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CONSENSUS CONFERENCE

Consensus statement of the Hellenic and Cypriot Gastric Cancer Study Group on the diagnosis, staging and management of gastric cancer

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Abstract

Gastric Cancer epidemics have changed over recent decades, declining in incidence, shifting from distal to proximal location, transforming from intestinal to diffuse histology. Novel chemotherapeutic agents combined with modern surgical operations hardly changed overall disease related survival. This may be attributed to a substantial inherent geographical variation of disease genetics, but also to a failure to standardize and implement treatment protocols in clinical practice. To overcome these drawbacks in Greece and Cyprus, a Gastric Cancer Study Group under the auspices of the Hellenic Society of Medical Oncology (HeSMO) and Gastrointestinal Cancer Study Group (GIC-SG) merged their efforts to produce a consensus considering ethnic parameters of healthcare system and the international proposals as well. Utilizing structured meetings of experts, a consensus was reached. To achieve further consensus, statements were subjected to the Delphi methodology by invited multidisciplinary national and international experts. Sentences were considered of high or low consensus if they were voted by $\geq 80\%$, or $< 80\%$, respectively; those obtaining a low consensus level after both voting rounds were rejected. Forty-five statements were developed and voted by 71 experts. The median rate of abstention per statement was 9.9% (range: 0–53.5%). At the end of the process, one statement was rejected, another revised, and all the remaining achieved a high consensus. Forty-four recommendations covering all aspects of the management of gastric cancer and concise treatment algorithms are proposed by the Hellenic and Cypriot Gastric Cancer Study Group. The importance of centralization, care by a multidisciplinary team, adherence to guidelines, and individualization are emphasized.

Keywords Gastric cancer · Greece · Cyprus · Guidelines

Introduction

The worldwide incidence of gastric cancer (GC) has declined rapidly over the recent few decades, the reasons for which are incompletely understood. Part of the decline may be due to the recognition of certain risk factors such as *Helicobacter Pylori* infection and other dietary and environmental risks. Despite the general decline, the absolute number of new cases per year is increasing, mainly due to aging of the world population. Thus, GC will continue to represent an important cause of cancer and cancer-related mortality for the foreseeable future [1].

In contrast to the decline in GC incidence overall, there has been an explosive increase in incidence of gastric cardia cancer [2]. The shift from distal to proximal stomach may in part be due to the decrease in the distal GC. However, it has also been proposed that carcinoma at the cardia is a different entity from that at the rest of the stomach. The histologic pattern of GC is also changing, with a decline in the intestinal-type as compared with the diffuse type [3, 4]. Several medical societies worldwide have developed consensus and guidelines for the systematic and evidence-based

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management of the disease [5, 6]. The common denominators of those consensa are the centralization of GC cases and their systematic referral to a dedicated multidisciplinary team (MDT) for decision-making.

According to the Hellenic pathology-based cancer registry of the 5-year period 2009–2013, GC was the fourth malignancy in males (5044 cases; 2.77%) and the ninth in females (2977 cases; 1.63%), with equal yearly distribution [7]. The Hellenic Authority for Statistics [8], registered 1344 deaths from GC in Greece in 2016. Also, GC is the eighth and sixth commonest neoplasia in male and female Cypriots respectively. Approximately, 117 new cases of GC (7,1/100,000 inhabitants/year in male and 4,1/100,000 inhabitants/year in females) are diagnosed in Cyprus annually. That figure is less than that of the European Union Countries [9, 10].

Recommendations (SOR: strength of recommendation, ROVC: rate of voters' consensus)

- Centralization of gastric cancer (GC) cases is strongly recommended (SOR: A; ROVC: 98%)
- GC patients should be referred to MDT before any treatment (SOR: A; ROVC: 99%)

Aim

Selected on the grounds of their expertise in gastro-intestinal cancer, members of the Gastro-Intestinal Cancer Study Group (GIC-SG) and the Hellenic Society of Medical Oncology (HeSMO) recruited an executive team, assigned to elaborate and develop a consensus document, form sentences-guidelines on the main issues of GC including genetics, staging, conservative and surgical management, and follow-up policies, aiming at their implementation in current practice in Greece and Cyprus. Cancer located at the gastric cardia will be discussed in the consensus of «esophageal cancer management», to be published elsewhere. For the development of the consensus document, current literature review, principles of evidence-based medicine, already published European consensa, and the Hellenic and Cypriot health care system status were considered.

Methods

To produce a draft on the consensus for the management of GC, a three-stage procedure was initially designed. At first stage (December 2011 to June 2013), a discussion on the evidence-based background and consensus statements and recommendations were developed, during one meeting and several on-line communications among the members of the executive team. Due to unforeseen circumstances, the draft was not finalized, and the executive team revised and updated the draft at a second stage, from June 2017 to June 2018. At a meeting in June 2018, members of the executive team produced a revised draft and new consensus statements, including level of evidence and grade of recommendation, which were then distributed among all members of the team for further elaboration. Level of evidence (LOE) and grading of recommendation strength (SOR) are shown in Table 1 [11].

At the third stage, all developed sentences-guidelines were subjected to the Delphi methodology [12], to strengthen consensus opinion. On the grounds of their expertise both national and international experts were selected and participated in this survey. The Delphi procedure comprised of two rounds of an on-line anonymous voting. Voting

Table 1 Level of evidence (LOE) and strength of recommendation (SOR)

Level of evidence	
I	Evidence from at least one large randomized control trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted RCTs without heterogeneity
II	Small RCTs or large RCTs with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Strength of recommendation	
A	A: strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	B: strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,.) optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

options on each individual sentence were «agree», «disagree» and «abstain». «Abstain» did not count to the overall percentage of agreement. The first round opened on 15th of July 2018 and closed on 15th of September 2018. Statements that achieved an agreement of > 80% (Rate of Voters Consensus: ROVC) of the participants were considered of sufficient consensus. Those achieving an agreement of < 80% were revised, after been circulated among the members of the executive team. Revised sentences re-entered the Delphi voting process for re-assessment. Only those who voted during the first round were asked to participate in the second one, which opened on 28th of October 2018 and closed on 20th of November 2018. The LOE, the SOR and the rate of voters' consensus (ROVC) are shown at the end of each sentence.

Results

There were 71 experts who responded to the invitation and participated to the survey. Among participants, the majority were surgeons (44; 62%), 15 were medical oncologists (21.1%), 4 (5.6%) radiologists, 4 (5.6%) radiotherapists/clinical oncologists, and 4 (5.6%) pathologists. At the first round, participants voted for 45 sentences/statements. The median rate of abstain was 9.9% (0–53.5%). Ten statements achieved a consensus by all voters, 25 achieved a consensus by 90–99% of the voters, and 8 by 80–89% of the voters. Two sentences achieved a consensus by 68% of the participants. The former one, referring to the adjuvant CRT, was revised by the executive team and entered the second round of voting, achieving a consensus of 79% of the participants. The executive team rejected the latter one, referring to the follow-up policies.

Discussion

General considerations (I)

Molecular basis

Multiple factors are related to the development of GC by causing chromosomal or microsatellite instability (MSI), epigenetic alterations and somatic gene mutations. All of these molecular events affect the normal function of in-tumor suppressor genes or oncogenes, with the final step in this progress being the development of GC.

Based on genomic and proteomic data from GC tissues, four molecular subtypes of GC have been established: (1) the Epstein-Barr virus (EBV) subtype, with an extreme DNA hypermethylation subtype, (2) the MSI subtype, (3) the genomically stable subtype, and (4) the subtype with chromosomal instability [13].

Hereditary GC

General aspects

Gastric adenocarcinoma may be part of hereditary neoplastic syndromes, such as Lynch Syndrome, various gastrointestinal polyposis syndromes (FAP, PGS, Cowden, etc.), and other hereditary cancer syndromes.

Hereditary diffuse GC (HDGC) is an autosomal dominant susceptibility for diffuse GC. The average age of onset of HDGC is 38 years (range: 14–69 years). The majority of the cancers in individuals with a CDH1 pathogenic variant occur before age 40 years. The estimated cumulative risk of GC by age 80 years is 70% for men and 56% for women. These women are also at a 42% risk for lobular breast cancer [14, 15].

Diagnosis

A clinical diagnosis of HDGC is established in a proband with diffuse GC confirmed on endoscopic biopsy and one of the following:

- A family history of one or more first- or second-degree relatives with GC
- A personal and/or family history of one individual with diffuse GC diagnosed before age 40 years
- A personal and/or family history of diffuse GC and lobular breast cancer, one diagnosed before age 50 years.

According to the latest International Gastric Cancer Linkage Consortium (IGCLC) Consensus.

Guidelines [16], HDGC should be suspected in a proband with any of the following:

- A diagnosis of GC and a family history of one or more individuals with GC, in which one affected individual has confirmed diffuse GC
- A diagnosis of diffuse GC occurring before age 40 years, regardless of family history
- A personal and/or family history of diffuse GC and lobular breast cancer, with at least one individual diagnosed with one of these cancers before age of 50 years

In addition, molecular genetic testing should be considered in a proband with any of the following:

- A diagnosis of diffuse GC and pathologically confirmed in situ signet ring cells and/or pagetoid spread of signet ring cells adjacent to diffuse GC
- A diagnosis of diffuse GC and a family history of two first- or second-degree relatives with diffuse GC or, lobular breast cancer
- A diagnosis of diffuse GC and a personal or family history of cleft lip/palate

Management

All individuals with suspected familial predisposition of GC should be referred for genetic counseling. All asymptomatic CDH1 mutation carriers between ages of 18 and 40 years, following appropriate counseling and informing about perioperative morbidity, should be referred for prophylactic gastrectomy (without a D2 lymph node dissection) in specialized centers. Prophylactic gastrectomy is not recommended before the age of 18 except for carriers with family members diagnosed with GC before the age of 25 years [5, 6, 16–18]. Although accuracy of surveillance endoscopy is disappointingly low, it constitutes the only resort for patients who decline prophylactic gastrectomy. Detailed white light high definition upper endoscopy utilizing Cambridge protocol on semiannual or annual basis, a meticulous image record for future comparisons, combined with endoscopic ultrasound and/or CT scans if suspicion arise are recommended [19].

Women presenting with CDH1 mutations are at high risk for breast cancer and should be treated similarly to BRCA1/BRCA2 mutation carriers [5, 6, 16, 18]. Regarding certain CDH1 carriers presenting with a family history of colon cancer, active screening with colonoscopy should be considered starting at the age of 40 years or 10 years younger than the youngest age of diagnosis of colon cancer in a family member, and repeated every 3–5 years [16].

Recommendations

- Individuals with suspected familial predisposition to hereditary GC should be referred for genetic counselling (SOR: A; ROVC: 100%)
- Prophylactic total gastrectomy (without a D2 lymph node dissection) should be offered to CDH1 mutation carriers at early adult life (LOE: III, SOR: A; ROVC: 94%)
- For patients who decline prophylactic gastrectomy detailed white light high definition upper endoscopy utilizing Cambridge protocol on semiannual or annual basis could be offered (LOE III, SOR: B, ROVC:94%)

Gastric cancer: prognostic and predictive factors

Advanced stage by the 8th edition of the staging system developed jointly by the AJCC and the IUCC confers a worse prognosis. T, N and M status, HER2 amplification/overexpression (3 +) and lymphovascular invasion and tumor grading are of main prognostic significance in GC [20, 21]. Host related factors of prognostic significance are age, performance status, and nutritional status (Table 2). Of paramount importance in outcomes is the quality of multimodality approach, both surgical and medical.

Also among the four molecular subtypes of GC, preliminary results show that patients with the Ebstein-Barr virus subtype seem to have the best prognosis, while those within the category of genomically stable subtype seem to have the worst prognosis [22]. Deficient mismatch repair genes or MSI predict response to anti-PDL1 immunotherapy in various PD-L1 positive solid tumors, including GC [23].

Recommendations

- HER2 overexpression should be tested in all patients with locally advanced or metastatic GC, as it is a predictive factor for response to chemotherapy combined with trastuzumab (LOE: I, SOR: A; ROVC: 100%)

Table 2 Prognostic factors for survival of cancer

Prognostic factors	Tumor related	Host related	Treatment related
Essential	T, N, M Category HER2 status		MDT approach Quality of Surgery: R0 (Residual Disease R1, R2)
Additional	Tumor Location *Cardia* *Distal Stomach* Histological type Vascular infiltration	Age	Extend of lymphadenectomy (D1, D1 +, D2, D3)
New/promising	Molecular Profile	Race Asian/non-Asian	

- Mismatch repair/microsatellite instability should be tested in all patients with locally advanced or metastatic GC who have received at least one line of previous chemotherapy, as they are predictive factors for response to immunotherapy (LOE: II, SOR: B; ROVC: 95%)

Histo-pathological characteristics

Two histological subtypes of Lauren classification are reportedly correlated with a distinctive clinical phenotype; the diffuse type gastric carcinoma is more often seen in female and young individuals, while the intestinal type adenocarcinoma is more often associated with intestinal metaplasia and Helicobacter pylori infection [24, 25]

However, the newest WHO 2019 classification of GC is most comprehensive, describing the morphologic characteristics of each subtype, in detail. In particular, it recognizes four major histological patterns of gastric carcinoma namely: papillary, tubular, (well, moderately and poorly differentiated), mucinous and poorly cohesive carcinoma (signet ring cell type and non solid type) [26]. Mixed types and rare histological variants are classified separately.

Recommendation

- The histo-pathological classification of gastric adenocarcinomas should be performed according to both Lauren and WHO 2019 classification schemes (SOR: A; ROVC: 98%)

General considerations (II)

Clinical presentation-alarming symptoms

Weight loss, asthenia due to anemia, dysphagia and persistent abdominal pain are the most common symptoms at initial diagnosis. The most common metastatic spread is to locoregional or distant lymph nodes, peritoneum and liver. Less commonly, ovaries, central nervous system, bone, pulmonary or soft tissue metastases occur.

Diagnosis

Prompt diagnostic evaluation should be commenced, when GC is suspected [27]. The early use of upper endoscopy, according to specific protocol, in patients presenting with persistent dyspeptic complaints may be associated with a higher rate of detection of early GC. A single biopsy has 70% sensitivity for diagnosing an existing gastric cancer, while performing seven biopsies from the ulcer margin and base increases the sensitivity to greater than 98%. Given the fact that diffused tumours tend to infiltrate the submucosa and muscularis propria, superficial mucosal biopsies may be falsely negative. For this reason, the combination of strip and bite biopsy techniques should be used when there is a suspicion of a diffuse type of gastric cancer [28].

Recommendations

- Upper GI dyspeptic symptoms of new onset in patients aged more than 45 years old is an indication for upper GI endoscopy (LOE: III, SOR: A; ROVC: 97%)
- Upper GI endoscopy with multiple (> 7) biopsies is the most sensitive diagnostic modality of gastric cancer. Strip and bite biopsies are required to detect carcinoma infiltrating the submucosa and muscularis propria (linitis plastica) (LOE: III, SOR: A; ROVC: 99%)

Staging

Endoscopic staging

Endoscopic ultrasound (EUS) could be used in the initial clinical staging of GC in cases where ongoing management is to be modified. This is especially important in patients considered as having early lesions amenable to endoscopic resection [29–31]. EUS could also be coupled to FNA to clarify regional N status.

Endoscopic mucosal resection (EMR) cannot be safely used for T staging, in any circumstances. In the contrary, endoscopic submucosal dissection (ESD) of focal nodules ≤ 1.5 cm can be performed, according to certain ESD criteria, in the setting of early stage disease to provide accurate T-staging, with the potential of being therapeutic [31–33].

Recommendations

- EUS offers information of T stage and N status of the disease and may guide treatment planning, especially in suspected early lesions suitable for endoscopic treatment (LOE: III, SOR: B; ROVC: 89%)

Cross sectional imaging

Multi Detector CT of the abdomen, chest, and pelvis is the imaging modality of choice for staging GC and should be performed after intravenous contrast administration (Contrast Enhanced Computed Tomography: CECT) and oral intake of 0.5 L of water as intraluminal contrast agent immediately prior to scan. Performed according to specific protocol, CECT may guide management [34, 35]. At CECT, positive lymph nodes are characterized on the basis of size,

shape, and enhancement pattern. In general, CECT is relatively insensitive and also nonspecific for detecting nodal metastases due to its inability to detect microscopic nodal invasion, which is common in GC, and the presence of reactive nodes that may be greater than 10 mm [36]. Routine use of MRI and FDG PET CT offer no additional information of clinical significance in daily practice.[37].

Recommendations

- Multidetector CT with a dedicated protocol is the imaging modality of choice in the initial assessment of GC (LOE: II, SOR: A; ROVC: 97%)
- EUS should be considered as a complementary modality for T stage and N status of GC, with the addition of EUS-guided biopsies, especially in lesions clinically judged as early (LOE: II, SOR: A; ROVC: 88%)
- MRI and FDG PET are not recommended for the initial preoperative staging of GC (LOE: II, SOR: A; 95%)

Staging laparoscopy

Staging laparoscopy in GC aims at reducing futile laparotomies and non-curative gastrectomies, whilst raising the likelihood of enrolling the patient in a neoadjuvant chemotherapy protocol. It consists of thorough inspection of visible peritoneal surfaces, biopsy of suspicious lesions or lymph nodes and, – although limited by low sensitivity-, cytology of peritoneal washings [38].

Clinical staging determines the need for staging laparoscopy, which can be avoided in cases of early GC that will be directed for immediate surgery and cases of clearly inoperable cancers. All cT3-T4 patients are eligible for laparoscopy and peritoneal cytology provided there are no distant metastases. Other factors, which should be considered are the degree of tumor differentiation, diffuse histological type and the burden of involved lymph nodes [39–42].

Recommendation

- Patients with cT3–T4, Nx, M0 tumors and adverse prognostic factors are eligible for staging laparoscopy and peritoneal cytology (LOE: I, SOR: A; ROVC: 95%)

Therapeutic plan

The determination of early GC implies a lesion that invades mucosa or submucosa (Tis/ T1a,b) irrespective of lymph node status.

The determination "limited-localized" for a gastric tumor implies that cancer burden can be totally removed by endoscopy or surgery with high probability. This comprises three pre-conditions: (1) the neoplasm grows within the gastric wall layers without serosa infiltration ($T \leq 3$), (2) judged by imaging modalities, nodal involvement, if any, is restricted within regional lymphatic basin and (3) no metastatic foci are detected (distant organs, peritoneum, bone marrow). Under these cumulative conditions the disease is considered localized and resectable and appropriate standardized surgical resection carries curative potential.

The determination "locally advanced" gastric tumor implies: (1) infiltration of the serosa and/or adjacent structures (2) nodal involvement outside the regional lymphatic basin, and (3) no detectable metastatic disease.

Early GC

A "small in size" or even subtle mucosal lesion might be restricted within the mucosal (Tis or T1a) or submucosal layer (T1b). The percentage of concomitant lymph node involvement ranges from 0–6% in case of Tis/T1a, to 7–21% in case of T1b. Thus, distinction between T1a and T1b is crucial, as only the former is amenable to endoscopic treatment provided: (1) the diagnosis is supported by endoscopic ultrasound, (2) the lesion is solitary, < 2 cm, well differentiated, non-ulcerated, and not located at the pyloric ring, cardia or incisura angularis, (3) pathologic lymph nodes are not depicted in CT scans, (4) an expert, trained endoscopist appropriately equipped and a specialized pathologist are available [43].

Lesions located at the pyloric ring, cardia and incisura angularis are much more technically demanding and this should be seriously considered before referring such a patient for ESD. ESD offers a residual- and recurrence-free survival rate of 98% and 93%, respectively [44–48]. If ESD is attempted and curability criteria are not met, surgical resection is indicated in patients with adequate physical reserve. Gastrectomy with D2 lymphadenectomy consists the operation of choice for early GC without jeopardizing prognosis. In case of elderly patients with high comorbidities, a D1 + a lymphadenectomy consists an acceptable modification (Fig. 1).

Recommendations

- Endoscopic treatment of GC by means of ESD is an option for cTis or cT1a, well differentiated intestinal, < 2 cm, non-ulcerated lesions (LOE: II SOR: A; ROVC: 88%)
- If cTis-cT1a diagnosis is unreliable, or ESD not available, or ESD is available and attempted but fails to meet curability criteria, surgical resection with or D2 lymphadenectomy, or D1 + a lymphadenectomy in the elderly, is indicated by an adequately trained surgeon.

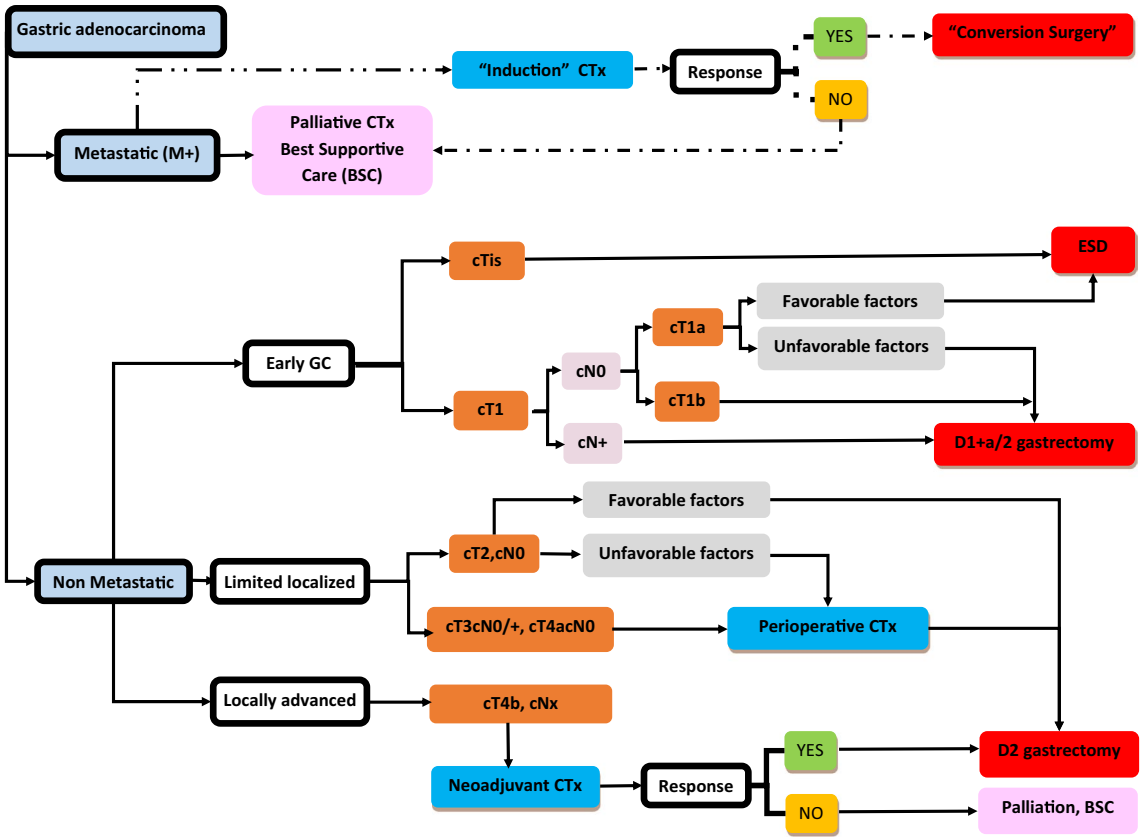

Fig. 1 Flowchart of gastric adenocarcinoma therapeutic management. *ESD* endoscopic submucosal dissection. In cases of non-early limited localized disease, perioperative chemotherapy should generally be considered as first choice. In the context of individualization, apart from clinical stage (cTcNcM), presence of intractable symptoms, patient's physiological reserve/fitness and other non-TNM prognostic factors could also be considered and alter algorithm selectively. Pressing-intractable symptoms: transfusion-demanding acute bleeding, gastric outlet obstruction. Adverse/unfavorable non-TNM prognostic factors: diffuse type histology, vascular invasion in diagnostic biopsy, age < 40 or > 75, proximal location. In strictly selected fit patients with limited non-peritoneal metastatic load, conversion therapy might be considered

Local resection without lymphadenectomy is not recommended as a standard procedure (LOE: II SOR: A; 100%)

Limited-localized GC

Despite surgery remains the mainstay of therapy in GC, currently its sequence in algorithm treatment has been disputed [49–51]. Recently published evidence has rapidly introduced neoadjuvant (perioperative) chemotherapy (CTx) in international western guidelines [52]. Currently, toxicity profile of proposed regimen (FLOT), -especially in elders-, need for a central venous catheter, lack of centralization in high specialization oncology units, clinician's resistance/distrust to adopt new practices or even ignorance, impede full acceptance of neoadjuvant CTx. Thus, adjuvant chemo-radiation (CRT) still remains the standard of care for advanced GC in most North American states [53, 54]. Adjuvant CTx following D2 surgery with curative intent is the standard of care in most Eastern countries [55, 56].

If the disease is clinically and 'radiographically' judged as early but not meeting criteria for ESD (ulcerated cT1a, > 2 cm, diffuse type, vascular invasion), or limited localized with no detectable metastasis (cT1b,T2 and cN0 cM0), upfront surgery is recommended. In presence of unfavorable prognostic factors, (such as vascular invasion in endoscopic biopsy specimen, diffuse type of histology, age < 40, proximal location), perioperative CTx should be seriously considered in preference against upfront surgery even in cases judged cT2 and/or cN0. In fit patients without pressing symptoms staged as cT3, cN0 or cT3, cN + "regional" (ie. lymph node stations 1–7) and cT4a, cN0, perioperative CTx should generally be considered as first choice (Fig. 1). Notwithstanding, in the context of individualization, in presence of pressing symptoms (obstruction, transfusion-demanding active bleeding), in aged individuals > 75yo with poor physical status not durable to suffer the aggregated stress/toxicity of both chemotherapy and surgery, upfront surgery may be considered selectively

if the tumor is judged resectable. Gastrectomy with D2 lymphadenectomy is the recommended procedure, entitled with a clearance potential of primary tumor and regional nodes of curative intent.

Irrespective of cT evaluation, imaging of pathologic nodes posterior to hepatoduodenal ligament, behind head of pancreas, in mesenteric root, in middle colic vessels and para-aortic area, should be considered "non-regional" and these cases preferably should be referred for neoadjuvant CTx and re-evaluation, prior to any further intervention (equivalent to locally advanced state) [57].

Locally advanced GC

Tumors with estimated depth of invasion judged as cT4a (serosal invasion) or cT4b (adjacent organ invasion) with pathological nodes (cN+) have a considerably worse prognosis, and should be spared upfront surgery. In the absence of pressing symptoms upfront CTx and restaging to assess response and potential downstaging is a reasonable option for these patients.

Although solid evidence on any survival benefit is lacking, if there is no peritoneal spread and/or "bulky nodes" (aggregates > 3 or block), a standardized D2 gastrectomy with a combined resection of the invaded adjacent organ such as transverse colon, or spleen, or segment of left liver lobe, or diaphragm might be an option in fit patients.

Recommendations

- Surgery remains the mainstay of therapy in localized resectable GC (SOR: A; ROVC: 100%)
- Surgery is the recommended first step of treatment algorithm for cT1b, or cT2, cN0 and cM0 cases (LOE: I, SOR: A; ROVC: 94%)
- For cT3 or cT4a or/and regional N+ tumors perioperative CTx should be the first choice (LOE: I, SOR: A; ROVC: 95%)
- In cases of cT4b cNx cM0, if peritoneal involvement is excluded by laparoscopy, induction CTx followed by combined resection of the stomach and the involved adjacent organ with D2 lymphadenectomy is recommended (LOE: III SOR: B; ROVC: 98%)
- In patients with pathologic stage II or III, adjuvant CRT should be considered, if surgical resection failed to achieve a D2-R0 resection and if neo-adjuvant CTx has not been offered (LOE: II SOR: A; 92%)

Metastatic disease

Presence of metastatic disease dictates upfront systemic treatment tailored to patient's performance status (PS). Due to multiple different incurability factors which usually coexist in these patients, it is difficult to define solid prognostic variables and predict response rate to induction chemotherapy. In presence of pressing symptoms, endoscopic interventions (hemostatic clips, stents etc.) or palliative surgery might be considered depending on patient's reserve. In absence of pressing symptoms, strictly selected metastatic fit patients with "adequate" response to induction chemotherapy are candidates for an R0 aiming operation known as conversion surgery. Scattered data from multiple retrospective,—predominantly Eastern series and one of Western origin [58]—, record a small but existent number of stage IV patients who benefit from chemotherapy and conversion surgery. Resectability criteria before and after chemotherapy, prognostic stratification of patients, objective assessment of response and timing of surgery have not yet been clearly defined [59]. Hopefully, the survival efficacy of conversion surgery may considerably improve in the rising era of targeted therapies.

Therapeutic modalities

Neo-adjuvant CRT

Preoperative treatment, compared to postoperative regimens, has the potential of tumor downstaging, thus an increase in complete R0 resection rate, and better patient tolerability and compliance [60]. The benefit of neoadjuvant RT for localized resectable GC is currently being investigated in TOPGEAR trial. The interim analysis demonstrated that preoperative CRT can be safely delivered without a significant increase in treatment toxicity or surgical morbidity [61].

Recommendation

- Neoadjuvant CRT for localized resectable GC could be offered in the context of clinical trials only (SOR: A; ROVC: 92%)

Perioperative CTx

The value of perioperative CTx was initially studied in two randomized trials, though with several methodological flaws MAGIC trial [49] and FNCLCC-FFCD centers trial [50]. A recent phase III trial established the benefit of perioperative chemotherapy with FLOT regimen (docetaxel, oxaliplatin, fluorouracil/leucovorin) over ECX (epirubicin, cisplatin, 5FU) in disease-free and overall survival [52] (Table 3).

Recommendation

- Perioperative CTx with the FLOT regimen is recommended for IIB-IVA tumors (LOE: I, SOR: A; 92%)

Table 3 Phase III randomized controlled trials of perioperative or adjuvant treatment in GC and cancer of the OGJ

Study	Clinical Stage	Study design (*n* pts)	Primary endpoint
Perioperative therapy			
MAGIC	Ib-III	Surgery ($n=253$), vs 3 cycles ECF →surgery → 3 cycles ECF ($n=250$)	5 years OS: 23 vs 36%, HR = 0.75, 95% CI: 0.6–0.93, $p=0.009$
FLOT 4-AIO	IIb-IVA	ECF/ECX periop (3–3 cycles) → surgery ($n=354$) vs FLOT periop (4–4 cycles) → surgery ($n=354$)	mOS: 35 vs 50 mo HR = 0.77, 95% CI: 0.63–0.94, $p=0.012$
CRITICS	Ib-IVA	ECX/EOX x periop (3–3 cycles) → surgery ($N=393$) vs ECX/EOX × 3 cycles → surgery → CRT ($n=395$)	No OS, DFS benefit
Adjuvant (postop CRT or CTx)	Pathological stage		
INT 0116	Ib-IVA	Surgery ($n=275$) vs surgery → 5-FU/LV/RT ($n=281$)	mOS: 27mo HR = 1.35, 95% CI: 1.09–1.66, $p=0.005$
S-1 *(ACTS-GC)*	II-III	surgery ($n=530$) vs surgery → S-1 (for 1 year) ($n=529$),	3 years OS: 70.1 vs 80.1%, HR = 0.68, 95% CI: 0.52–0.87, $p=0.003$
CLASSIC	II-IIIb	surgery ($n=515$) vs surgery → CapeOx ($n=520$)	3 years DFS: 59 vs 74%, HR = 0.56, 95% CI: 0.44–0.72, $p<0.0001$
ARTIST	Ib-IVA	XP × 6 cycles ($n=228$), vs XP × 2 cycles→XPRT→ XP × 2 cycles ($n=230$),	DFS / OS: no difference Subgroup analysis: N+, intestinal type XPRT: DFS benefit

CapeOx Capecitabine, Oxaliplatin; *CTx* chemotherapy; *CRT* chemoradiotherapy; *DFS* disease free survival; *5-FU* 5-fluorouracil; *ECF* epirubicin, cisplatin, 5-FU; *ECX* epirubicin, cisplatin, capecitabine; *EOX* epirubicin, oxaliplatin, capecitabine; *FLOT* docetaxel, oxaliplatin, 5-FU; *LV* leucovorin; mo months; *mOS* median overall survival; *n* number; *periop* perioperative; *postop* postoperative; *pts* patients; *5 yr OS* 5 year overall survival; *RT* radiation therapy; *XP* Capecitabine, Cisplatin; XPRT Capecitabine + RT 45 Gy

Surgery

Extent of gastric resection-indications

Gastrectomy (partial or total) with D2 lymphadenectomy is the recommended standard operation of curative intent for GC [62]. Sufficient proximal resection margin is defined at least 3 cm for T2 or deeper tumors with an expansive growth pattern, and 5 cm for those with infiltrative growth pattern and diffuse Lauren histotype. When these rules cannot be respected, it is advisable to examine the proximal resection margin by frozen section [63]. For tumors invading the esophagus, a 5 cm margin is not necessarily required, but frozen section examination of the resection line is desirable to ensure an R0 resection. Distal gastrectomy should be preferred when an adequate proximal resection margin can be obtained for distal tumors. Pancreatic or spleen invasion by tumor requiring pancreatico-splenectomy necessitates total gastrectomy, regardless of tumor location. Total gastrectomy should be considered for tumors that are proximally located, along the greater curvature of the corpus. It might also be necessary for patients with signet ring cell GC due to the commonly encountered diffuse submucosal spread.

Regarding extent of lymphadenectomy D2 resection is the universally proposed procedure. It is strictly necessary to follow the correct procedure of D2 lymphadenectomy, according to the type of gastrectomy performed, to an accurate and complete removal of defined stations. In case of total gastrectomy: infrapyloric (station 6), right gastric artery (station 5) right and left paracardial (stations 1, 2), left gastric artery (station 7), celiac axis (station 9), hepatic artery (station 8a), splenic artery (station 11p/d), hepatoduodenal ligament (12a), along greater curvature (4sa, 4sb, 4d), along lesser curvature (station 3). In case of subtotal/partial gastrectomy all the above mentioned stations are dissected with the exemption of 2, 4sa and 11d. D2 lymph node dissection results in lower rates of locoregional recurrence, and this may translate into a survival benefit for gastric adenoCa patients [62]. Only in carefully selected cases (high-risk patients, early tumors not treatable by endoscopic resections)

more limited procedures could be considered. One of these is a modification of D2 lymph node dissection (mD2), which is often described as D1,5 or D1 + .

Splenectomy is generally associated with an increased risk of postoperative complications in GC surgery,—and as pancreatic tail excision—, is not a prerequisite for D2 lymphadenectomy, even in prophylactic terms [64] or after total gastrectomy for proximal GC [65]. Total gastrectomy with splenectomy should be recommended for tumors located in the upper third of the stomach along the greater curvature, or when a macroscopic involvement of stations 4sa or 10 is present, or in case of direct invasion of splenic hilum.

The role of total omentectomy is still questionable, particularly for serosa-negative advanced GC [66]. Removal of the greater omentum is usually integrated in the standard gastrectomy for T3 or deeper tumors [67]. For T1/T2 tumors, the omentum more than 3 cm away from the gastroepiploic arcade may be preserved. When the posterior gastric wall serosa is infiltrated by the tumor, removal of the inner peritoneal surface of the bursa omentalis used to be performed to remove microscopic tumor deposits in the lesser sac. In T1/T2 tumors, bursectomy should be avoided to prevent injury to the pancreas and adjacent vessels. Although a previous randomized controlled trial [68] and a meta-analysis [69] showed a clear trend toward improved survival after bursectomy mainly for pathologically serosa-positive tumors located in the middle or lower third, a recent well designed and adequately powered multicenter RCT from Japan ended the debate by clearly demonstrating the futility of bursectomy in cT3, cT4a tumors [70].

Following distal gastrectomy, Billroth II or Roux-en Y gastrojejunostomy are the popular reconstructions [71]. Billroth I reconstruction has never been popularized in western centers [72]. After total gastrectomy, Roux-en-Y reconstruction remains the easiest solution, with satisfactory functional results. Pouch creation can improve functional outcomes and quality of life especially in younger patients with early GC where a long-life expectancy is anticipated [73].

Surgical approach

Gastrectomy with D2 lymphadenectomy is accomplished by the open approach. The laparoscopic approach could be an alternative option. The results of minimally invasive surgery in terms of quality of life and long-term survival proved to be equal at least for distal gastrectomy and stage I tumors [74]. Preliminary data seem to indicate that laparoscopic surgery is feasible, but solid data on the advantages and oncological efficacy of this approach deriving from randomized trials are lacking, whilst the presence of a serosal invading cancer should still be considered a questionable indication to minimally invasive surgery (MIS). Finally, beyond disease stage it should be considered that the available evidence concerns only subtotal resections; total gastrectomy includes some technical steps that are not ideally standardized by the laparoscopic approach yet.

Recommendations

- Total or partial gastrectomy, depending on tumor location, with D2 lymphadenectomy consists the standard recommended surgical procedure for operable and resectable GC irrespective of concomitant therapies (LOE: II, SOR: A; ROVC: 100%)
- A 3–5 cm proximal resection margin should be obtained during gastric resection, confirmed by frozen section, if in doubt. A circumferential margin pursued by bursectomy is not recommended. Although currently disputed, total omentectomy might be considered in ≥ cT3 in the context of operation standardization (LOE: II SOR: A; ROVC: 91%)
- Splenectomy and/or pancreatic tail resection are not part of D2 gastrectomy. Splenectomy is recommended in tumors of the upper/middle third of greater curvature, or invading the gastro-splenic ligament (LOE: II SOR:A; ROVC: 88%)
- Laparoscopically assisted subtotal D2 gastrectomy in patients with low probability of nodal involvement (≤ cT2, cN0, cM0, intestinal well differentiated) is an acceptable alternative surgical approach addressed by surgeons adequately trained both in D2 gastrectomy and laparoscopy (LOE: II SOR: A; ROVC: 98%)

Cytoreductive surgery (CS) and HIPEC

Peritoneal carcinomatosis (PC) may be synchronous to primary tumor in about 14–43% of patients with GC [75]. Metachronous peritoneal carcinomatosis is a frequent event in the natural history of GC with an estimated 50% of patients with advanced disease developing PC, in spite of supposedly radical surgery. There is no solid evidence that CS with HIPEC in GC patients with peritoneal carcinomatosis is of benefit [76].

Recommendation

- There is insufficient evidence to support CS and HIPEC outside the context of clinical trials (SOR: A; ROVC: 90%)

Adjuvant treatment

Chemoradiotherapy (CRT)

The US Intergroup 0116 trial demonstrated an improvement in OS and RFS with the addition of postoperative

CRT over surgery alone [53, 54]. Nowadays, capecitabine has substituted for *iv* 5FU [77, 78]. The benefit of adjuvant CRT according to the extent of lymphadenectomy has been widely studied, but results are inconclusive [79]. The addition of cisplatin and epirubicin to the aforementioned regime is of no benefit [80]. The phase III CRITICS trial shows that the addition of postoperative RT to perioperative CTx and curative surgery is of no benefit [81]. On the contrary, the addition of RT to CTx after D2 dissection did not reduce recurrence in Asian population except in a subgroup of patients with positive LNs [82, 83]. The benefit of adjuvant radiotherapy in this group is being investigated in ARTIST II.

After R1 resection postoperative CRT is associated with a significant improvement in 2-year OS in the CRT group as compared with the surgery-only R1 group (66% vs 29%) and a significant decrease in the local recurrence rate in the CRT R1 group (6% vs 26%) but no significant differences in distant recurrence rates [84]. Notably, highly conformal RT techniques are appropriate for gastric cancer radiotherapy to reduce toxicity from surrounding normal tissues.

Recommendations

- Adjuvant CRT in GC patients should be given when indicated with highly conformal techniques (SOR: A; ROVC: 93%)
- Adjuvant CRT may be recommended for ≥ stage IB GC patients after equal or less than D1 dissection with D + disease and after R1 or R2 resection (LOE: II, SOR: A; 89%)
- Adjuvant CRT might be considered for GC patients who have not received preoperative CTx and have either node-positive disease after D2 dissection or any < D2 dissection irrespective of node status (LOE: III, SOR: B; ROVC: 79%)

Chemotherapy (CTx)

Following radical resection of GC, adjuvant treatment with CTx has been tested in many randomized control trials, without any established benefit in Western populations (Table 3). Two meta-analyses of RCTs on adjuvant CTx in GC have demonstrated a small but significant survival benefit but a large part of enrolled patients derive from Asian countries. [85, 86]. A Korean study that included patients after curative D2 resection showed significant improvement in DFS after adjuvant combination CTx [87]. There is no evidence, so far, regarding potential benefit from the addition of a targeted agent in operable GC.

Recommendations

- Patients with clinical and pathological stage IA (T1a,b, N1) and IB (T2, N0) after a D2 dissection do not derive additional benefit from adjuvant CTx (LOE: I SOR: A; ROVC: 86%)
- After D2 surgery, adjuvant CTx with fluoropyrimidins only or in combination with oxaliplatin might be considered for stage II and IIIB gastric cancer patients with unfavorable prognostic factors, if they have not received preoperative chemotherapy (LOE: II, SOR: B; ROVC: 98%)

The resected specimen—histopathological assessment

Macroscopic assessment

Specimen preparation and sampling

The surgical specimen is preferably sent to the pathology department immediately after removal from the patient, formalin free. A specimen photograph should be used as a template to identify the exact location of the tissue blocks (a schematic map/diagram can be used for that purpose), and afterwards the stomach should be sectioned completely.

Gross description

The gross description report of the fresh specimen must contain at least the following parameters: (a) the nature of the specimen (endoscopic resection, partial, total gastrectomy), (b) length of greater and lesser curves of the stomach, length of duodenum and length of esophagus, (c) site of the tumor, (d) distance of the tumor from the proximal and distal margin, and distance of the tumor from the OGJ, (e) tumor size at three dimensions, (f) tumor macroscopic appearance according to Bormann types (polypoid: type 1, fungating: type 2, ulcerated: type 3 and diffuse infiltrating: type 4), (g) depth of invasion, (h) for lesions of the cardia, the distance from the tumor to the circumferential resection margin (CRM), (i) appearance of the serosa, and (j) number of dissected lymph nodes. For gastrectomy specimens ideally at least ≥ 16 lymph nodes should be removed and assessed histopathologically, the total number reflecting not only pathologist's diligence but quality of surgery as well.

Microscopic assessment

Surgical resected specimen

A pathology report of gastric cancer resected specimen should include: (1) histological type and grade, (2) pattern of

growth, (3) depth of invasion (T stage), (4) lymphatic, vascular, perineural invasion, (5) distal and proximal resection and circumferential margins, (6) lymph nodes (ratio of involved over total number of retrieved LNs. At least 16 LNs must be retrieved for adequate staging according to TNM 8th edition, (7) findings in the adjacent mucosa, (8) other important factors (T- lymphocytes peri-tumoral, intra-tumoral infiltration, MSI, and specific histologic subtypes), and (9) HER-2 score. In Tables 4, 5, 6, the 8th edition of TNM clinical and histopathological staging is demonstrated [88].

Table 5 Clinical staging of gastric cancer (TNM 8th edition)

Stage I	T1, T2	N0	M0
Stage IIA	T1, T2	N +	M0
Stage IIB	T3, T4a	N0	M0
Stage III	T3, T4a	N +	M0
Stage IVA	T4b	N any	M0
Stage IVB	T any	N any	M1

Recommendation

- The following parameters should be included in the pathology report of the resected specimen: (1) tumor dimensions and maximum tumor diameter, (2) site of tumor, (3) macroscopic appearance of the tumor (4) depth of invasion, (5) histological type according to the WHO and the Lauren classification, (6) histological grade, (7) resection margins, (8) vascular and perineural invasion, (9) number and status of lymph nodes, and (10) HER-2 score (SOR: A; ROVC: 100%).

ESD specimen

The specimen obtained from ESD must be stretched and pinned on firm surface (wax). Lateral and deep margins should be inked. At the gross description, the size of the specimen, the appearance and the dimension of the lesion must be included. Complete blocking is recommended (blocks should be taken at 2 mm interval). In the histological

Table 4 TNM classification—8th edition

Primay tumour (T)
Tx: primary tumor cannot be assessed
T0: no evidence of primary tumor
Tis: carcinoma in situ (high grade dysplasia, intraepithelial tumor without invasion of lamina propria)
T1: primary tumor invades lamina propria, muscularis mucosae or submucosa
T1a: primary tumor invades lamina propria or muscularis mucosae
T1b: primary tumor invades submucosa
T2: primary tumor invades muscularis propria
T3: primary tumor invades sub serosa
T4: primary tumor perforates visceral peritoneum, invades adjacent structures*
T4a: primary tumor perforates serosa
T4b: primary tumor invades adjacent structures
Regional Lymph Nodes (N)
Nx: regional lymph nodes cannot be assessed
N0: no regional lymph nodes metastasis
N1: metastasis to 1–2 regional lymph nodes
N2: metastasis to 3–6 regional lymph nodes
N3: metastasis to ≥ 7 regional lymph nodes
N3a: metastasis to 7–15 regional lymph nodes
N3b: metastasis to > 16 regional lymph nodes
Distant metastasis (M)
M0: no distant metastasis
M1: distant metastasis

(*)

Adjacent structures to stomach: diaphragm, spleen, liver, transverse colon, pancreas, small intestine, retro peritoneum, adrenal glands, kidney

Intramural extension into: the esophagus or duodenum is classified by depth of greatest invasion in any of the sites

Tumor extension into: gastro-colic, gastro-hepatic ligaments, or greater or lesser omentum, without perforation of visceral peritoneum is classified as T3

Table 6 Pathological staging of gastric cancer (TNM 8th edition)

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T1	N1	M0
	T2	N0	M0
Stage IIA	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
Stage IIB	T1	N3a	M0
	T2	N2	M0
	T3	N1	M0
	T4a	N0	M0
Stage IIIA	T2	N3a	M0
	T3	N2	M0
	T4a	N1, N2	M0
	T4b	N0	M0
Stage IIIB	T1, T2	N3b	M0
	T3, T4a	N3a	M0
	T4b	N1, N2	M0
Stage IIIC	T3, T4a	N3b	M0
	T4b	N3a, N3b	N0
Stage IV	T any	N any	M1

Detection of free cancer cells in peritoneal washings (positive cytology Cy +), upgrades stage to IV irrespective of T and N status

report the histological type, histological grade, depth of invasion and the status of the margins must be described. The status of the depth margin is important for the local recurrence risk. Additional finding of importance is the presence of lymphatic or vascular invasion. Histological grade, depth of invasion and lymphovascular invasion play an important role for the risk of lymph node or/and distant metastasis. If depth of invasion and status of margins cannot be clearly defined, the patient should be referred for surgery.

Follow up

Follow-up after multi-modal treatment for GC has several purposes, including management of side effects, oncological recurrence surveillance, psychological support, and data collection for research. The prognostic relevance of post-therapeutic follow up remains to be verified by future studies. Despite the fact that guidelines from Western health professional organizations and recommendations produced by an International Consensus Conference are quite unanimous in recommending symptom driven recurrence surveillance only, practice often differs [89, 90]. Upper GI endoscopy for non-totally gastrectomized patients, cross- sectional CT imaging and laboratory tests, (CBC, BMP, vitamin B12, vitamin D, liver function tests, prealbumin, iron levels, neoplasia markers) every 6 months in the first 2 years and every 12 months thereafter is a widely used plan, which can be liberally tailored to the individual patient and the stage of the disease. Follow up should be discontinued upon completion of 5 years. In patients with a genetic predisposition, one should also make note of secondary primary malignancies.

Recommendation

- Upper GI endoscopy in patients with partial gastrectomy, CT imaging and lab tests, repeated in time intervals tailored to every patient and the stage of the disease, for no more than 5 years, comprise the current trend of post therapeutic follow up (LOE: III, SOR:B; 85%).

Metastatic disease

Chemotherapy (CTx)

Systemic treatment is used in patients with performance status PS < 3 metastatic GC with the intent to improve quality of life and probably survival [91]. As first line treatment the combination of fluoropyrimidines (5-FU, capecitabine, S-1) and platinum analogs are widely used. Based on patient's performance status and organ function, a third agent may be added. The ECF, ECF-like (ECX, EOF, EOX) and DCF regimens have shown survival benefit in RCTs over 5-fluorouracil and cisplatin combination [92, 93]. Alternatively, FOLFIRI can be used, especially in patients not suitable for platinum analogs-based treatment [94]. As second-line CTx, irinotecan or weekly paclitaxel are considered as a standard of care offering survival benefit over best supportive care [95, 96]. Third line systemic treatment could be proposed in selected cases.

Targeted treatment

Trastuzumab should be added to first line CTx for HER2 overexpressing metastatic gastric or OGJ adenoCa in combination with either fluoropyrimidine and cisplatin [20], or with other chemotherapeutic agents but not with anthracyclines. The combination of weekly paclitaxel and ramucirumab is the new gold standard in the second line treatment of metastatic GC, based on the RAINBOW phase III study [97]. Single agent ramucirumab, in the second line setting and after prior platinum or fluoropyrimidine CTx, in patients for whom paclitaxel is not appropriate [98]. Pembrolizumab is offered as second or subsequent line to patients with metastatic MSI-H or dMMR tumors [99, 100].

Recommendations

- Systemic treatment for advanced—metastatic GC should be offered in the context of performance status, medical comorbidities, toxicity profile, and HER2-neu expression (LOE: I, SOR: A; ROVC: 100%)
- The backbone of modern CTx regimes consists of a platinum compound with a fluoropyrimidine (LOE: I, SOR: A; ROVC: 98%). An alternative regime for patients intolerant to platinum is a fluoropyrimidine/irinotecan combination (LOE: II, SOR: B; ROVC: 98%).
- The use of three-drug regimens should be reserved for patients who are medically fit, with PS of 0 or 1 (LOE: I, SOR: A; ROVC: 98%)
- Trastuzumab should be added to first line CTx for HER2 overexpressing metastatic disease in combination with fluoropyrimidine and cisplatin (LOE: I, SOR: A; ROVC: 100%)
- Ramucirumab could be used in the second or subsequent line setting in combination with paclitaxel or as single agent, in metastatic GC (LOE: I, SOR: A; ROVC: 95%)
- Administration of second line CTx with irinotecan or weekly paclitaxel should be offered to patients with contraindication to anti-angiogenic treatment in metastatic disease (LOE: I, SOR: A, ROVC: 100%)
- Pembrolizumab should be used in 2nd-line CTx and beyond in MSI-high metastatic GC (LOE: III, SOR: A; ROVC: 100%)

Palliation

For patients with symptomatic locally advanced unresectable or metastatic disease, RT aims to alleviate distressing symptoms, such as bleeding, pain or dysphagia. Concurrent use of CTx, as mentioned in the chapter of metastatic disease, increases median overall survival [101, 102]. Although there are large variations in RT regimens as a single modality or in combination with CTx, the overall response rates for bleeding, pain and obstruction are 74%, 67% and 68%, respectively [103]. Endoscopic treatment with the use of cautery, radiofrequency, laser and stent placement may provide relief of bleeding and gastric outlet obstruction. In selected patients, nutritional support can be achieved with by-pass gastrojejunostomy or feeding jejunostomy.

Recommendations

- Palliative short course RT is effective for symptom control in locally advanced unresectable or metastatic GC (LOE: III, SOR: B; ROVC: 91%)
- Symptom control can be achieved by endoscopic or surgical intervention for the remaining life in the majority of patients with unresectable or metastatic GC (LOE: III, SOR: B; ROVC: 87%)

Conclusions

According to current evidence and practice, patients with GC should be referred for care to highly specialized centers with adequate case volume, as this ensures better outcomes in terms of morbidity, mortality, local recurrence, and survival. At those centers, a multidisciplinary team of surgeons, oncologists, pathologists, radiotherapists, and radiologists should be taking care of the patients at any stage of the treatment, from initial evaluation to follow-up, according to the recommendations listed above.

Audit and quality control of therapeutic services require compulsory patient's full data collection and registration according to regional or national programs. Registered data should include all preoperative characteristics, intraoperative outcomes and quality of surgery parameters, postoperative morbidity and mortality, follow-up details and oncological outcomes, as also defined above. A case-mixed adjusted feedback is crucial in the whole process of the "quality assurance" concept. If suboptimal performance is encountered, the responsible treating team should be instructed to improve results by further and more intensive training or to cease treating such cases.

Legal disclaimer

The study group considers adherence to these guidelines to be voluntary. The ultimate determination regarding their application is to be made by the physician in light of each patient's individual circumstances. In view of the consulting and non-binding nature, these guidelines cannot form the basis for legal action or litigation for compliance or absence of compliance in the clinical practice setting, but can only be considered as general guidelines based on best available evidence for assistance in decision-making. Any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. HCGC-SG makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way. In addition, these guidelines describe evaluations and administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that such clinical studies are designed to test innovative management strategies in a disease for which better treatment is sorely needed. However, by reviewing and synthesizing

the latest literature, this practice guideline serves to identify questions for further research and the settings in which investigational therapy should be considered.

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Compliance with ethical standards

Conflict of interest Dr. Kalogeridi reports non-financial support from Sanofi, outside the submitted work; Dr. Oikonomopoulos reports personal fees from Roche, personal fees from MSD, personal fees from Bristol, outside the submitted work; and ESMO Member; Dr. Xynos reports non-financial support from Johnson & Johnson, outside the submitted work; Dr. Souglakos reports grants from Amgen, grants and personal fees from Roche, grants and personal fees from Sanofi, personal fees from Servier, personal fees from MSD, personal fees from Merck Serono, personal fees from CellGene, outside the submitted work.

Research involving human participants and/or animals No human participants or animals were involved during execution of this research project.

Informed consent For this type of article, informed consent is not required.

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