Updates in Surgery (2020) 72:341–353
https://doi.org/10.1007/s13304-020-00736-3

REVIEW ARTICLE

Global updates in the treatment of gastric cancer: a systematic review. Part 1: staging, classification and surgical treatment

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Received: 1 January 2020 / Accepted: 25 February 2020 / Published online: 10 March 2020

Abstract

Gastric cancer (GC) is the fifth malignancy and the third cause of cancer death worldwide, according to the global cancer statistics presented in 2018. Its definition and staging have been revised in the eight edition of the AJCC/TNM classification, which took effect in 2018. Novel molecular classifications for GC have been recently established and the process of translating these classifications into clinical practice is ongoing. The cornerstone of GC treatment is surgical, in a context of multimodal therapy. Surgical treatment is being standardized, and is evolving according to new anatomical concepts and to the recent technological developments. This is leading to a massive improvement in the use of mini-invasive techniques. Mini-invasive techniques aim to be equivalent to open surgery from an oncologic point of view, with better short-term outcomes. The persecution of better short-term outcomes also includes the optimization of the perioperative management, which is being implemented on large scale according to the enhanced recovery after surgery principles. In the era of precision medicine, multimodal treatment is also evolving. The long-time-awaited results of many trials investigating the role for preoperative and postoperative management have been published, changing the clinical practice. Novel investigations focused both on traditional chemotherapeutic regimens and targeted therapies are currently ongoing. Modern platforms increase the possibility for further standardization of the different treatments, promote the use of big data, and open new possibilities for surgical learning. This systematic review in two parts assesses all the current updates in GC treatment.

Keywords Gastric cancer · Molecular classification · Biomarkers · Gastrectomy · Lymphadenectomy · Minimally invasive surgery

Introduction

Gastric cancer (GC), the fifth most frequent malignancy and the third leading cause of cancer death [1], represents a major social and health issue globally. The curative treatment for non-early gastric cancer (> Stage Ia) is mainly surgical, in a context of multimodal strategy developed to optimize its prognosis. The improvement of the survival outcomes is currently being persecuted through the integration of efforts in many fields: pathological, surgical, and multimodal. In 2018, the eight edition of the AJCC-TNM staging system took effect [2]. Contemporary, after many years of standard schemes for classification and unmodified guidelines for treatment, new discoveries in the field of genetics, surgery, and targeted therapies were presented. These discoveries are opening new courses for research, and are progressively being integrated in the treatment protocols [3–11]. Most of the translational improvements are consequential to the establishment of the genomic classifications

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and molecular characterization of GC [3, 4]. There has been an increasing attention toward implementing the surgical technique on the basis of anatomy and the natural history of disease [10, 12–18], aided by new technologies [19]. Finally, the Western standard for perioperative chemotherapy has recently changed [20], and is further evolving to integrate the new discoveries on prognostic and predictive factors [21–23]. Other multimodal strategies, as the use of radiotherapy and the role for HIPEC, are still debated [8, 24–31]. In this systematic review, we synthesize the current surgical oncology evidences for the treatment of GC. In part 1, we summarize the updates relative to GC staging, classification, and surgical treatment.

Methods

This systematic review of the literature was conducted according to the following method:

- A preliminary screening of the abstract book of the 2019 International Gastric Cancer Congress (8–11 May 2019, Prague, Czech Republic) was conducted to identify the most relevant and timely topics relative to the treatment of GC.
- According to the results, a search was conducted on Pubmed and clinicaltrials.gov. The search on PubMed was limited to articles published between 2017 and 2019. The search for this review (Part 1) was conducted for the following terms: "gastric cancer" and/or "gastrectomy": " staging", "TNM" "histopathological classification", "node ratio", "LODDS", "nomogram", "signet-ring cell", "genomic classification", "molecular classification", "Japanese classification", "Japanese guidelines", "Korean guidelines", "ESMO guidelines", "guidelines", "PD-L1", "HER2", "microsatellite instability", "MIS", "MMR", "prognostic biomarkers", predictive biomarkers", "tumor microenvironment", "gastrectomy", splenectomy", "station 10", "splenic hilum nodes", "bursectomy", "omentectomy", "mesogastrium", "fifth route", "membrane-anatomy surgery", "lymphadenectomy", "D3 lymphadenectomy", "D2 plus lymphadenectomy", "extended lymphadenectomy", "laparoscopic gastrectomy", and "robotic gastrectomy".
- The abstract were screened by two authors (AA and AB) and the articles selected from the abstract were evaluated in full text.
- After evaluation of the full text, the articles were selected according to their levels of evidence (with maximal priority given to randomized controlled trials (RCTs), meta-analyses and guidelines, followed by high-quality observational studies), their timeliness and their innovativeness in influencing the treatment of GC. Ongoing clinical trials were selected according to relevance, sample size (preferentially > 100 patients), and phase of the study (preferentially phase III, followed by phase II).
- The reference list of the articles evaluated in full text was screened for any other relevant article.
- Articles published before 2017 were included only if relevant to the establishment of the current evidence.

Staging

In 2016, the eighth edition of the AJCC-TNM classification for tumors of the esophagogastric (EGJ) junction and of the stomach was published [2]. The changes introduced by this new edition took effect in 2018. They can be summarized as

- Change in the belonging of EGJ tumors to the esophageal or GC staging system: tumors with an epicenter within 2 cm of the EGJ and extension to the EGJ are classified as esophageal, while only cancers whose epicenter is more than 2 cm distal from the EGJ are staged as GCs (even if the EGJ junction is involved);
- New clinical stage (cTNM) prognostic groups: the changes included a simplification of the cN categorization, characterizing patients only as cN0/cN1 (lymph nodes not involved or involved, respectively) and consideration for the poor prognosis of patients in the cT4b NX M0 category that where included in stage IV;
- Introduction of post-neoadjuvant prognostic stages (ypTNM);
- Introduction of different pathological stages (pTNM) through a change in the stage grouping of gastric cancer (Fig. 1). This change was mostly based on the results from the study of Sano et al. [32]. The new stage grouping accounts for the pN3a and pN3b categories, aiming to improve the prognostic resolution of the TNM and minimize the risk of "stage migration", a phenomenon of understaging that occurs when the number of examined lymph nodes is inadequate [33]. However, the new edition is still subject to the risk of stage migration when the node count is < 16. For this reason, various authors have investigated the use of alternative staging systems based on the node ratio and the LODDS (log ODDS of positive lymph nodes), which demonstrated a greater prognostic resolution when compared to the pN status and the pStage, respectively [34–36]. These alternative classification systems have been proposed as correctors for the pathological TNM staging when the node count is suboptimal. The renewed attention to the strong prognostic value of pathological node staging has led to other proposals of alternative nodal staging, as the classification in the pN1 category of pN0 patients with an incom-

TNM7 stage grouping				
	N0	N1	N2	N3a, N3b
T1	IA	IB	IIA	IIB
T2	IB	IIA	IIB	IIIA
T3	IIA	IIB	IIIA	IIIB
T4a	IIB	IIIA	IIIB	IIIC
T4b	IIIB	IIIB	IIIC	IIIC

TNM8 stage grouping					
	N0	N1	N2	N3a	N3b
T1	IA	IB	IIA	IIB	IIIB
T2	IB	IIA	IIB	IIIA	IIIB
T3	IIA	IIB	IIIA	IIIB	IIIC
T4a	IIB	IIIA	IIIA	IIIB	IIIC
T4b	IIIA	IIIB	IIIB	IIIC	IIIC

Fig. 1 Comparison between the AJCC-TNM 8th and 7th stage grouping

plete node count and LVI [37]. The future edition of the TNM is expected to assess the criticisms to the current pathological node staging flaws.

In addition, in 2017, the Japanese Classification of Gastric Carcinoma was updated to the 15th edition. This edition (thus far available only in Japanese) reflected the AJCC/TNM 8th edition, with some relevant additions, in particular the subclassification of n.6 nodal stations in 6a (gastroepiploic artery), 6v (gastroepiploic vein and infrapyloric vein) and 6i (6i, lymph nodes along the infrapyloric artery) and some consideration for the stage migration phenomenon and the use of node ratio for patients with incomplete node count. Moreover, it included n.19, 20, 110, and 111 lymph nodes as regional lymph nodes when the esophagus is invaded and n.13 lymph nodes as regional when the duodenum is invaded (Fig. 2). Last, a revision of macroscopic peritoneal metastasis staging was reported: PX, unknown; P0, no peritoneal metastasis; P1, peritoneal metastasis, subclassified into P1a, P1b, P1c, and P1x according to the sites of peritoneal dissemination [38, 39].

Histological, molecular, and genomic updates

Histopathological classifications

GC is a heterogeneous disease, composed of different phenotypes. Each phenotype is characterized by a different morphology and biological behavior. Several morphological

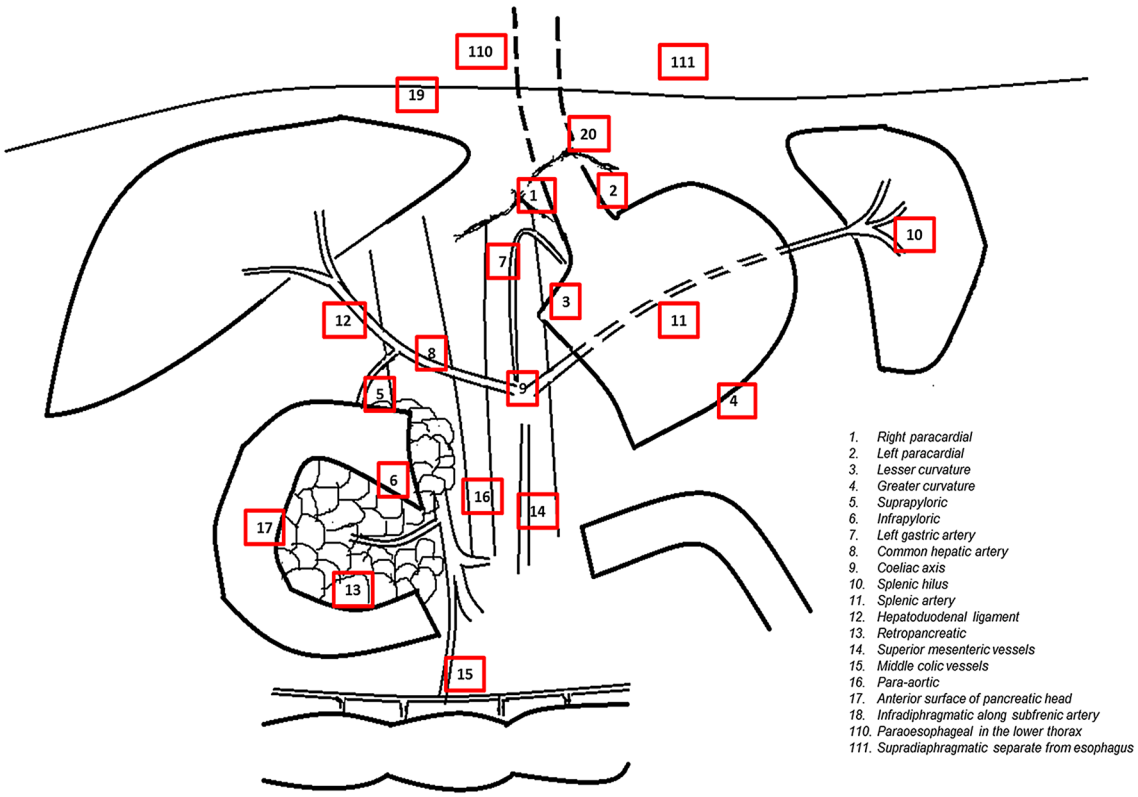

Fig. 2 Nodal stations of the upper abdomen

classification systems based on the macroscopic and microscopic features of GC have been established during the last century: the Borrmann classification, the Lauren classification, and the WHO classification [40–42]. The Borrmann classification is a macroscopic classification (Borrmann I to IV, based on the infiltrative pattern), mostly used in Eastern countries [40]. The Lauren classification is a microscopic classification based on cell architecture and infiltration pattern. It distinguishes the diffuse, the intestinal, the mixed, and the indeterminate types [41]. The WHO classification is a microscopic classification, which defines five main types of GC: tubular, papillary, mucinous, poorly cohesive (including signet ring cell carcinomas (SRCs) and other variants), and mixed adenocarcinomas [42]. The WHO classification also describes four types of stromal reaction (desmoplasia/scirrhous reaction, lymphocytic infiltration, stromal eosinophilia and granulomatous response) and presents a tumor grading (well, moderate, poorly differentiated or well and poorly differentiated), which should be applied only to tubular and papillary variants of GC. The different phenotypes, as described by the histopathological and molecular classifications, seem to be related. Indeed, Lauren diffuse carcinomas often have a poorly cohesive histotype according to the WHO classification and presents with a Borrmann III or IV appearance, while intestinal tumors are usually tubular or papillary, may be well or moderately differentiated, and presents with a Borrmann I or II appearance [43]. The current microscopic classifications are not completely reproducible, due to the frequent coexistence of different histologic features in the same tumor and to some difficulties in their interpretability. Inter-observer disagreement has been detected in 17–32% of cases for the Lauren classification and in 21–32% of cases for the WHO classification on resected specimens [44].

A recent update in the histopathologic field is the publication of an international consensus statement on poorly cohesive and SRC carcinomas by the European Chapter of International Gastric Cancer Association (IGCA) [45]. In the previous years, there were some controversies in the application of the WHO classification. Indeed, many authors followed the standard definition provided by the WHO, defining a SRC carcinoma as a tumor composed of SRCs in a proportion > 50%, while other authors documented a prognostic relevance even for the presence of a small percentage of SRCs (far below < 50%) and defined this GC as a SRC GCs [31, 46]. The incidence of poorly cohesive and signet ring cell GC is increasing in Western countries [47, 48]. The role for SRCs has recently emerged in the literature as a possible predictive and prognostic factor, and SRC GC is being investigated as a possible non-responder to the conventional perioperative regimens [49, 50]. Therefore, the need for clarification in the classification of the poorly cohesive subtype has emerged. The novel consensus statement by the European Chapter of the IGCA proposes an alternative classification for poorly cohesive WHO histotype, including the following subtypes:

- SRC type when the poorly cohesive carcinoma has > 90% of signet ring cells;
- Combined poorly cohesive not otherwise specified (NOS) and SRC Carcinoma (PC-NOS/SRC; < 90% but > 10% of SRCs);
- Poorly cohesive NOS (PC-NOS; < 10% of SRCs).

The prognostic and predictive relevance of this new classification has still to be investigated. This novel proposal is in line with the results of a Korean molecular study that identified different mutation patterns between poorly cohesive and SRC carcinomas. This study distinguishes a "pure" SRC type when SRCs are > 95%, a "pure" poorly cohesive carcinoma when there are no SRCs, a mixed SRC-predominant type when the SRC component is > 50%, and a mixed poorly cohesive-NOS-predominant type when the poorly cohesive component is greater than the SRC component [51].

In the novel Japanese classification, a revision of the lymphatic and venous invasion classifications was included: Ly0, negative lymphatic invasion; Ly1, positive lymphatic invasion, sub-classified into Ly1a, Ly1b, and Ly1c according to the extent of lymphatic invasion. Venous invasion was classified accordingly [38, 39].

Genomic classifications

Another initiative with the potential to overcome the unreliability of the standard histologic classifications is the implementation of the molecular classifications that occurred in recent years. In 2014, the Cancer Genome Atlas group (TGCA) established a molecular classification based on the genomic features of the GCs of 295 patients. This classification defines four major genomic subtypes: EBV-positive, microsatellite instable (MSI), genomically stable (GS), and chromosomally instable (CIN) tumors [3]. In 2015, the Asian Cancer Research Group (ACRG) conducted the gene expression profiling of 300 GCs, identifying four subtypes of GC: MSI, microsatellite stable with epithelial/mesenchymal transition (MSS/EMT), MSS/TP53-positive, and MSS/TP53-negative subtypes. In this study, the genomic subtypes were related to prognosis, with the worst prognostic value for MSS/EMT tumors [52]. The genomic classifications correlate with the histopathologic classifications. Indeed, the GS and MSS/EMT subtypes are partially overlapped with the Lauren diffuse subtype (80% concordance with the MSS/EMT subtype), while MSI tumors correlate with the Lauren intestinal subtype (in > than 60% of cases in the TGCA classification) [3, 52]. The advantages of the genomic

classifications are their accuracy and reproducibility, their possible link to the biological behavior of the tumor and their role as predictive factors. They also allow for the development of targeted therapies. Their main disadvantage is the high cost associated with gene profiling [53, 54]. As a possible lower cost alternative, surrogate genomic classifications have been proposed. In particular, in 2016, Gonzalez et al. proposed an immunohistochemistry-based surrogate TGCA classification that identified four different subtypes of GC: the EBER-positive subtype, the MLH1-deficient subtype, the aberrant p53 staining/EBER-negative/retained MLH1 subtype and the "unremarkable staining" subtype, but presented some difficulties in identifying patients in the CIS TGCA subtype [55]. These classifications are still undergoing a translational development and have not been codified for use in the clinical practice so far.

Role of the tumor microenvironment

Most of the GC classifications are based on a "cancer cell-centered" approach. However, attention has been recently focused on the tumor microenvironment. The tumor microenvironment or stroma (composed by fibroblast, endothelial cells, extracellular matrix and immune cells) is actively involved in the mechanism of cancer growth, invasion, and metastasis. There are evidences that the interaction between cancer cells and stroma is actually one of the primary driving forces for cancer progression [56]. The assessment of the stroma quantity and quality seems to have a considerable prognostic value [57–60]. Peng et al. and Kemi et al. documented the tumor/stroma ratio as a strong independent prognostic factor for GC patients. In their studies, worse survival outcomes were associated with a greater stromal proportion [58, 61]. Specific GC phenotypes have been linked to specific stromal features, i.e., signet ring cell tumors are often accompanied by a desmoplastic stroma, while EBV-associated gastric cancer are often rich in tumor-infiltrating lymphocytes [56, 62]. Signet ring cell tumors, in particular, are characterized by a complex interaction between cancer cells and cancer-associated fibroblasts (CAFs). The origin of CAFs is under investigation; it seems to be heterogeneous, as they may be local fibroblasts, cells recruited from the bone marrow, or pericytes which undergo endothelial to mesenchymal transition [63]. Even the inflammatory component of the stroma has a role as a predictive and prognostic factor, and a correlation with the CAF activity. Indeed, some studies showed that CAFs can affect tumor immunity through M2 (immunosuppressive) polarization of tumor-associated macrophages (TAMs), and the role of TAMs has associated with a worse prognosis [63, 64]. Other recent studies demonstrated that immunoscores based on the PD-L1 expression and proportion of CD8 + T cells or on the proportion of CD3 +, CD8 +, CD45 + and CD66b + cells, in adjunct to the TNM, are better prognostic indicators than the TNM alone [65, 66]. One of these studies identified an association between a high immunoscore and a favorable response to adjuvant chemotherapy in Stage II/III GC patients [66].

Molecular markers

Other GC molecular features have been investigated as prognostic and predictive markers. The overexpression of the human epidermal growth factor receptor 2 (HER2) was initially reported in GC as an independent unfavorable prognostic factor. Its overexpression is associated with proximal tumors and intestinal histotype [67]. Currently, HER2 is tested by means of immunohistochemistry and scored as 0, 1+, 2+, 3+. GCs that are 2+ should be further tested by fluorescent in situ hybridization (FISH) [11]. The recent ToGA trial demonstrated an improvement in survival associated with the administration of Trastuzumab in combination with chemotherapy in patients with metastatic or recurrent GC setting, in particular in patients that are HER2 positive (2+ confirmed and 3+) [5]. However, some HER2 positive patients are resistant to Trastuzumab and genomic profiling studies have been conducted to identify this subset of patients. In particular, a recent Spanish and another recent Italian study identified the activation of the PI3K/Akt/mTOR pathway and the panels of EGFR/MET/KRAS/PI3K/PTEN mutations and EGFR/MET/KRAS amplifications as predictive factors for resistance to Trastuzumab in HER2-positive patients [68, 69].

MSI is usually assessed by polymerase chain reaction (PCR) or IHC testing for the MMR proteins. PCR identifies MSI-H and MSI-low or MSS GCs and IHC identifies deficient MMR (dMMR) patients [11]. The MSI-positive GC is a different subtype according to the TGCA and the ASCG classifications. It is usually a distal tumor with intestinal histology according to Lauren and a good prognosis [3, 52]. Preliminary in vitro investigations have shown a resistance of MSI GC to both 5-FU and cisplatinum [70]. Accordingly, the role for MSI has been investigated in some trials on chemotherapy as a predictive factor of resistance to conventional perioperative or adjuvant chemotherapy. A post hoc analysis of the MAGIC trial identified an overall better prognosis in dMMR/MSI patients compared with non-dMMR/MSI patients, but worse survival outcomes in dMMR/MSI patients treated with perioperative chemotherapy compared with upfront surgery [71]. A post hoc analysis of the CLASSIC trial reported that adjuvant chemotherapy improved survival in the microsatellite-stable (MSS) group, but it did not confer any survival benefit in the MSI-H group. In the MSS group, PD-L1 assessment was useful to stratify patients with a significant benefit derived from adjuvant therapy, as only PD-L1-negative/MSS patients had a significant survival benefit from adjuvant chemotherapy compared

with surgery only, while PD-L1-positive/MSS patients had no benefit [72].

Programmed cell death-ligand 1 (PD-L1) is a transmembrane protein involved in the immune-regulatory system that is activated by its ligand, PD-1. The activation of the PD-L1 signaling pathway promotes an immunosuppressive tumor microenvironment, which results in immune evasion by tumor cells [73]. PD-L1 positivity is usually assessed by IHC, dividing the number of PD-L1-positive cells by the number of tumor cells and multiplying the result per 100. The result obtained is the combined positive score (CPS). According to previous studies, the cut-off used to define PD-L1 positivity is CPS ≥ 1 [11]. The Eastern phase III trial ATTRACTION-02 documented an increased survival in patients receiving the anti-PD-1 antibody nivolumab as a third-line treatment [74]. Then a phase II clinical trial (KEYNOTE-059) showed that the anti-PD-1 antibody pembrolizumab as a third-line treatment was safe and gave durable response in recurrent, locally advanced or metastatic PD-L1-positive and -negative patients. The objective response rate was greater in PD-L1-positive and MSI-H patients [75]. Following this trial, the FDA approved pembrolizumab as a third-line treatment for PD-L1-positive and MSI-H GC [76]. However, pembrolizumab did not demonstrate its efficacy as a second-line therapy in a following Western phase III study [77]. These results were ascribed to different populations in the third-line and second-line trials [78]. Recent studies identified relevant molecular associations for PD-L1 expression, MMR status and EBV positivity (PD-L1 was expressed in dMMR patients and EBV positive patients), while the association of PD-L1 positivity with prognosis was controversial [79–81]. In one of these studies, two microenvironment immune types of GC were identified: a type I (PD-L1 + /CD8 + high), characterized by immune escape responses and a high chance of sensitivity to immunotherapy and a type II (PD-L1 − /CD8 + low), characterized by an immune-ignorant state and a low sensitivity to immunotherapy [81]. Studies continue to report dramatic response to anti-PD-1 antibodies in microsatellite instability-high and Epstein–Barr virus-positive tumors, at the point that these molecular assessments have been proposed as the most reliable predictive marker of the efficacy of PD-L1 blockage [52].

Surgery

Evolution in the concept of radicality

D2-lymphadenectomy has been introduced as the standard surgical procedure in the European Society for Medical Oncology guidelines since the early 2010s, after many years of controversies [82]. This decision was based on the 15-year results of the Dutch trial, demonstrating D2 lymphadenectomy as associated with lower locoregional recurrence and gastric-cancer-related death rates than D1 surgery [83]. Instead, in the National Comprehensive Cancer Network Guidelines, D2 lymphadenectomy is recommended only in experienced centers and D1 or modified D2 lymphadenectomy is recommended for patients with resectable GC [8]. Radical D2 lymphadenectomy is considered the cornerstone of the management of gastric cancer in Eastern countries, in particular in Japan, since 1961, and is usually followed thoroughly [84, 85].

Globally, the concept of "high-quality" radical surgery is currently being refined through the investigation of specific topics and technical variants:

Splenectomy and hilum node (n.10 station) dissection

Splenectomy in association with total gastrectomy used to be performed to obtain the removal of all the lymph nodes of the splenic hilum. Since early 2000s, there have been many controversies on whether the performance of splenectomy increases the survival rate and/or the mortality and morbidity rate in patients undergoing total gastrectomy [86–88]. Two previous South American and Korean RCTs investigated the role of splenectomy reporting a slightly better but non-significant survival rate in patients undergoing total gastrectomy plus splenectomy [87, 88]. In these trials, the morbidity and mortality rate were heterogeneous (15.4–50% and 1.9–4.4%, respectively). Contrarily, a 1999 RCT comparing D1 and D2 gastrectomy had reported its data on splenectomy, finding a high mortality (16%) and morbidity rate (54%) associated with this procedure and a possible detrimental impact on survival [89]. In 2017, results of the Japanese RCT JCOG0110 were reported [90]. This RCT investigated D2 gastrectomy plus splenectomy versus gastrectomy without splenectomy in patients with Borrmann I–III, T2/T3/T4 GC without invasion of the greater curvature. In the non-splenectomy arm of this trial, most dissections (76.9%) completely excluded the n.10 station. This trial reported high morbidity (30%) and low mortality (0.4%) for patients in the splenectomy arm, while the survival outcomes (overall and disease-free survival) were equivalent in patients of the splenectomy and non-splenectomy arm. Interestingly, the rate of n.10 node metastases in the splenectomy arm was only 2.4%, while in 58 non-splenectomy patients in which n.10 sampling or dissection was performed, the rate of metastases was 3.5%, all occurring in patients with a high nodal burden that had a poor prognosis. After the results of the JCOG0110 trial, there has also been controversy on the role of n.10 node dissection and on the positivity of n.10 nodes as a poor prognostic factor [91]. The reported rate of n.10 station metastases in advanced, proximal GC is usually 8.8–20.9%. For this reason, most authors still advocate the performance of a thorough splenic hilum node dissection in patients not undergoing splenectomy [91, 92]. However, in the most recent Japanese guidelines, splenectomy is not

recommended and the n.10 station is excluded from standard D2 dissection in patients undergoing total gastrectomy, unless the tumor is infiltrated into the greater curvature or there are greater curvature node metastases [10]. Active trials on this topic are the Chinese NCT02333721 and NCT04050787 trials, which are evaluating the prognostic value of lymphadenectomy of the n.10 station in advanced proximal GC treated by laparoscopic total gastrectomy.

Lymphadenectomy Lymphadenectomies beyond D2 have been mostly investigated in retrospective studies, but only in few prospective trials. The role of 14v nodal dissection in adjunct to D2 lymphadenectomy is controversial, as retrospective studies addressing the topic reported discordant results, including an uncertain survival benefit [93–95] and a higher morbidity associated with this procedure [95]. The role of D2 plus PAND dissection has been investigated in the phase III Japanese RCT JCOG9501, which compared gastrectomy with D2 or D2 plus PAND lymphadenectomy in patients with clinical stage II–III disease and cT2b, cT3, or cT4 GC. The results of JCOG9501 reported comparable morbidity and equivalent survival outcomes between the two arms of treatment [96]. Following this negative results, D2-lymphadenectomy has remained the standard of care both in Western and Eastern countries. Extraregional/third-level node metastasis is included in stage IV disease according to the 8th edition of the TNM [2] and for these cases > D2 lymphadenectomy is suggested only in the setting of conversion surgery, in experimental settings and after neoadjuvant therapy [9, 11, 84]. However, the last edition of the Japanese guidelines [10] allows for the performance of upfront D2 plus lymphadenectomy in the following cases:

- Proximal GC that invades the larger curvature or with metastatic greater curvature nodes (splenectomy or D2 plus n.10);
- Distal GC with infrapyloric node metastases (D2 plus n.14v);
- GC invading the duodenum (D2 plus n.13).

Active phase III trials on > D2 lymphadenectomy are the Indian ELANCe trial (NCT02139605), investigating the role of D2 versus D3 lymphadenectomy after neoadjuvant therapy for patients with non-metastatic GC, the recently registered Italian Neo-D2plus (NCT03961373) trial, comparing D2 to D2 plus lymphadenectomy in patients with stage IIA-IIIC undergoing NAD therapy, and the Korean 14VIGTORY (NCT03264807) Trial, comparing D2 versus D2 plus 14v station in patients with T3N + and T4N + GC.

Omentectomy Omentectomy has traditionally been considered an essential component of curative-aim gastrectomy for advanced GC. Nevertheless, its impact on survival is controversial, and there are technical and theoretical advantages in preserving the omentum, especially during mini-invasive surgery [14, 97]. In 2016, the results of the prospective cohort OMEGA trial were reported. This trial investigated the presence of omental metastasis in 100 GC patients undergoing curative-aim gastrectomy. In the pathology specimens, the incidence of omental node metastasis was only 5%. Omental metastases occurred exclusively in patients undergoing R1 resection, and were significantly correlated with linitis plastica, location in the proximal third of the stomach, tumor diameter ≥ 5 cm, stage III–IV disease, and pM1 category [14]. Another 2016 study conducted on 50 advanced GC patients reported a rate of omental node metastases of 2% (1 patient free of disease at 20 months from surgery) and a rate of omental tumor deposits of 8% (4 patients of whom all died at 1 year, 3 of 4 for the development of peritoneal carcinomatosis) [97]. In 2019, a retrospective cohort study conducted on 284 patients documented a 1.8% incidence of omental node metastases, occurring only in patients with stage III–IV GC. The presence of omental node metastases was associated with tumor dimension > 5.25 cm, N stage, clinical stage, and venous invasion growth. The survival outcomes associated with omental metastases were recurrence in the peritoneum, liver, ovary, and death [98]. The survival outcomes associated with omentectomy are currently being investigated in the phase II Japanese RCT UMIN000005421 [99] and in the Chinese RCT TOP1 (NCT04108494).

Currently, the ESMO, NCCN and Korean guidelines do not give specific indications on omentectomy [8, 9, 11]. In the Japanese guidelines, omentectomy is indicated for ≥ T3 tumors, while the omentum more than 3 cm away from the gastroepiploic arcade may be spared for T1/T2 tumors [84].

Bursectomy Bursectomy has been associated with radical gastrectomy in Japan since the 1960s, but throughout the years, it remained a controversial procedure due to its uncertain survival benefit. Two recently updated systematic review and meta-analyses confirmed the non-significant association between the performance of bursectomy, overall survival, disease-free survival [100] and recurrence [101], while bursectomy increased the operative time [100, 101] and the intraoperative blood loss [101]. These results were confirmed by the final results of the phase III JCOG1001 trial, which investigated bursectomy versus omentectomy alone (no bursectomy) in patients with cT3/cT4a GC. The results reported no difference in 5-year overall survival and a significantly greater incidence of pancreatic fistula in bursectomy patients [15].

Membrane-anatomy surgery Following the standardization of the surgical oncology procedures based on the principles of embryology and membrane anatomy for rectal and colon cancer [102, 103], the performance of gastrectomy plus lymph node dissection based on the principles of membrane anatomy has recently been proposed [104, 105]. The anatomical landmarks of the mesogastrium have been

defined and a specific metastatic route (type V) of the GC cancer cells in the mesogastrium has been theorized, based on the hypothesis that an interruption in the envelop membrane of the mesogastrium could result in a leakage of cancer cells in the surgical field and the peritoneum. This leakage would increase the risk of locoregional recurrence [12]. One prospective study and one retrospective comparison study have been conducted to assess the safety and feasibility of gastrectomy plus mesogastrium excision, reporting no significant concerns and minor blood loss in patients undergoing mesogastrium excision [104, 105]. A Chinese phase III RCT (NCT01978444) comparing subtotal gastrectomy with standard D2 lymphadenectomy to subtotal gastrectomy with D2 lymphadenectomy plus complete mesogastrium excision (D2 + CME) in terms of 3Y DFS is currently ongoing [106].

Mini-invasive surgery

The use of mini-invasive (laparoscopic and robotic) techniques has been implemented in recent years, following the negative results of the extended surgery trials and the standardization towards a rigorous D2 technique. The theoretical advantages of laparoscopic gastrectomy (LG) are reduced postoperative pain, faster recovery of bowel function and shorter postoperative stay. The key points to address when validating this technical variant are the safety of the procedure and its oncologic equivalence (in terms of radicality) when compared to open gastrectomy [107].

The main setting in which LG has been validated so far is the treatment of early stage gastric cancer, which has less risk of node metastases and local recurrence. In the current ESMO guidelines, LG is accepted for early gastric cancer, while further evidences are required to validate laparoscopic gastrectomy in patients requiring D2 lymphadenectomy [9]. In the NCCN guidelines, LG is considered a feasible strategy that still requires further investigation [8]. In Korea, LG is the current standard for treatment of early gastric cancer according to the 2018 guidelines; in Japan, the latest Gastric Cancer Treatment Guidelines (2018, ver.5) accepts laparoscopic distal gastrectomy (LDG) for clinical stage I disease as the standard option [10]. These recommendations follow the results of many Eastern trials. Indeed, a Japanese phase II study, conducted on 176 cStage I patients (JCOG0703), reported a similar rate of AL and pancreatic fistula [108]. This trial was followed by a phase III study (JCOG0912), whose short-term results showed less bleeding, a shorter time to first flatus and less pain, but a longer operation time for the laparoscopic arm [109]. In Korea, the oncological safety of LDG compared to open distal gastrectomy (ODG) was tested in the KLASS-01 trial. Short-term outcomes were reported in 2016, demonstrating LDG safety and a lower occurrence of wound complications when compared to ODG [110]. Long-term results were reported in 2019, demonstrating non-inferiority to ODG according to the overall and cancer-specific survival rates [18]. The safety and feasibility of laparoscopic total gastrectomy for early GC has been investigated in the phase II KLASS-03 trial, whose results were recently published, reporting acceptable postoperative morbidity and mortality rate [17]. The JCOG1401 trial investigated the safety of laparoscopic total and proximal gastrectomy in the treatment of early GC. Its recently published results do not raise any safety concern for laparoscopic total/proximal gastrectomy [111]. Laparoscopic total gastrectomy for early GC is currently under investigation in the CLASS02-01 trial [112].

The use of laparoscopic gastrectomy for advanced gastric cancer (AGC) is more controversial and more cautiously applied. The Chinese CLASS-01 trial demonstrated the non-inferiority of LDG to open distal gastrectomy for patients with non-early gastric cancer. The short-term results of the CLASS-01 trial confirmed non-significant differences in morbidity and mortality between the two groups [113]. The long-term results confirmed its non-inferiority to the open technique from an oncological point of view, reporting comparable 3-year survival outcomes [16]. Other trials investigating the role of laparoscopic gastrectomy for the treatment of AGC are in progress. In Eastern countries, the JLSSG0901 (comparing laparoscopic versus open distal gastrectomy) and KLASS-02 trials (comparing laparoscopic and open distal gastrectomy) are ongoing. The phase II part of the JLSSG0901 demonstrated the safety and feasibility of LDG and the short-term results of the phase III of the trial demonstrated its non-inferiority in terms of complications [114, 115]. The short-term results of the KLASS-02 trial documented significant benefits of laparoscopy in terms of lower complication rate, faster recovery, and less pain when compared with OG [116]. However, the long-term results of these trials in terms of oncologic outcomes are still awaited. The KLASS-06 is an ongoing phase III RCT (NCT03385018) comparing D2 laparoscopic total gastrectomy and D2 open total gastrectomy proximal advanced gastric cancer. In the Western setting, the LOGICA trial and the STOMACH trial are ongoing [117, 118]. The LOGICA trial is a randomized clinical trial comparing laparoscopic and open total/subtotal gastrectomy in patients with resectable gastric cancer. Its primary outcome is the length of postoperative stay, while the secondary outcomes are postoperative morbidity and mortality, oncologic outcomes, readmissions, quality of life and cost-effectiveness [117]. The STOMACH trial is a RCT comparing the performance of neoadjuvant therapy followed by open or laparoscopic gastrectomy. Its primary endpoint is the quality of oncological resection, while its secondary outcomes include quality of life, postoperative complications, and cost-effectiveness of the procedures [118]. The recruitment of these trials is finished and the short-term results are expected soon.

Robot-assisted gastrectomy (RG) using the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA, USA) is a second mini-invasive technique that is being increasingly performed. RG has many theoretical advantages over LG. Indeed, it enables the performance of ergonomic mini-invasive surgery, thanks to the use of flexible robotic arms, to the availability of instruments with seven grades of freedom, to the possibility to eliminate the human tremor, and to a three-dimensional (3D) high-resolution vision. The drawbacks of RG are the loss for tactile feedback, the high costs, and the low availability [119]. The appropriateness of RG has been less investigated than that of LG, as no RCTs were conducted so far. In previous retrospective and prospective trials, RG showed longer operative time, greater total costs, but reduced blood loss compared to LG. No significant differences in overall survival, disease-free survival, overall complication and mortality rates, rates of open conversion, or length of hospital stay were detected [119]. It is has been suggested that robotic gastrectomy may provide some benefits for more complicated procedures (i.e., more advanced cancer disease with the need for D2 or D2 plus lymphadenectomy) [119] without clear evidences to support this statement. In the clinical practice, RG is increasing in both the Eastern and the Western settings [11, 120]. The key points to address in RCTs on RG are the clinical indications, the short- and long-term outcomes and the cost-effectiveness. Registered trials comparing RG and LG are the phase II Chinese NCT03524300 and **NCT03313700, the phase III Japanese** UMIN000031536 [121], and the multicenter international prospective trial IMIGASTRIC (comparing patients undergoing open, laparoscopic or robotic gastrectomy) [122].

Conclusions

In recent years, the treatment of GC has evolved within different fields. The pathological classification of GC is being refined through the valorization of specific cellular and stromal components, while the molecular approach is opening doors to a better understanding of GC behavior and to the development of more advanced targeted medicine. The surgical treatment is being standardized and is evolving according to new anatomical concepts and to the recent technological developments, including mini-invasive techniques and enhancers of the surgical performance (robotics, image-guided surgery). In the next years, these innovations are expected to substantially change the traditional approach to GC treatment.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, no informed consent is required.

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