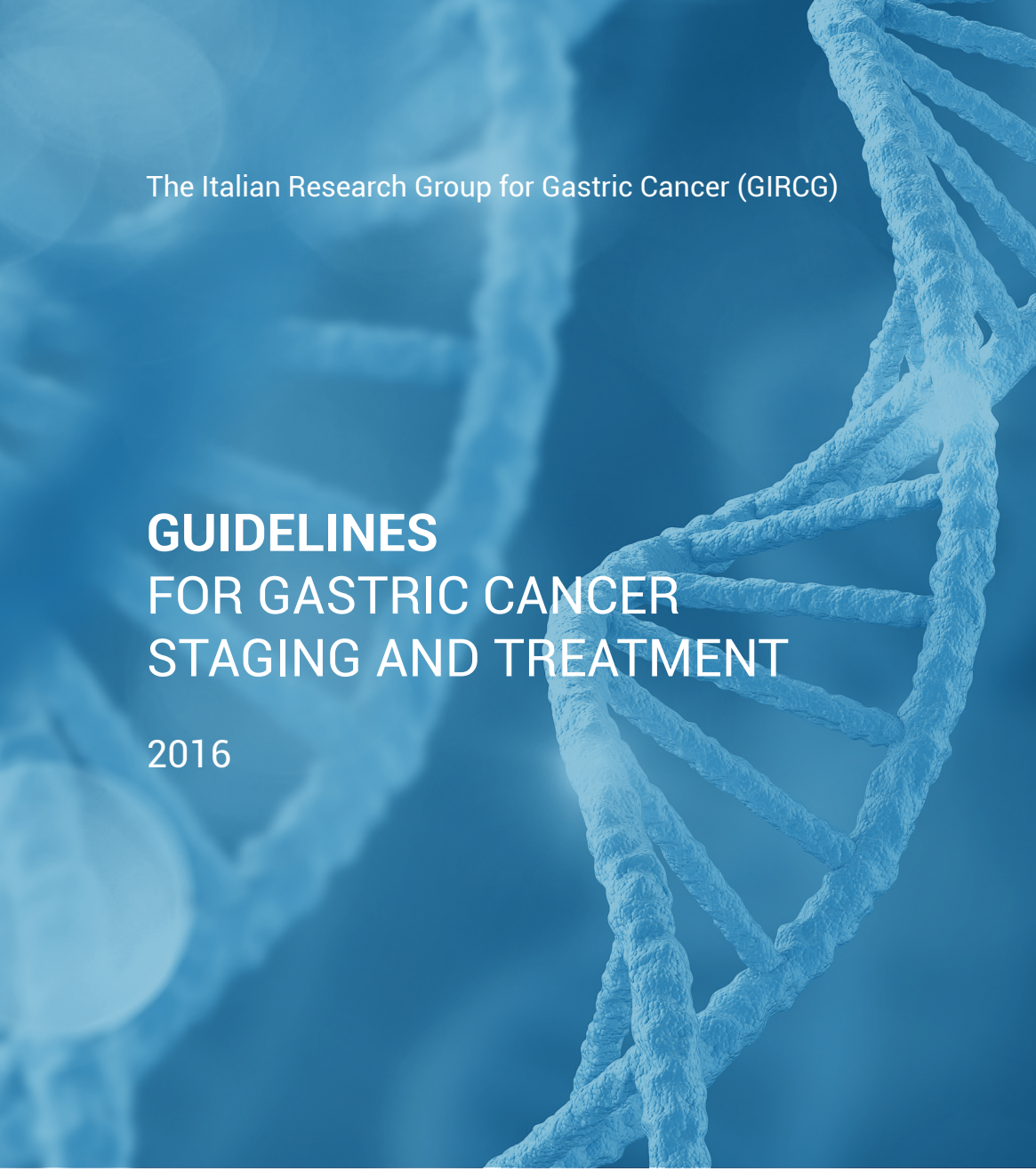
The Italian Research Group for Gastric Cancer (GIRCG)

GUIDELINES
FOR GASTRIC CANCER STAGING AND TREATMENT

2016



RICERCHIAMO

GIRCG
Gruppo Italiano Ricerca Cancro Gastrico

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On behalf of **GIRCG** and in collaboration with **RICERCHIAMO ASSOCIATION**

16 dicembre 2016

Caro Collega,

nell'occasione delle imminenti festività natalizie il Gruppo Italiano per la Ricerca sul Cancro Gastrico (GIRCG) e l'associazione RicerChiAmo sono liete di omaggiarti le Linee Guida per la Stadiazione ed il Trattamento del Cancro Gastrico, recentemente pubblicate sulla prestigiosa rivista internazionale Gastric Cancer.

Il GIRCG è una ONLUS nata nel 2001 con l'obiettivo di raccogliere e aggregare dati provenienti da centri italiani con interesse specifico per la cura del cancro dello stomaco e di sviluppare protocolli di ricerca multicentrici. Negli ultimi 10 anni il GIRCG ha pubblicato 45 articoli scientifici su riviste indicizzate e una monografia a diffusione internazionale, ha organizzato 12 workshop, un master postuniversitario, e il 10º congresso mondiale della IGCA (International Gastric Cancer Association) nel 2013 a Verona.
RicerChiAmo è un'Associazione senza scopo di lucro nata nel 2016 con l'obiettivo statutario di promuovere, anche attraverso la raccolta di fondi, la ricerca scientifica sulle neoplasie dell'apparato digerente, nei suoi aspetti di laboratorio e clinici, e di diffondere la conoscenza delle attività di studio e di ricerca oncologica nazionali ed internazionali sia all'interno della comunità medico-scientifica che tra i cittadini.

La pubblicazione delle Linee Guida qui allegate - le ultime in ordine cronologico nel panorama internazionale - rappresenta un importante traguardo della ricerca clinica italiana, che corona molti anni di lavoro multicentrico e multidisciplinare. Esse vanno intese come strumento guida nelle scelta del percorso stadiativo e terapeutico minimo per una buona pratica oncologica. L'Associazione RicerChiAmo ha con piacere promosso la pubblicazione in forma cartacea di queste Linee Guida, sicura di poter con ciò contribuire ad un miglioramento della qualità di cura dei nostri pazienti.

Cogliamo l'occasione per augurare a te, ai tuoi collaboratori e alle vostre famiglie un sereno Natale e un Felice Anno Nuovo.

INTRODUCTION

Gastric cancer (GC), despite the declining incidence, is still the third cancer-related cause of death after lung and liver neoplasms [1]. Although surgery remains the mainstay of therapy, in recent years there have been relevant progresses in endoscopic treatment of early forms and in neoadjuvant, adjuvant and palliative chemotherapy of advanced cancers. Furthermore, radiological and pathological protocols have been standardized. Thus, a multidisciplinary team is required for a correct management of patients, from preoperative staging to follow-up.

From an historical perspective, Italian surgeons were among the first in the West to acknowledge the indications of Eastern Centers; owing to the high incidence of this tumor in their Countries, the Japanese surgeons developed a surgical approach based on extended (D2) and superextended (D3) lymphadenectomy, while the intervention more frequently performed in Europe and in USA provided for a limited lymphadenectomy (D1). This gave rise to a scientific conflict, which rested on an impressive difference in long-term survival (overall, 5-year survival rate of a patient with GC was around 75% in Japan [2] and 25% in Europe [3]). In this context, a number of Italian surgeons started in the 80's concentrating their efforts on more meticulous and aggressive nodal clearance, and providing a contribution in the worldwide spreading of Japanese therapy and results.

The Italian Research Group for Gastric Cancer (GIRCG) is a multidisciplinary research group, officially founded in 2001, which includes clinicians with recognized expertise in GC diagnosis, care and research from over 25 specialized Centers in Italy. The aim of GIRCG is to obtain results similar to those reported by Eastern Centers in terms of recurrence rate and survival. It involves a variety of medical professionals, ranging from surgeons, pathologists, gastroenterologists, medical oncologists, radiologists, nutritionists and statisticians,

who all practice within the modern concepts of a multidisciplinary approach. The main targets of the group are the standardization of surgical treatment and extended lymphadenectomy, pathological assessment, clinical staging, and multimodal treatment of GC in Italy, surgical, endoscopic, pathological and radiological training, as well as the conduction of clinical studies and translational research. A mean of three meetings per year are conducted to ensure a continuity of collaboration. In the last 10 years the GIRCG published 45 papers in indexed journals and an international book [4], organized 12 workshops and 1 post-universitary masterclass, and finally the 10th International Gastric Cancer Congress in June 2013 in Verona. Several research studies are still ongoing.

In September 2013, surgical guidelines for GC were issued by the GIRCG and the Italian Society of Surgery (SIC), at the end of 3-months, web-based and Delphi method-based Consensus Conference [5]. The final version included 9 statements (Staging, Endoscopic Treatment, Neoadiuvant Therapy, Extent of Gastric Resection, Lymphadenectomy, Associated Resections, Palliative Therapy, Mini-invasive Surgery, Follow-up), which were approved in plenary session during the 105th SIC National Congress, October 2013, in Turin. Starting from these statements, in the following months a Commission was established inside the GIRCG, with the aim to translate those results into comprehensive indications for clinical management, including radiological, endoscopic, surgical, pathological and oncological paths. The result is herein exposed under the title of "GIRCG guidelines for GC staging and treatment – 2015", and should be re-evaluated in 3 years. The present guidelines have not already been published elsewhere,
even in Italian language nor other forms. The present paper has been approved by the Scientific Committee of the GIRCG.

Diagnosis and Staging

Diagnosis of GC is usually done – and should in every case be confirmed – by upper gastrointestinal (GI) endoscopy. Basic informations to be given by endoscopy are: location (upper, middle, lower third, esophago-gastric junction (EGJ), divided in Siewert type I, II or III), size, macroscopic appearance and actual complications (obstruction/bleeding). Biopsies from the tumor should always be taken, in order to confirm histology and to classify into potentially useful classifications (Lauren histotype, WHO, see later). Chromoendoscopy and biopsies of the gastric mucosa far from the tumor may be useful, in order to exclude multifocal disease. The suspicion of Barrett's oesophagus should be specified and eventually confirmed by separate biopsies.

The pretreatment staging of GC should include in all the cases a contrast-enhanced thoraco-abdominal Multidetector row Computed Tomography (MDCT) with 16 or more rows. The MDCT examination should be performed with a spiral technique, using a dedicated protocol optimized to detect serosal invasion and minimal peritoneal disease, and images should be analyzed by an experienced reader (see appendix 1). Endoscopic ultrasound (EUS) may improve diagnostic accuracy of T stage, particularly in discriminating T1a from T1b or T2, or in case of an inadequate CT examination; however it is not strictly necessary in advanced forms, whereas it is formally indicated in the selection of patients for endoscopic treatment. Staging laparoscopy is also not strictly required, but it is recommended in cases deemed to be at risk of peritoneal carcinomatosis not visible or doubtful at CT examination. Staging laparoscopy is required also in many randomized clinical trials of adjuvant and neoadjuvant therapy. The cytological examination of peritoneal lavage, although limited by a low sensitivity, is a useful completion of the final pathologic staging.

Endoscopic treatment of Early Gastric Cancer (EGC)

Due to the excellent prognosis of EGC, endoscopic procedures have been increasingly adopted for the treatment of selected cases with low risk for nodal metastases, with the aim of avoiding greater-than-necessary morbidity and mortality related to gastrectomy. The GIRCG recognizes the criteria for appropriate endoscopic therapy of EGC reported in the Gastric Cancer Treatment Guidelines 2010, published by the Japanese Gastric Cancer Association (JGCA) [6]: the absolute criteria for standard treatment (including both EMR, endoscopic mucosal resection and ESD, endoscopic submucosal dissection) are differentiated-type adenocarcinoma, no ulcerative findings (UL(-)), depth of invasion clinically diagnosed as T1a (mucosal stage) and diameter not greater than 2 cm; the expanded criteria, to be proposed as an investigational treatment (only ESD should be employed) are tumors clinically diagnosed as T1a and (a) of differentiated-type, UL(-), but greater than 2 cm in diameter, or (b) of differentiated-type, UL(+), and not greater than 2 cm in diameter. The resection is judged as curative when all of the following conditions are fulfilled: en-bloc resection, tumor size not greater than 2 cm, histology of intestinal-differentiated-type, pT1a, negative horizontal (lateral) margin (HM0), negative vertical margin (VM0), and no lympho-vascular invasion [7]. It is rea-

sonable to treat EGC that meet the above mentioned characteristics by endoscopic techniques (EMR or ESD) only in experienced, high volume centers. Extended criteria may be proposed only to patients who accept to undergo long-term endoscopic surveillance and/or to participate into investigational programs. In centers with low volume of endoscopic advanced procedures, gastrectomy remains the gold standard for treatment of EGC [8].

Neoadjuvant treatment

The indication to perioperative chemotherapy should be considered and discussed within a multidisciplinary team in every case of locally advanced GC. The randomized studies MAGIC [9] and FNCLCC [10] are the principal reference, in Europe, for integrated protocols: these studies have demonstrated a survival benefit for neoadjuvant and peri-operative treatment in GC staged >T1 and/or N+. In MAGIC trial, the 5-year OS rates were 36% among those who received perioperative chemotherapy and 23% in the surgery group (hazard ratio (HR): 0.75; P = 0.009). In FNCLCC trial, the 5-year OS rate was 38% for patients in the perioperative chemotherapy group and 24% in the surgery only group (HR: 0.69; P = 0.02). The corresponding 5-year DFS rates were 34% and 19% (HR: 0.65; P = 0.003), respectively. Multidisciplinary evaluation must consider several data which are important in the choice of an individualized treatment plan: an accurate preoperative stage of GC is difficult to achieve; the symptoms related to advanced tumors, obstructing or bleeding, may contraindicate neoadjuvant treatment; very limited data exist in the possibility to predict the response of a single neoplasm to neoadjuvant treatment; only response to treatment determines the survival advantage. Serosal infiltrating tumors, cancers with bulky (enlarged, clearly metastatic) nodes or Bormann type 4 cancers are a common indication for neoadjuvant treatment, mainly with the aim of increasing the R0 resectability rate [11-13]. At present, there are doubts about the response rate of signet ring cell tumors to neoadjuvant treatment, due to a presumed intrinsic chemo-resistance of these cancers. It is possible that these cancers necessitate a different integrated treatment pathway. The GIRCG suggests to consider a neoadjuvant treatment for GC T>3 and/or with metastatic nodes on preoperative work-up, because the five-year survival probability of T1/T2 node-negative cases largely overcomes 80% in GIRCG series [14]. Selection of neoadjuvant treatments should take into consideration some elements that may determine collateral effects and related postoperative morbidity: patient's age, for example, can be a parameter to decide the use of intensive regimens. There still remains to define the rate of postoperative morbidity directly related to neoadjuvant treatment and the most effective treatment between preoperative and perioperative schema.

SURGICAL THERAPY

Resection

Curative surgery is distinguished in standard gastrectomy (total or subtotal gastric resection and D2 lymphadenectomy), modified gastrectomy (the extent of gastric resection and/or lymphadenectomy is reduced compared to standard surgery) and extended gastrectomy (gastric resection plus surgical removal of adjacent involved

organs and/or D2 plus lymphadenectomy). A sufficient resection margin should be ensured when determining the resection line in gastrectomy with curative intent. A proximal margin of at least 3 cm is recommended for T2 or deeper tumors with an expansive growth pattern and 5 cm is recommended 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. 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. For T1 tumors, a gross resection margin of 2 cm should be obtained. When the tumor border is unclear, preoperative endoscopic marking by clips of the tumor border will be helpful for decision-making regarding the resection line. Distal gastrectomy should be preferred when an adequate proximal resection margin can be obtained for distal tumors. Pancreatic or spleen invasion by tumor requiring pancreaticosplenectomy necessitates total gastrectomy regardless of the tumor location. Total gastrectomy should be considered for tumors that are located along the greater curvature of the corpus (when there is not an adequate surgical margin) or the fundus.

After distal gastrectomy, Roux-en-Y reconstruction seems superior to Billroth I and Billroth II reconstructions in terms of functional outcomes and long-term endoscopic results; however, no clear conclusions are available in literature, and the choice of the procedure could be based on surgeon's experience [15, 16]. After total gastrectomy, Roux-en-Y reconstruction remains the easiest solution, with satisfactory functional results.

Splenectomy is generally associated with an increased risk of post-operative complications in GC surgery. Final survival analysis of a randomized controlled trial (JCOG0110), designed to evaluate the role of splenectomy in total gastrectomy for proximal GC which does not invade the greater curvature, demonstrated significant non-inferiority of spleen preservation [17]. Total gastrectomy with splenectomy should be recommended for tumors that are located along the greater curvature or when a macroscopic involvement of stations 4sa or 10 is present.

Combined cholecystectomy for asymptomatic gallstone in GC surgery may be considered in young patients; otherwise, it is no clear if cholecystectomy is indicated in patients without gallstones; a recent GIRCG multicenter study showed no difference in medium-term outcome between patients receiving or not prophylactic cholecystectomy [18].

The role of total omentectomy is still questionable, particularly for serosa-negative advanced GC. Removal of the greater omentum is usually integrated in the standard gastrectomy for T3 or deeper tumors. 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 may be performed in order to remove microscopic tumor deposits in the lesser sac. In T1/T2 tumors, bursectomy should be avoided in order to prevent injury to the pancreas and/or adjacent vessels. A small-scale RCT showed a trend toward improved survival after bursectomy for tumors in the middle or lower third and for pathologically serosa-positive tumors [19].

Lymphadenectomy

The GIRCG takes strictly into account the Guidelines of the JGCA for indications, surgical procedure and classification of lymphadenectomy [6]. In particular, the following points are emphasized: the standard treatment for potentially curative resection is the D2, even after neoadjuvant treatment. Only in carefully selected cases (high-risk patients, early tumors not treatable by endoscopic resections) more limited procedures should be considered (D1, D1 plus). Otherwise, it is strictly necessary to follow the correct procedure of lymphadenectomy, with special reference, along with other perigastric nodes, to an accurate and complete removal of infra-pyloric (station 6), right paracardial (station 1), left gastric artery (station 7), celiac axis (station 9), hepatic artery (station 8a), splenic artery (station 11p/d) and hepatoduodenal ligament (12a) nodes. It is also emphasized that in Italy the preoperative diagnosis of early forms is often unreliable, and the incidence of Lauren diffuse histotype, which is associated with a higher risk of lymph node metastases even in early forms, is high [20]. The D2 plus, which involves the lymphadenectomy of posterior stations (8p, 12p/b, 13), station 14v, and the additional removal of para-aortic nodes (16a2, 16b1), may be justified in patients at high risk of metastases at these stations (advanced tumors of the upper third, advanced tumors and diffuse histotype located in the distal two-thirds of the stomach). However, these procedures should be performed in Centers specialized with the D2, or in clinical trials [21]. The lymph node mapping on the fresh specimen is advisable, in order to check the quality control of lymphadenectomy, and potentially increases the number of examined nodes, thus allowing a more correct staging of the disease.

Minimally invasive resective surgery (MIS)

Laparoscopic gastric resection for GC is an option that should be considered in patients with EGC: this approach carries advantages in terms of reduction of postoperative stay, postoperative pain and return to normal activities. However, the results of MIS in terms of quality of life and long term survival are still under evaluation [22, 23]. Preliminary data seem to indicate that laparoscopic surgery is feasible also for AGC, but solid data on the advantages and oncologic efficacy of this approach coming from randomized trials are lacking, and the presence of a serosal cancer should still be considered a contraindication to MIS. There are some limitations to a diffuse application of these data, which come mainly from eastern RCT, including patients with BMI generally lower than those of Western patients, with less comorbidities and with tumors with a different biological behavior [24]; there would also be a problem concerning the learning curve for this procedure, that requires a caseload difficult to be reached in a short time in regions with a low prevalence of GC; in most of the studies coming from the East, a "laparoscopically assisted" technique was used, and such results are not directly transferrable to a totally laparoscopic approach; 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 standardized and which still make the procedure uncommon.

Pathological report

EGC is a malignant epithelial neoplasia limited to the mucosa and/or submucosa [25]. From a macroscopic point of view, EGCs are divided into 3 main types according to their endoscopic appearance: type 1 (protruding), type 2 (superficial), type 3 (excavated). Kodama's classification should also be mentioned, as it could provide additional prognostic implications [26]. Advanced carcinomas should be classified into 4 macroscopic types according to the criteria proposed by Borrmann: polypoid, fungating, ulcerated and infiltrative. The diffuse variant may affect most of the stomach and is commonly called linitis plastica or leather bottle stomach. The most widely used histological classification, both for early and advanced cancers, is the Lauren classification [27], which classifies GC according to 4 different types: intestinal, diffuse (signet-ring cell carcinoma belong to this group), mixed and indeterminate. The WHO classification should be also used in pathological report.

EMR/ESD complete and appropriated pathological report should provide all the following items, in order to be considered as diagnostic and clinically useful:

- Number of specimens examined (en bloc vs. piecemeal resection)
- Macroscopic size of the specimen (all three dimensions should be reported)
- Macroscopic and microscopic size of the lesion
- Macroscopic tumor type
- Lauren histotype
- WHO classification with histologic grade
- Depth of invasion
- Presence or absence of intra-tumoral ulcer
- Presence or absence of lymphovascular invasion
- Resection margins status (horizontal and vertical, with the measurement of the distance from the lesion)
- Curative resection (yes/no)

When endoscopic, macroscopic and histological sizes of the lesion are discordant, the microscopic measure is considered the gold standard. The depth of invasion of the tumor into the submucosal layer must be measured from the deepest part of muscularis mucosae.

Surgical pathological report of AGC should be conceived according to the following check list:

- Type of gastrectomy and lymphadenectomy
- Tumor location
- Macroscopic type of the tumor
- Maximum tumor size
- Macroscopic distance of the lesion from the proximal and distal cut ends
- Resection margins status
- Lauren histotype
- WHO classification with histologic grade
- Depth of infiltration
- Presence or absence of lymphovascular invasion
- Total number of examined lymph nodes
- Total number of positive lymph nodes
- Topography of examined and positive lymph node stations (optional)
- Peritoneal cytology or metastatic lesions (when performed)
- pTNM Classification (7th Edition)
- In addition, in EGC, Kodama's Classification should be also added to the pathological report.

In order to evaluate the histological response of the tumor to neoadiuvant therapy, the

Becker classification [28] should be mentioned: grade 1, complete or subtotal regression (<10% residual tumor per tumor bed; grade 1a is complete regression and grade 1b is subtotal regression); grade 2, partial tumor regression (10%–50% residual tumor per tumor bed); grade 3, minimal or no tumor regression (>50% residual tumor per tumor bed).

Adjuvant treatments and integrated therapies

Adjuvant therapy (chemotherapy, radiotherapy or chemo-radiotherapy) could be recommended in patients surgically treated for GC at stage II-III, in R1 resection or in case of lymph node metastases. A large meta-analysis confirmed the benefit of a 5-FU based adjuvant treatment in stage II-III, showing a reduced 5-y mortality of 18% in the experimental group [29]. In Asian populations, an overall survival benefit from adjuvant chemotherapy was confirmed following D2 resection in the ACTS-GC trial evaluating adjuvant S-1; the 5-year survival rate was 71.7% in the chemotherapy group versus 61.1% in the surgery-only group (HR: 0.67) [30]. The CLASSIC trial evaluated an adjuvant capecitabine–oxaliplatin doublet chemotherapy after D2 gastrectomy, and reported significantly improved overall survival (5-year survival rate was 78% in chemotherapy group versus 69% in the observation group) and disease-free survival (HR: 0.58) with a 5-year disease-free survival of 68% in the adjuvant chemotherapy group and 53% in the surgery alone group [31]. However, it should be noted that the benefit of postoperative chemotherapy following a D1 or D0 lymph node dissection has not been documented in these trials.

Cytoreductive surgery (CRS) plus HIPEC represents a multidisciplinary approach for a selected subgroup of GC patients with peritoneal carcinomatosis (PC) and for advanced resectable cases at high risk of developing PC. Given that curative treatment failure in Western countries is mainly due to peritoneal recurrence and that a meta-analysis composed almost entirely of Asian studies suggests the benefit of HIPEC as an adjuvant treatment [32], a European study on a Caucasian population is clearly warranted. In the meantime, HIPEC can be performed in selected patients having limited peritoneal carcinomatosis index (PCI<6) and in selected patients with metachronous PC. In cases with positive peritoneal cytology without a macroscopic peritoneal carcinomatosis and in adjuvant setting, HIPEC would be better carried out in the context of clinical trials.

Palliation

Palliative treatment is addressed to patients affected by symptoms related to GC such as bleeding and obstruction. The main modalities of palliation are surgical procedures (resection and bypass), endoscopic therapies (stenting), bleeding control procedures (endoscopic and/or angiographic), chemotherapy, and analgesic cares. The choice of modality depends on a variety of factors, including symptoms, performance status, potential response to combined therapies and individual patient prognosis, and should be made on case-by-case basis.

Palliative gastrojejunostomy is beneficial for gastric outlet obstruction caused by unresectable advanced distal cancer in terms of improvement of oral food intake, with acceptable morbidity and mortality. However, its indication for patients with

poor performance status is less clear, and in many cases endoscopic palliation is effective as well. Reduction surgery includes gastrectomy made in a metastatic disease to reduce the tumour volume and its related symptoms. This approach remains controversial. Recent results of REGATTA trial, conducted in Asian patients, did not show any survival benefit of gastrectomy followed by chemotherapy compared with chemotherapy alone in advanced GC with a single non-curable factor with an overall 2-year survival of 31.7% for patients treated with chemotherapy alone vs. 25.1% for those treated with gastrectomy plus chemotherapy [33]. Palliative gastrectomy associated to liver resection and chemotherapy, when R0 resection can be obtained in patients fit for heavy surgery, has been reported to improve overall survival in selected groups of patients [34].

In medically fit patients with metastatic or locally advanced, not resectable GC, chemotherapy is recommended. Chemotherapy can provide palliation, improved survival, and improved quality of life compared to best supportive care in patients with metastatic disease [35, 36]. Currently, platinum-based and fluoro pyrimidine-based combinations are accepted as first-line drug regimens [37]. Higher response rates were observed in patients who received combination chemotherapy versus monotherapy. ECF (epirubicin, cisplatin, and 5-FU) and DCF (docetaxel, cisplatin, and 5-FU) regimens are recommended as first-line chemotherapy. However, DCF was associated with increased myelosuppression and infectious complications. Oxaliplatin may represent an alternative to cisplatin with at least comparable activity and a favourable global toxicity profile. Capecitabine is an orally administered fluoropyrimidine that is converted to fluorouracil intracellularly. Several studies have evaluated capecitabine, as a single agent or in combination regimens, in patients with GC. The REAL-2 study compared capecitabine with fluorouracil and oxaliplatin with cisplatin [38]. Results from this study suggest that capecitabine and oxaliplatin are as effective as fluorouracil and cisplatin, respectively, in patients with previously untreated esophagogastric cancer with an HR: 0.86 for the capecitabine-fluorouracil comparison, and an HR: 0.92 for the oxaliplatin-cisplatin comparison. Irinotecan as a single agent or in combination can be an alternative when platinum-based therapy cannot be delivered.

The ToGA trial [39] showed a significant improvement in overall survival with the addition of trastuzumab to a cisplatin-fluoropyrimidine doublet. However, the benefit of trastuzumab was limited to patients with a tumor score of IHC 3 + or IHC 2+ and FISH positive (HR: 0.74). Thus, for patients with metastatic adenocarcinoma the assessment of HER2-neu overexpression using immunohistochemistry and fluorescenze in situ hybridation is recommended. REGARD trial demonstrated a survival benefit for ramucirumab for patients with advanced gastric adenocarcinoma progressing after first-line chemotherapy (HR:0.77) [40]. Based on the results of the REGARD trial, ramucirumab as a single agent is recommended for advanced GC with disease progression, or after prior treatment by platinum-based or fluoro pyrimidine-based chemotherapy.

Follow-up

There is no evidence that routine follow-up after curative treatment of GC is associated

with improved long term survival. However, routine follow-up should be offered to all patients for the following reasons: oncological (detection and management of cancer recurrence), gastroenterologic (endoscopic surveillance and management of postgastrectomy symptoms), research (collection of data on treatment toxicity, time to and site of recurrence, survival, and cost-benefit analyses), and pastoral (psychological and emotional support) [41, 42]. Follow-up should include lifetime monitoring of the nutritional sequelae of gastrectomy, including, but not limited to, adequate vitamin B12, iron, and calcium replacement. Follow-up should be offered by members of the multidisciplinary team who managed the initial diagnosis, staging and treatment, including the gastroenterologist, the surgeon, the medical and radiation oncologists, and the general practitioner. Follow-up modalities should be tailored to the individual patient, to the stage of their disease, and to the treatment options available in the event that recurrence is detected. Physical examination rarely detects asymptomatic recurrence of GC, thus a program intended to detect asymptomatic recurrence should be based on cross-sectional imaging. Upper GI endoscopy may be used to detect local recurrence or metachronous primary GC in patients that have undergone a subtotal gastrectomy. Routine screening for asymptomatic recurrence of GC may be discontinued after five years, as recurrence beyond that interval is infrequent [43].

EGJ

The latest TNM classification defines junctional carcinoma as oesophageal cancers, with the exception of upper third GC not infiltrating the Z line. The Siewert classification, even with the limitations caused by using only a topographical definition, often not unequivocal, remains of primary importance in determining therapeutic strategies. In case of early junctional cancers, the en-bloc endoscopic resection (EMR-ESD) should be considered therapeutic in T1a, well-differentiated, non-ulcerated and ≤ 2 cm lesions. In early tumors outside from these criteria, endoscopic resection, even with free margins, plays only a role of staging, for the high rate of lymph node metastases [44]. Thus, T1 lesions that do not meet the above described criteria should be treated with surgery; the choice of resection strategy is strictly dependent on the location with respect to the cardia: Siewert II T1 tumors can be treated with abdominal approach if it is possible to ensure an oesophageal margin of at least 2 cm, otherwise a thoraco-abdominal approach is necessary.

In case of advanced junctional tumor, in recent years a multimodal therapy has gradually become the standard of care: for T≥2, regardless of N, Siewert I and II, as for squamous cell carcinoma of oesophagus, surgery should be preceded by neoadjuvant chemo-radiotherapy [45, 46] or chemotherapy [9]. Siewert type III tumors follow the rules of advanced GC and should be treated by neoadjuvant chemotherapy. Siewert I tumors are considered tumors of the distal oesophagus and the approach is the same. The best choice should be a trans-thoracic subtotal oesophagectomy, in order to allow an adequate lymphadenectomy. In Siewert III tumors the procedure of choice is total gastrectomy with D2 lymphadenectomy associated with trans-hiatal lower mediastinal lymphadenectomy or, in selected cases, by left thoraco-phreno-laparotomy or right thoracotomy. A macroscopic proximal

margin of at least 6 cm has been reported to increase the chance of surgical curability [47]; if this margin cannot be guaranteed, analysis of margin by frozen section is recommended. Siewert II tumors have the chance of having in about one third of the cases both abdominal and thoracic lymph node involvement [48]. For this reason, surgery cannot disregard a trans-thoracic way. The reconstruction by gastric conduit is preferable except in cases of major involvement of the stomach, where a total gastrectomy with intra-thoracic esophago-jejuno anastomosis should be provided.

GIST

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. They occur with an incidence of at least 10 to 20 per million worldwide [49]. GISTs typically occur in older adults, and the median patient age varies between 60 and 65 years. Some series have shown a mild male predominance. Over half of the GISTs occur in the stomach. Almost all GISTs express the KIT receptor tyrosine kinase, similar to the GI Cajal cells that regulate the GI autonomic nerve system and peristalsis, while approximately 85% to 90% of GISTs contain oncogenic KIT or PDGFRA mutations. A distinct subset of GISTs, characterized by wild type KIT/PDGFRA, defects of succinate dehydrogenase (SDH) complex and peculiar prognostic features, tends to occur at earlier ages, including infancy, and to prevail in females, sometimes arising in the context of Carney triad or Carney-Stratakis syndrome [50]. Most patients have symptoms or a palpable tumor at presentation, but about 25% are discovered incidentally. Tissue for pathological analysis can be obtained from tumor biopsies, done through endoscopic ultrasound guidance, or through an ultrasound/CT-guided percutaneous approach or surgical specimens. The risk of peritoneal contamination in biopsies is minimal if the procedure is adequately carried out. Tumors at risk in this sense (e.g. cystic masses) should be biopsied only in high volume centers. Tumor tissue should be fixed in 4% buffered formalin; Bouin's fixative should be avoided in order to avoid problems for mutational analysis. The diagnosis of GIST is based on a consistent morphology associated with immunohistochemical positivity for CD117 and/or DOG1 [51]. In order to reduce the risk of false positives, it is advisable to carry out the immunoreaction for CD117 without unmasking of antigenic sites. About 5% of GISTs are CD117-negative. Any double negativity of CD117 and DOG1 may be surrogate for diagnostic purposes by the finding of a "canonical" mutation in exons 9, 11, 13 or 17 of KIT or in exons 12, 14 and 18 of PDGFRA.

Detected or suspected gastric GISTs that are 2 cm or more should be removed whereas smaller tumors can be excised or monitored by endoscopy and/or imaging every 6-12 months [52]. R0 of the tumor without rupturing the pseudocapsule is the goal of surgery, if possible with a macroscopic margin of 1-2 cm. Gastric or oesophageal GISTs should not be excised at endoscopy because R0 resection is difficult to achieve. Lymph-node dissection is generally not indicated because the prevalence of lymph-node metastases is about 1%. Small gastric GISTs can be excised by laparoscopy by a skilled surgical team using an extraction bag.

Preoperative imatinib should be considered when an extended procedure is needed to

remove the tumor. Tumor mutation analysis should be done to identify patients who do not benefit from preoperative imatinib. Five-year and 15-year recurrence-free survival rates for GISTs treated with surgery alone are estimated to be 70•5% and 59•9%, respectively. Only few tumors recurred after the first 10 years of follow- up, suggesting that most patients (about 60%) with operable GIST are probably cured by surgery. Imatinib is the only treatment for GISTs that has been evaluated in the adjuvant setting, with results available from two randomized trials: adjuvant imatinib for at least 3 years has been recommended after surgery for high-risk patients. Patients with a small metastatic tumor burden have the longest progression-free survival times on imatinib treatment and, hypothetically, reduction of tumor mass by surgery might prolong the time to drug resistance. Excision of a single metastasis progressing during kinase inhibitor treatment could be considered.

The prognostic factors for GISTs are anatomic location, size and mitotic count per 5 mm2. It should be noted that the latter value is achieved with a different number of fields at high magnification depending on the microscope used. Therefore, it is necessary to have a setup calibrated for the microscope adopted allowing for a count of 5 mm2 in place of the ambiguous 50 high-power fields (HPF) previously recommended in literature. The combination of these parameters defines the risk of relapse. Tumor rupture in vivo (including during surgical procedures) represents another high-risk parameter, regardless of the intrinsic prognostic features of a tumor [53].

Conclusions

The above reported guidelines represent the official GIRCG position in clinical management of GC, comprehensively covering the course of the disease, from diagnosis to follow up. They can be a useful tool to address physicians in managing patients with GC. According to the principles set out in these statements, physicians comply with the best, internationally accepted, actual standard of care.

Conflict of Interest

The authors declare that they have no conflict of interest.

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