling paraesthesia/dysaesthesia	Stop oxaliplatin	Stop oxaliplatin	Stop oxaliplatin
Acute dysaesthesia, laryngopharyngeal spasm	Extend the duration of the next infusion to 6 h		

Dose modifications for carboplatin plus 5-FU or capecitabine

Haematological dose modifications

Neutrophil count (×10^9/L) on the day treatment is due	**CTCAE grade**	**Action**
≥1.5	0–1	Full dose of carboplatin and 5-FU/capecitabine
1.0–1.4	2	Continue 5-FU/capecitabine and delay carboplatin until count recovers and restart at the same dose.
0.5–0.9	3	Stop 5-FU/capecitabine and delay carboplatin until recovery. Restart 5-FU/capecitabine at the same dose and reduce carboplatin to area under the curve 4 for subsequent courses.
<0.5	4	Stop 5-FU/capecitabine and delay carboplatin until recovery. Restart 5-FU/capecitabine at the same dose and reduce carboplatin to area under the curve 3 for subsequent courses.

Platelet Count (×10^9/L)	**CTCAE grade**	**Action**
≥100	0	Full dose of carboplatin and 5-FU/capecitabine.
75–99	1	Continue 5-FU/capecitabine and delay carboplatin until recovery (>100). Restart at the same dose.
50–74	2	Continue 5-FU/capecitabine and delay carboplatin until recovery. Reduce carboplatin to area under the curve 4 for subsequent courses.
25–49	3	Stop 5-FU/capecitabine and delay carboplatin until recovery. Restart 5-FU/capecitabine at the same dose and reduce carboplatin to area under the curve 3 for subsequent courses.
<25	4	Stop 5-FU/capecitabine and delay carboplatin until recovery. Restart 5-FU/capecitabine at the same dose and reduce carboplatin to area under the curve 3 for subsequent cycles

Dose modifications for CF

Dose modifications for infused 5-FU: non-haematological toxicity

Dose reductions apply to 5-FU in the following regimens: CF, carboplatin-5-FU, ECF, epirubicin-carboplatin-5-FU, or mitomycin C-5-FU

	Grade I	Grade II	Grade III	Grade IV
Stomatitis	Supportive measures	Stop chemotherapy. Restart with 50 mg/m^2 dose reduction	Stop chemotherapy. Restart with 100 mg/m^2 dose reduction.	Stop chemotherapy. Restart with 150 mg/m^2 dose reduction.
	Commence sucralfate and mouthwash.			
*Palmar-plantar syndrome	Supportive measures	Stop chemotherapy. Restart with 50 mg/m^2 dose reduction.	Stop chemotherapy. Restart with 100 mg/m^2 dose reduction.	–Not applicable
Diarrhoea	Supportive measures	Stop chemotherapy. Restart with 50 mg/m^2 dose reduction.	Stop chemotherapy. Restart with 100 mg/m^2 dose reduction.	Stop chemotherapy. Restart with 150 mg/m^2 dose reduction.
	Commence codeine phosphate or loperamide.			

*The development of chronic toxicity, in particular plantar-palmar erythema, with protracted venous infusion 5-FU is well recognized. In view of this and knowledge of the toxicity profiles associated with protracted venous infusion 5-FU, for patients developing common toxicity criteria grade 2 or 3 toxicity unresponsive to symptomatic measures after 10 weeks of treatment have been completed, treatment should be stopped until the toxicity is resolved. These patients do not need dose reduction.

Renal function

Glomerular filtration rate > 60 mL/min: Full dose of cisplatin

Glomerular filtration rate = 40–60 mL/min: Consider carboplatin or reduced dose cisplatin (same dose as GFR, e.g. GFR = 50 mL/min, cisplatin dose = 50 mg/m^2)

Glomerular filtration rate < 40 mL/min: Use carboplatin

Neutrophils ≥ 1.0×10^9/L, platelets ≥ 75 to proceed

If treatment is delayed because of haematological toxicity, the dose should be reduced appropriately.

Dose modifications for CF/CX and trastuzumab

Haematological and non-haematological toxicity except for cardiac toxicity:

Follow guidance for CF or CX

The trastuzumab dose is modified only in case of cardiac toxicity, when it is withheld or discontinued.

If chemotherapy is deferred, trastuzumab may be deferred for convenience until chemotherapy is next administered. However, if trastuzumab is delayed by 8 days or more, a re-loading dose is required.

Dose modifications for CX

Cisplatin: as for CF

Capecitabine dose modifications

Non-haematological toxicity

Renal Toxicity: Creatinine clearance should be calculated or measured at baseline and before each cycle of chemotherapy. Calculations can be made according to local practice. If the serum creatinine level is above normal or if the calculated creatinine clearance is borderline abnormal, creatinine clearance should be measured and not estimated. If creatinine clearance is ≤ 50 mL/min during treatment, the dose of capecitabine should be reduced.

Creatinine clearance (mL/min)	Capecitabine dose
≥51	100%
30–50	75%
<30	Omit capecitabine

Liver toxicity

Bilirubin: Capecitabine can induce a rise in bilirubin levels. If the bilirubin level increases to >3 × the upper limit of normal range, capecitabine should be omitted until the bilirubin level returns to acceptable levels i.e. ≤3 × ULN.

Elevated transaminase levels: Capecitabine undergoes hepatic metabolism. Patients receiving capecitabine may show temporary treatment-related elevation of transaminase levels. An isolated rise in transaminase levels above 2.5 × ULN during treatment is likely to be treatment-related, and capecitabine administration should be interrupted until recovery, i.e. ≤ 2.5 × ULN.

Toxicity grading according to NCI CTC	During the course of therapy	Dose adjustment for the next cycle (% of the starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
First appearance	Interrupt until resolved to grade 0–1	100%
Second appearance	Interrupt until resolved to grade 0–1	75%
Third appearance	Interrupt until resolved to grade 0–1	50%
Fourth appearance	Discontinue treatment permanently	
Grade 3		
First appearance	Interrupt until resolved to grade 0–1	75%
Second appearance	Interrupt until resolved to grade 0–1	50%
Third appearance	Discontinue treatment permanently	
Grade 4		
First appearance	Discontinue treatment permanently or If a physician deems it to be in the patient's best interest to continue treatment, interrupt until resolved to grade 0–1	50%

Supportive measures:

- Stomatitis: sucralfate and mouthwash
- Diarrhoea: loperamide, codeine phosphate
- Palmar-plantar erythema: emollients
- Haematological toxicity: Omit capecitabine if the neutrophil count is $<1.0 \times 10^9$/L or the platelet count is $<75 \times 10^9$/L.

In cases of febrile neutropenia, a neutrophil count <0.5 × 10^9/L or a platelet count <50 ×10^9/L, omit until resolved to grade 0–1 (neutrophil count ≥ 1.5 × 10^9/L, platelet count ≥75 × 10^9/L) and re-start capecitabine at a 75% dose.

Dose modifications for ECF/ECX

Haematological toxicity

Neutrophil count: (×10^9/L)	CTCAE grade	Action
≥1.0	0–2	Full dose of all drugs
0.5–0.9	3	Stop 5-FU/capecitabine and delay epirubicin and cisplatin until recovery (e.g. 1 week later). Restart 5-FU/capecitabine at full dose. Reduce the epirubicin dose by 25% for subsequent cycles.
<0.5	4	Stop 5-FU/capecitabine and delay epirubicin and cisplatin until recovery (e.g. 1 week later). Restart 5-FU/capecitabine at full dose. Reduce the epirubicin dose by 50% for subsequent cycles.
Platelet count (×10^9/L)	CTCAE grade	Action
≥75	0–1	Full dose of all drugs
50–74	2	Stop 5-FU/capecitabine and delay epirubicin and cisplatin until recovery (e.g. 1 week later). Restart 5-FU at full dose. Reduce the epirubicin dose by 25% for subsequent courses.
25–49	3	Stop 5-FU/capecitabine and delay epirubicin and cisplatin until recovery (e.g. 1 week later). Restart 5-FU/capecitabine at full dose and reduce the epirubicin dose by 50% for subsequent courses.
<25	4	Stop 5-FU/capecitabine and delay cisplatin until recovery. Restart 5-FU/capecitabine at full dose. Omit epirubicin for subsequent cycles.

Epirubicin: neutropenia/infection/fever

Grade 3 infection/fever associated with neutropenia (absolute neutrophil count < 1 × 10^9/L) at any time during treatment requires a subsequent 25% dose reduction.

Grade 4 infection/fever associated with neutropenia at any time during treatment requires a subsequent 50% dose reduction for epirubicin.

- **Liver toxicity**

If the bilirubin level increases to >1.5 × ULN, epirubicin should be omitted until the bilirubin level returns to acceptable levels. If the bilirubin level is >3 × ULN, omit capecitabine until the level recovers to <3× ULN.

- **Cardiac toxicity**

Any patient who develops unexplained cardiac failure during treatment should undergo evaluation of cardiac function with a MUGA scan or echocardiogram. If the LVEF is less than the lower limit of the normal range, epirubicin should be omitted.

Dose modifications for EOX

Haematological toxicity: Neutrophils

Neutrophil count ($\times 10^9$/L)	CTCAE grade	Action
≥1.0	0–2	Full dose of all drugs
0.5–0.9	3	Stop capecitabine and delay epirubicin and oxaliplatin until recovery (e.g. 1 week later). Restart capecitabine at full dose. Reduce the epirubicin dose by 25% for subsequent cycles. Reduce the oxaliplatin dose to 100 mg/m^2 for subsequent cycles.
<0.5	4	Stop capecitabine and delay epirubicin and oxaliplatin until recovery (e.g. 1 week later). Restart capecitabine at full dose. Reduce the epirubicin dose by 50% for subsequent cycles. Reduce the oxaliplatin dose to 100 mg/m^2 for subsequent cycles.

Febrile neutropenia:

Grade 3 infection/fever associated with neutropenia (absolute neutrophil count <1 × 10^9/L) at any time during treatment requires a subsequent 25% dose reduction for all the 3 drugs.

Grade 4 infection/fever associated with neutropenia at any time during treatment requires a subsequent 50% dose reduction for epirubicin.

Platelets

Platelet count ($\times 10^9$/L)	CTCAE grade	Action
≥75	0–1	Full dose of all drugs
50–74	2	Stop capecitabine and delay epirubicin and oxaliplatin until recovery (e.g. 1 week later). Restart capecitabine at full dose. Reduce the epirubicin dose by 25% for subsequent cycles. Reduce the oxaliplatin dose to 100 mg/m^2 for subsequent cycles.
25–49	3	Stop capecitabine and delay epirubicin and oxaliplatin until recovery (e.g. 1 week later). Restart capecitabine at full dose. Reduce the epirubicin dose by 50% for subsequent cycles. Reduce the oxaliplatin dose to 100 mg/m^2 for subsequent cycles.
<25	4	Stop capecitabine and delay oxaliplatin until recovery (e.g. 1 week later). Restart capecitabine at full dose. Omit epirubicin for subsequent cycles. Reduce the oxaliplatin dose to 100 mg/m^2 for subsequent cycles.

Anaemia

If a patient has a haemoglobin level < 8 g/dL on the day that treatment is due, the patient should receive a blood transfusion and all treatment should be withheld (for a maximum of 1 week), until anaemia is corrected. Anaemia with a haemoglobin level > 8 g/dL on the day of treatment may be corrected by transfusion after the administration of treatment, unless the patient is symptomatic. No dose reduction is necessary for anaemia. Significant or persistent anaemia that is not consistent with chemotherapy-induced myelosuppression and should be investigated appropriately.

Non-haematological Toxicity

Liver toxicity

- Bilirubin: If the bilirubin level increases to >1.5 × ULN, epirubicin should be omitted until the bilirubin level returns to an acceptable value, i.e. ≥ 1.5 × ULN. Administration of capecitabine should be interrupted if treatment-related elevation in bilirubin levels of >3 × ULN occur and resumed when this level decreases to <3 × ULN.
- Elevated transaminase levels: Capecitabine undergoes hepatic metabolism. Patients receiving capecitabine may show temporary treatment-related elevation of transaminase levels. An isolated rise in the transaminase level above 5 × ULN during treatment is likely to be treatment-related, and capecitabine should be interrupted until recovery, i.e. <2.5 × ULN.

Renal toxicity

Creatinine clearance should be calculated or measured at baseline and before each cycle of chemotherapy. Calculations can be made according to local practice. If the serum creatinine level is above normal or if the calculated creatinine clearance is borderline abnormal, creatinine clearance should be measured and not estimated. If creatinine clearance is < 50 mL/min during treatment, the dose of capecitabine should be reduced:

Creatinine clearance (mL/min)	Capecitabine dose
≥51	100%
30–50	75%
<30	Omit capecitabine

CHAPTER

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CHAPTER

12 ABBREVIATIONS

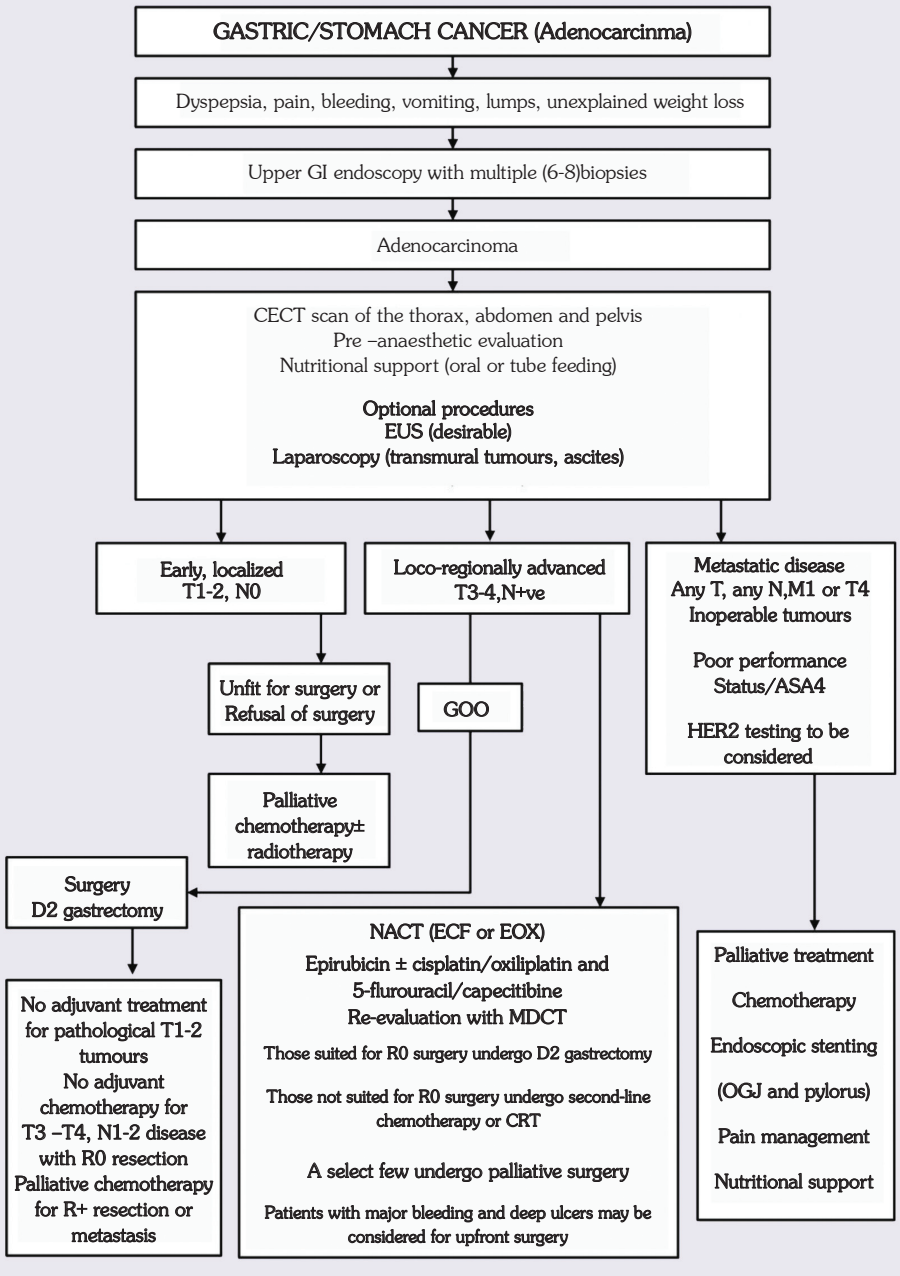
AAR	Age-adjusted incidence rate
ACHm	Muscarinic acetylcholine receptors
AP-PA	Anteroposterior-posteroanterior
ASA	American Society of Anaesthesiologists
BD	Twice a day
BMI	Body mass index
BRAF	Proto-oncogene that makes a protein called B-raf
BSC	Best supportive care
CA 19-9	Carbohydrate antigen 19-9
CAPOX	Capecitabine and oxaliplatin
CDH-1	E-cadherin
CEA	Carcinoembryonic antigen
CECT	Contrast-enhanced computed tomography
CF	Cisplatin and 5-FU
CI	Confidence interval
CX	cisplatin and capecitabine
CRT	Chemoradiotherapy
CT	Computed tomography
CTV	Clinical target volume
ECHO	Echocardiogram
D2	Dopamine receptor
DCF	Docetaxel, cisplatin, and 5-FU
DGE	Delayed gastric emptying
ECF	Epirubicin, cisplatin, and 5-fluorouracil
ECOG	Eastern Cooperative Oncology Group
ECX	Epirubicin, cisplatin, and capecitabine
EMR	Endoscopic mucosal resection
EOF	Epirubicin, oxaliplatin, and 5-fluorouracil
EOX	Epirubicin, oxaliplatin, and capecitabine
ESMD	Endoscopic submucosal dissection
EUS	Endoscopic ultrasonography
5-FU	5-Fluorouracil
FDG	Fludeoxyglucose glucose
FOLFIRI	Leucovorin, 5-fluorouricil, and irinotecan
GFR	Glomerular filtration rate
GI	Gastrointestinal

GIST	Gastrointestinal stromal tumour
Gy	Gray
GOO	Gastric outlet obstruction
H1	Histamine 1
5-HT	5-Hydroxytryptamine receptors
HER2	Human epidermal growth factor receptor 2
HPF	High-power field
ICMR	Indian Council of Medical Research
IMRT	Intensity-modulated radiation therapy
IV	Intravenous
LVEF	Left ventricular ejection fraction
MDCT	Multi-detector computed tomography
MRI	Magnetic resonance imaging
MUGA	Multi-gated acquisition scan
NACT	Neoadjuvant chemotherapy
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NJT	Nasojejunal tube
OD	Once daily
OGJ	Oesophagogastric junction
PBCR	Population based cancer registry
PET	Positron emission tomography
PDGFRA	Platelet derived growth factor receptor A
PO	Per oral
PPI	Proton pump inhibitor
PR	Per rectum
PS	Performance status
PTV	Planning target volume
QDS	Four times a day
RR	Relative risk
SC	Subcutaneous
SEMS	Self-expanding metal stents
TDS	Thrice a day
ULN	Upper limit of normal range
USA	United States of America
WHO	World Health Organization

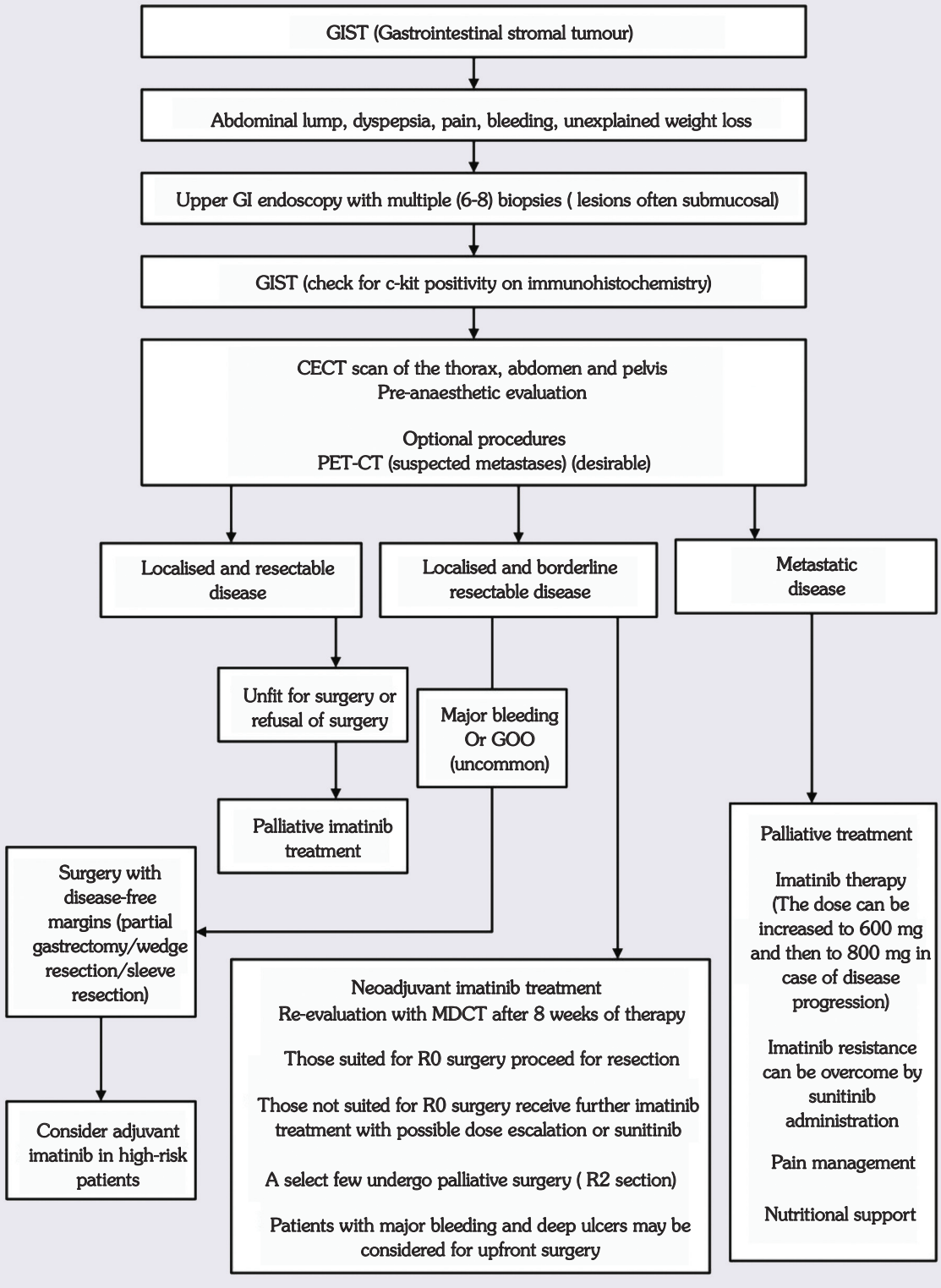
*Desirable/Ideal	:	Tests and treatment that may not be available at all centres but the centres should aspire to have them in near future.
Essential	:	Rare minimum that should be offered to all the patients by all centres treating patients with cancer.

CHAPTER

13 ALGORITHMS FOR GASTRIC CANCER AND GASTROINTESTINAL STROMAL TUMOUR



GI, gastrointestinal; CECT, contrast-enhanced computed tomography ;EUS, endoscopic ultrasonography; PET-CT, positron emission tomography-computed tomography; GOO, gastric outlet obstruction; NACT, neoadjuvant chemotheraphy; ECF, epirubicin, cisplatin and 5-flurouracil; EOX, epirubicin, oxaliplatin and capecitibine ; MDCT, multi-detector computed tomography; CRT, chemoradiotherapy; ASA4, American Society of Anaesthesiologists 4; OGJ, oesophagogastric junction.



GI, gastrointestinal; GIST, gastrointestinal stromal tumour; CECT, contrast-enhanced computed tomography; PET-CT, positron emission tomography-computed tomography; GOO, gastric outlet obstruction; MDCT, multi-detector computed tomography

CHAPTER

14 SUMMARY

This consensus document may be used as framework for more focused and planned research programmes to carry forward the process. The aim of this document is to assist oncologists in making major clinical decisions encountered while managing their patients, while realizing the fact that some patients may require treatment strategies other than those suggested in these guidelines.

- Histological confirmation is mandatory prior to the commencement of definitive treatment.
- All patients should be staged according to the TNM staging system and risk should be assessed at diagnosis. A baseline contrast-enhanced computed tomography (CECT) scan of the chest, abdomen, and pelvis should be considered.
- Selected cases should be referred to genetics clinics.
- Patients should receive multidisciplinary care under the care of a surgical, medical, and radiation oncologist.
- Siewert type III (oesophageal) and gastric cancer: Primary surgery remains the standard of care. Patients with early cancer may be offered upfront surgery with adjuvant treatment (observation versus chemotherapy versus chemoradiotherapy [CRT]) determined on the basis of the pathological examination of the resected specimen. Neoadjuvant chemotherapy (NACT) should be considered for locally advanced tumours for disease downstaging, and this can be followed by surgery in patients with stable or partial response. This may be followed by adjuvant chemotherapy (as part of the perioperative chemotherapy regimen).
- HER2 testing should be considered in patients with metastatic disease.
- Patients with metastatic gastric cancer beyond the regional lymph nodes should be assessed on an individual basis to determine whether chemotherapy or best supportive care should be provided.
- Preferred regimens for adjuvant and neoadjuvant therapy: epirubicin, oxaliplatin, and capecitabine (EOX); epirubicin, oxaliplatin, and 5-fluorouracil (5-FU) (EOF); epirubicin, cisplatin, and 5-FU (ECF); or epirubicin, cisplatin, and capecitabine (ECX).
- 5-FU may be replaced with capecitabine if patients do not have gastric outlet obstruction (GOO).
- Cisplatin may be replaced with oxaliplatin in the regimens
- First-line chemotherapy for metastatic gastric cancer: same as those used in the adjuvant setting followed by second-line taxane or inrinotecan-based regimens.
- Targeted therapy (trastuzumab) may be considered in select cases.

- Patients should be offered regular surveillance after completion of curative resection or treatment of advanced disease.
- Encourage participation in institutional and ethical review board-approved, registered controlled clinical trials.
- Refer for early palliative care, if indicated.

Gastrointestinal Stromal Tumour

- The stomach is the most common primary site for gastrointestinal stromal tumours (GISTs)
- All patients suspected to have GIST should be tested for c-kit
- Risk stratification of patients with early GIST should be performed in order to decide on adjuvant therapy
- Patents with high-risk GIST may be considered for adjuvant imatinib therapy for 3 years
- For patients with advanced GIST, imatinib is the first-line of therapy and sunitinib may be considered in patients who are intolerant of imatinib or those who have shown disease progression with imatinib.

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