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REVIEW ARTICLE

Global updates in the treatment of gastric cancer: a systematic review. Part 2: perioperative management, multimodal therapies, new technologies, standardization of the surgical treatment and educational aspects

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Abstract
Gastric cancer 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 · ERAS · Neoadjuvant therapy · Conversion surgery · Indocyanine green · Artificial intelligence

Introduction

Gastric cancer (GC), as 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 and molecular characterization of GC [3, 4]. There has been an increasing attention toward implementing the surgical technique on the base of anatomy and the natural history of disease [10, 12–18], aided by new technologies [19]. Lastly, the Western standard for perioperative chemotherapy has

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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 2, we summarize the updates relative to perioperative management, to different multimodal treatments (chemotherapy, chemoradiotherapy, targeted therapies, regional therapies), to the use of new technologies, including enhancers of the surgical performance and AI-based strategies, and to the standardization of the surgical treatment and of the surgical training.

Methods

This systematic review of the literature was conducted with 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 associated to the terms "gastric cancer" and/or "gastrectomy": "ERAS protocol", "ERAS", "fast-track", "ERAS guidelines", "nasogastric tube", "NG tube", "abdominal drain", "early feeding" "neoadjuvant therapy", "preoperative therapy", "adjuvant chemotherapy", "postoperative chemotherapy", "chemoradiotherapy", "HIPEC", "intraperitoneal chemotherapy", "peritoneal carcinomatosis", "conversion therapy", "conversion surgery", "extranodal metastasis", "NIPS", "bimodal chemotherapy", "new technologies", "indocyanine green", "near infrared imaging", "sentinel node", "image-guided surgery", "artificial intelligence", "machine learning", "deep learning", "support vector machine", "learning curve", "standardization", "high-volume", "hospital-volume".
- The abstract was 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 included 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.

Perioperative management: ERAS protocol applied to gastrectomy

Enhanced recovery after surgery (ERAS) protocols consist of a bundle of recommended perioperative management strategies that have the aim to promote patients' postoperative recovery by reduction of the surgical stress response and organ dysfunction. The ERAS society (www.erassociety.org) is a scientific society born in 2001 to develop research around the ERAS protocol and produce international guidelines for perioperative protocols in different fields of surgery. The ERAS guidelines on gastrectomy were published in 2014 [32]. They are divided into two parts, the "general" enhanced recovery items and the "procedure-specific" guidelines, focused on the need to balance the ERAS measures and the gastrectomy-specific associated risks. After 2014, the application of the ERAS guidelines has been investigated by various studies that compared patients managed with the ERAS protocol with patients managed with standard perioperative protocols. The main points of controversy have been the safety of the ERAS protocol in terms of complications and readmission, administration of preoperative nutrition, need for a nasogastric/nasojejunal (NG/NJ) decompression tube, early oral feeding, positioning of drains in light of the risk of lymphatic fistulas/pancreatic leaks and indications for laparoscopic surgery.

The safety and effectiveness of the ERAS gastrectomy protocol have been investigated in various recent RCTs and meta-analyses. In a Japanese 2017 RCT, patients managed with the ERAS protocols had shorter postoperative stay, increased postoperative physical activity, lower rate of postoperative complications of grade III or higher and reduced costs of hospitalization [33]. A Chinese RCT investigated the feasibility and safety of laparoscopic radical gastrectomy within ERAS programs. This trial confirmed a shorter return to normal diet, time to the first defecation and postoperative stay, without significant differences in postoperative complications and C-reactive protein levels. The results of a recent small Chinese RCT, conducted on 60 patients undergoing radical gastrectomy, reported that the ERAS protocol leads to faster recovery and shorter postoperative hospital stay when compared with the standard protocol, with shorter time to first flatus, defecation and resumption of

the oral feeding, and lower rate of postoperative complications. These authors also documented higher postoperative serum albumin and pre-albumin, IGM, IgG, T-lymphocytes and lower postoperative C-reactive protein and neutrophil count [34]. Another RCT recently investigated the feasibility and safety of laparoscopic radical gastrectomy within ERAS programs in locally advanced gastric cancer patients (T2-4, any *N*, M0) In this study, the time to return to normal diet the first defecation and postoperative stay were significantly shorter in the ERAS group, and the protocol was safe and feasible [35]. A recent Korean RCT tested the safety of the ERAS protocol in the perioperative management of total laparoscopic distal gastrectomy. Its results documented that the ERAS protocol was safe and that the ERAS arm had a faster recovery time and significantly less pain through postoperative days 1–4, without any difference in complications, mortality and readmission [36]. The results of recent meta-analyses consistently report reduced length of postoperative stay, reduced cost associated with the application of ERAS protocols and no effect on postoperative complications, but there was no accordion on the rate of readmission. Indeed, Ding et al. reported shorter time to first flatus, reduced levels of C-reaction protein and interleukin-6, reduced postoperative stay and reduced costs for ERAS, but an increased readmission rates for ERAS patients [37]. Wang et al. reported that ERAS protocols significantly decreased the length of postoperative stay and the medical costs, the time to first flatus and defecation, the serum inflammatory response, and increased short-term quality of life (QOL). No difference was observed in the rate of total complications and ≥ grade III complications, apart from the incidence of pulmonary infection that was significantly reduced in ERAS patients. However, the readmission rate after GC surgery nearly tripled in the ERAS arm [38]. Liu et al. found a shorter postoperative hospital stay, an earlier first flatus, lower level of postoperative C-reactive protein (CRP) and cost reduction for ERAS patients. No effect on postoperative complications was observed [39]. Two authors focused on the outcomes of ERAS in patients undergoing laparoscopic gastrectomy, detecting shorter postoperative stay and minor costs for patients in the ERAS arm, but no significant difference in time to first flatus [40], complication rate [40, 41] or rate of readmission rate [41]. The most recent and largest meta-nalysis of RCT (14 studies) and high-quality prospective (6 studies) and retrospective (3 studies) studies from Wee et al. alongside the good results in terms of reduction of the hospital stay and costs and of the reduction in the return of the gut function, noticed no significant impact of ERAS on postoperative complications and confirmed a significant highest rate of 30 days readmission in the ERAS group [42].

Preoperative artificial nutrition is not recommended in the ERAS guidelines (very low evidence) except for severely malnourished patients [32]. In 2017, a Chinese prospective study confirmed that the group of patients with malnourishment, when compared to well-nourished patients, is a subgroup at significant risk of incision infection and with significantly lower 3-year OS and DFS rates. In the group of malnourished patients, the correction of preoperative hypoproteinemia led to a significant reduction in incision infection in all patients and a significant effect on OS and DFS in stage II–III patients [43].

Decompression by NG/NJ tubes is strongly discouraged by the ERAS guidelines (high evidence) [32]. One Japanese RCT published in 2017 documented no significant difference in the rate of complications between patients undergoing 1-day NG tube decompression after distal gastrectomy, and a greater physical discomfort in patients with the NG tube [44]. A 2015 meta-analysis investigating postoperative outcomes in patients with or without NG/NJ tube decompression, stratified by the type of gastrectomy or gastrojejunostomy, found no significant differences in postoperative complications in the NG/NJ tube group. The no-NG/NJ group displayed a significantly shorter time to oral diet and shorter end of hospital stay [45].

The positioning of drains is also discouraged in ERAS guidelines (high evidence) [32]. In 2015, an updated meta-analysis of RCTs from the Cochrane Collaboration did not find any significant difference between the drain and no-drain group in mortality, re-operations, morbidity, anastomotic leak rate or initiation of soft diet. Moreover, the addition of a drain prolonged the operation time and the post-operative hospital stay, even if the difference was significant only for patients undergoing subtotal gastrectomy after the subgroup analysis. However, the level of evidence for this topic was defined between low and very low, and only four RCTs were included [46].

The ERAS guidelines promote early oral feeding after gastrectomy (moderate evidence) [32]. In 2018, a Japanese RCT investigated patients undergoing early or delayed oral feeding following distal and total gastrectomy. While the TG group showed advantages in the length of postoperative stay, this subgroup did not reach the target sample size. Patients in the distal gastrectomy group had no shorter postoperative stay, and they showed a greater incidence of postoperative complications [47]. A recently reported Chinese RC T (SOFTY-1) compared patients undergoing total laparoscopic radical gastrectomy receiving early or delayed oral feeding. The results reported a significantly lower postoperative stay in the early feeding group and no significant differences in morbidity between groups [48]. In 2019, a systematic review of RCTs assessing the evidence of safety and benefits of early oral feeding after gastrectomy in patients with gastric cancer was published. Early oral feeding was associated with decreased length of hospital stay time to first flatus, without increasing the postoperative complication risk [49].

The ERAS guidelines also suggest the use of laparoscopic surgery, with respect to the current indication for oncological surgery [32]. Accordingly, laparoscopic distal gastrectomy is progressively becoming the standard treatment for early gastric cancer; while, results for advanced GC are still awaited and, therefore, the recommendation could not be extended so far [50].

No mention of the ERAS guidelines is present in the current Western or Korean guidelines. In the latest Japanese guidelines, some recommendation on the early removal of the NG/NJ tube and the early feeding have been introduced [10]. This is probably due to the fact that the specific evidence for some of the items of the ERAS protocol is somewhat controversial. Moreover, it is still unclear how all the reported evidences are related to distal or to total gastrectomy. A last matter of concern for the full application of the ERAS protocol in the Western setting is that most of the recent trials validating the ERAS protocol were conducted in Eastern countries [49, 50]. Active RCTs bond to clarify some of the current issues are the Japanese NCT03079596 (ERAS Protocol after Laparoscopic Total Gastrectomy and Proximal Gastrectomy) and the Chinese NCT03160924 (Impact of ERAS Program on Clinical Immunological Outcomes for Minimally-invasive Gastrectomy).

In conclusion, the number of high-quality studies reporting on the application of the different ERAS items is still scant. The recent publication of the guidelines, united to some resistance to the full application of the items of the ERAS protocol in the different centers, seems the principal limit [41]. The ERAS protocol proved benefits overall, as the reduction in the time of bowel recovery, and a reduction in postoperative complications, in the postoperative stay and in the medical costs. However, there were some reports of increased readmission rates after the application of the protocol. Further high-quality studies and RCTs are needed to clarify the safety issues and validate the previous results.

Multimodal therapies

5a) Neoadjuvant/preoperative therapy: In Western countries, the standard treatment for advanced gastric cancer is multimodal, including perioperative therapy in adjunct to radical surgery [51, 52]. The recommendation for perioperative chemotherapy mostly derives from previous trials (the MAGIC and FNCLCC/FFCD 9703 trials), that compared patients undergoing NAD (with epirubicin–cisplatin–fluorouracil, ECF, and cisplatin–fluorouracil, respectively) and patients undergoing upfront surgery, detecting an overall survival benefit in patients undergoing the NAD protocols. The results of these trials, however, are still controversial, as they included many patients with gastroesophageal junction tumors and patients treated by inadequate surgery (D0 and D1 lymphadenectomy) [53–55]. In particular, concern has been raised for the treatment strategy of patients with GC subtypes that are poorly responsive to conventional chemotherapy regimens, in particular the signet ring cell subtype and the MSI subtype [56, 57]. A French phase II/III multicenter trial evaluating the efficacy of NAD with ECF in resectable SRC gastric cancer is currently ongoing (NCT01717924). The recent phase II/II FLOT4 trial compared NAD with ECF/ECX to NAD with the triplet fluorouracil–oxaliplatin–docetaxel (FLOT) in gastroesophageal cancer and GC resectable patients. In 2016, the results of the phase II part of the FLOT4 trial were published, reporting that the FLOT regimen was superior to ECF/ECX in terms of complete pathological regression [58]. In 2019, the results of the phase III part of the FLOT4 trial were reported. The FLOT regimen significantly increased the resection rate after NAD, the overall survival and the disease-free survival with acceptable toxicity [59]. Since the publishing of its results, the FLOT regimen became the new therapeutic standard for perioperative chemotherapy. To note, in the FLOT4 trial, the comparison arm did not include patients undergoing upfront surgery (the trial compared the FLOT and ECF regimens). The subgroup analysis of the trial documented a significant advantage in survival only for the intestinal histotype (Tables 1, 2 and 3).

In Eastern countries, the evidence for resectable GC currently favors the performance of upfront D2 gastrectomy followed by adjuvant therapy [11, 60]. However, the role of NAD is being investigated, as the prognosis for stage III gastric cancer is considered unsatisfactory even after D2 gastrectomy and adjuvant chemotherapy [60]. Results from the Japanese phase II COMPASS trial showed a 10% rate of complete pathologic response after NAD with four cycles of S1/cisplatin or paclitaxel/cisplatin regimens in patients with resectable GC [61] and the long-term results of this trial reported a 3-year survival of > 60% [62]. Instead, the phase III JCOG0501, specifically conducted on the population of patients with type III/IV Borrmann GC, did not demonstrate a significant survival benefit for the adjunction of NAD with S1/cisplatin when compared to upfront surgery followed by S1 adjuvant chemotherapy [63]. A subgroup analysis of this trial reported that a survival advantage was present only in patients with an non-signet ring histology [64]. The phase III NAGISA trial (JCOG1509) trial is evaluating the efficacy of NAD with S1/oxaliplatin followed by adjuvant S1, compared to adjuvant S1 alone or S1 plus docetaxel in cT3-4N1-3M0 gastric cancer [65]. In Korea, a phase II trial of NAD docetaxel–oxaliplatin–S1 (DOS) followed by surgery and adjuvant S1 in cStage II/III GC patients reported a 97.6% R0 resection rate and a 90% 2-year disease-free survival [66]. The phase III PRODIGY trial (NCT01515748) is comparing NAD DOS with upfront surgery for patients with cStage II/

Table 1 Recent phase II/III trials evaluating neoadjuvant therapy

Title	Authors/PI	Status	Publication year	Country	Phase	Population	Intervention	Control	Results
MAGIC	Cunningham D	Completed	2006	UK	III	Resectable adenoca of stomach, EG junction, or lower esophagus	ECF + surgery + ECF ($n=250$)	Surgery alone ($n=253$)	OS 5-year: 36% v 23%; HR: 0.75; 95% CI 0.60 to 0.93 ($p=0.009$)
FNCLCC/FFCD	Ychou M	Completed	2011	FR	III	Resectable adenoca of stomach, EG junction, or lower esophagus	5-FU/C preop + surgery + 5-FU/C postop ($n=113$)	Surgery alone ($n=111$)	OS 5-year: 38% v 24%; HR: 0.69; 95% CI 0.50 to 0.95 ($p=0.02$) DFS 5-year: 34% v 19%; HR; 0.65; 95% CI 0.48 to 0.89 ($p=0.003$) Curative resection rate: 84% v 73% ($p=0.04$)
PRODIGE 19	Piessen G	Ongoing	2013	FR	II/III	Stage IB–III gastric signet ring cell tumour	Perioperative CT (2×3 cycles of ECF) + surgery	Primary surgery + adjuvant CT (6 cycles of ECF)	
FLOT 4	Al-Batran SE	Ongoing	2016	DE	II	Locally advanced resectable gastric or EG junction cancer	FLOT + surgery ($n=128$)	ECF/ECX + surgery ($n=137$)	Pathological complete regression: 16% v 6%; 95% CI ($p=0.02$)
FLOT 4	Al-Batran SE	Completed	2019	DE	III	Locally advanced resectable gastric or EG junction cancer	FLOT + surgery ($n=356$)	ECF/ECX + surgery ($n=360$)	OS increased in the FLOT group compared with the ECF/ECX group; HR 0.77; 95% CI 0.63 to 0.94 Median OS: 50 months vs 35 months
COMPASS	Yoshikawa T	Ongoing	2014	JP	II	Locally advanced resectable gastric cancer	Arm A: 2 courses of S-1/C ($n=21$) Arm B: 4 courses of S1/C ($n=20$)	Arm C: 2 courses of P/C ($n=21$) Arm D: 4 courses of P/C ($n=21$)	Pathological response rate was 43% in arm A, 40% in arm B, 29% in arm C, and 38% in arm D Pathological complete response was only observed in arms B (10%) and D (10%)
COMPASS	Yoshikawa T	Ongoing	2016	JP	II	Locally advanced resectable gastric cancer	Arm A: 2 courses of S-1/C ($n=21$) Arm B: 4 courses of S1/C ($n=20$)	Arm C: 2 courses of P/C ($n=21$) Arm D: 4 courses of P/C ($n=21$)	OS 3-year: 60.9% for SC v 64.3% for PC; 64.3% for the 2 courses v 61.0% for the 4 courses

Table 1 (continued)

Title	Authors/PI	Status	Publication year	Country	Phase	Population	Intervention	Control	Results
JCOG0501	Terashima M	Completed	2019	JP	III	Linitis plastica (type 4) and large (≥ 8 cm) ulcero-invasive-type (type 3) gastric cancer	S1/C + surgery + AdCT ($n = 151$)	Surgery + S-1 AdCT ($n = 149$)	No significant differences in Grade 2–4 morbidity and mortality (15.8% v 25.2% and 0.7% v 1.3% respectively)
NAGISA (JCOG1509)	Tokunaga M	Ongoing	2017	JP	III	Locally advanced resectable gastric cancer	S1/oxaliplatin + surgery + adjuvant S1	Surgery + adjuvant S1 or Surgery + S1 plus docetaxel	
DOS trial	Park I	Completed	2013	KO	II	Resectable adenoca of stomach or EG junction	DOS + surgery + S1 ($n = 41$)		R0 resection: 97,6% DFS 2-year: 90%
PRODIGY (NCT01515748)	Kang Y-K	Ongoing	2015	JP	III	Resectable locally advanced adenoca of stomach or EG junction	DOS + surgery	Upfront surgery	
CROSS	Shapiro J	Completed	2015	NE	III	Resectable locally advanced cancer of the oesophagus or EG junction	carboplatin/paclitaxel/RT + surgery ($n = 178$)	Surgery alone ($n = 188$)	Median OS: 48.6 months v 24.0 months ($p = 0.003$)
TOPGEAR	Leong T	Ongoing	2017	AU/NZ /EU/CA	III	Gastric and EG junction adenoca	ECF with 5-FU/RT + surgery + ECF	ECF + surgery + ECF	NAD therapy completion rate: 98% v 93% Adjuvant therapy completion rate: 53% v 65% Proceeding to surgery rate: 85% v 90%
Neo-AEGIS	Reynolds J V	Ongoing	2017	IR	III	Locally advanced adenoca of the oesophagus and EG junction	ECF + surgery + ECF	carboplatin/paclitaxel/RT + surgery	
ESOPEC	Hoeppner J	Ongoing	2016	DE	III	Localized esophageal adenocarcinoma	FLOT + surgery	carboplatin/paclitaxel/RT + surgery	
CRITICS II	Slagter AE	Ongoing	2018	NE	II	Resectable gastric adenocarcinoma	Arm A: 4 cycles of DOC	Arm B: 2 cycles of DOC + carboplatin/paclitaxel/RT Arm C: carboplatin/paclitaxel/RT	

Table 2 Recent phase II/III trials evaluating adjuvant therapy

Title	Authors/PI	Status	Publication Year	Country	Phase	Population	Intervention	Control	Results
CLASSIC	Bang Y-J	Completed	2013	KO	III	Locally advanced gastric cancer	Surgery (D2 resection) + capecitabine/oxaliplatin ($n=520$)	Surgery alone (D2 resection) ($n=515$)	DFS 3-year: 74% v 59%; HR: 0.56; 95%CI: 0.44–0.72 ($p<0.0001$)
ACTS-GC	Sakuramoto S	Completed	2007	JP	III	Locally advanced gastric cancer	Surgery (D2 resection) + S1 ($n=529$)	Surgery alone (D2 resection) ($n=530$)	OS 3-year: 80.1% v 70.1%; HR: 0.68; 95%CI: 0.52–0.87 ($p=0.003$)
JACCRO GC-07	Yoshida K	Ongoing	2019	JP	III	Pathologic stage III gastric cancer	Surgery + S1/docetaxel (n = 454)	Surgery + S1 (n = 459)	Relapse-FS 3-year: 66% v 50%; HR: 0.632; 99.99% CI 0.400–0.998 ($p<.001$)
INT-0116	Macdonald JS	Completed	2001	US	III	≥ T3 and/or node-positive gastric cancer	Surgery + 5-FU/LV/RT ($n=281$)	Surgery alone ($n=275$)	Median OS: 36 months v 27 months; HR: 1.35; 95%CI: 1.09–1.66 ($p=0.005$) Updated analysis (2012): OS and RFS data demonstrate continued strong benefit from postoperative RT-CT HR for OS: 1.32 (95% CI 1.10 to 1.60; $p=0.0046$) HR for RFS: 1.51 (95% CI 1.25 to 1.83; $p<0.001$)
ARTIST	Park SH	Completed	2015	KO	III	D2-resected gastric cancer	Surgery (D2 resection) + capecitabine/cisplatin/RT ($n=230$)	Surgery (D2 resection) + capecitabine/cisplatin ($n=228$)	OS 5-year: 75% v 73%; HR: 1.130; 95% CI 0.775 to 1.647 ($p=0.5272$) [Subgroup analyses] CT-RT significantly improved DFS 3-year in: - N + disease: 76% v 72% ($p=0.04$) - Intestinal-type GC: 94% v 83% ($p=0.01$)
ARTIST II	Park SH	Ongoing	2019	KO	III	Node-positive, D2-resected gastric cancer	Surgery (D2 resection, N + only) + capecitabine/cisplatin/RT	Surgery (D2 resection, N + only) + capecitabine/cisplatin	
CRITICS	Cats A	Ongoing	2018	NE	III	Stage IB–IVA resectable gastric or EG adenoca	ECX/EOX + surgery + capecitabine/cisplatin/RT ($n=245$)	ECX/EOX + surgery + ECX/EOX ($n=233$)	Median OS: 37 months v 43 months; HR from stratified analysis 1.01; 95% CI 0.84–1.22 ($p=0.90$)

Table 3 Recent phase II/III trials evaluating conversion surgery

Title	Authors/PI	Status	Publication Year	Country	Phase	Population	Intervention	Control	Results
JCOG0405	Tsuburaya A	Completed	2014	JP	II	Gastric cancer with bulky lymph node (BN) and/or PAN metastasis	S1/cisplatin + gastrectomy with D2 plus PAN dissection ($n=51$)		R0 resection rate: 82% Clinical and pathological response rates: 65% and 51% OS 3-year and 5-year: 59% and 53%
JCOG1002	Takahari D	Completed	2019	JP	II	Gastric cancer with bulky lymph node (BN) and/or PAN metastasis	S1/cisplatin/docetaxel + gastrectomy with D2 plus PAN dissection + S1 ($n=53$)		OS 5-year: 54.9% Relapse-FS 5-year (among 44 eligible patients with R0 resection): 47.7%
JCOG1704	Hashimoto T	Ongoing	2018	JP	II	Advanced gastric cancer with extensive lymph node metastasis	Docetaxel/oxaliplatin/S1 + surgery		
FLOT3	Al-Batran S-E	Completed	2017	DE	II	Resectable or metastatic gastric or EG junction adenoca	Arm A, resectable: FLOT + surgery + FLOT ($n=51$)	Arm B, limited metastatic: FLOT + surgery (if a chance of R0) ($n=60$) Arm C, extensive metastatic: FLOT + surgery (if required for palliation) ($n=127$)	Median OS: 22.9 months for arm B, 10.7 months for arm C ($p<.001$) Response rate: 60% for arm B (complete 10%; partial 50%), 43.3% for arm C In arm B, 36 of 60 patients (60%) proceeded to surgery. Median OS: 31.3 months for patients who proceeded to surgery, 15.9 months for the other patients
RENAISSANCE/FLOT5	Al-Batran S-E	Ongoing	2017	DE	III	Gastric and EG junction limited-metastatic adenoca	FLOT or FLOT/Trastuzumab + surgery	FLOT or FLOT/Trastuzumab + CT prosecution	

III GC [67]. The recruitment of PRODIGY is completed, and its long-term results are expected in 2022.

The results of a phase III RCT investigating the role of NAD chemoradiotherapy versus upfront surgery in the treatment of resectable esophageal or EGJ cancer (CROSS trial) were presented in 2015 [68]. Patients treated with CRT had a higher R0 resection rate than patients treated with surgery alone and 29% of patients showed a pathological complete response (23% in patients with adenocarcinoma and 49% in patients with squamous cell carcinoma). A doubling of the median overall survival was observed in patients treated with NAD chemoradiotherapy (24 months vs. 49.9 months, $p = 0.003$). Based on the results of this trial, NAD chemoradiotherapy became the preferred approach for localized adenocarcinoma of the EGJ (Siewert I and II) in the United States [8]. The TOPGEAR trial is currently comparing two groups of patients with gastric and gastroesophageal carcinoma, one treated with NAD ECF followed by chemoradiation and another treated with NAD ECF. The interim results were reported in 2017. Patients undergoing NAD chemoradiotherapy and chemotherapy had a NAD therapy completion rate of 98% (chemoradiation group) and 93% (ECF group) and an adjuvant therapy completion rate of 53 and 65%, respectively. Patients proceeding to surgery were 85% in the chemoradiation group and 90% in the ECF group. The complication rate was similar [69]. Both the ICORG 10–14/NeoAegis and ESOPEC trials are comparing patients with esophageal and esophagogastric adenocarcinoma undergoing NAD chemotherapy according to the MAGIC (NeoAegis) or the FLOT (ESOPEC) protocol vs. chemoradiotherapy according to the CROSS protocol, with survival as the main outcomes [70, 71]. The CRITICS II trial is a three-arm phase II RCT testing the safety and feasibility of (1) NAD chemotherapy followed by surgery versus (2) NAD chemotherapy and subsequent chemoradiotherapy followed by surgery versus (3) NAD chemoradiotherapy followed by surgery, in resectable gastric cancer [72].

Even for the administration of NAD chemoradiotherapy, there are some evidences of the reduced sensitivity of certain GC subtypes. Indeed, some studies reported a worse response to preoperative chemoradiotherapy in patients with esophagogastric tumors with a SRC phenotype and a reduced response in patients with localized GC with a greater proportion of SRCs [31].

5b) Adjuvant/Postoperative therapy: The role for adjuvant chemotherapy after gastrectomy has been investigated in the Eastern CLASSIC, Japanese ACTS-GC and the JACCRO GC-07 trials. The CLASSIC trial (2012) investigated the administration of postoperative capecitabine plus oxaliplatin after D2 gastrectomy [73]. The ACTS-GC (2007) investigated the administration of S1 monotherapy after D2 gastrectomy [74]. The JACCRO GC-07 compared postoperative S1 plus docetaxel to S1 alone in patients with stage III GC. Its interim results were recently reported (2019), demonstrating a survival advantage for the combination regimen [75]. Following these results, in Korea, S1 or adjuvant capecitabine plus oxaliplatin (XELOX) after curative D2 gastrectomy is considered the standard of treatment, while in Japan, S1 postoperative chemotherapy is the standard adjuvant treatment for stage II patients and S1 plus docetaxel the standard adjuvant therapy for stage III patients [10, 11].

The survival benefit of postoperative chemoradiotherapy over observation alone after < D2 lymph node dissection was demonstrated in the US INT-0116 trial [76]. In the 10-year update of the INT-0116 trial, the survival benefit was confirmed in almost all subgroups, except for diffuse cancers [77]. Instead, the Korean phase III ARTIST trial showed that adjuvant chemoradiotherapy was ineffective after standard D2 lymph node dissection [78]. However, in accordance with the update of the INT-0116 trial, the subgroup analysis of the ARTIST trial documented a survival benefit for adjuvant chemoradiotherapy in intestinal and pN1–3 patients [78]. For this reason, the phase III ARTIST II trial is currently investigating the role of adjuvant S1 versus S1/oxaliplatin vs chemoradiotherapy in node-positive patients (and the Lauren histotype has been included in the randomization criteria). The interim results of the ARTIST II trial were reported in 2019, documenting no safety concerns for all the adjuvant treatments proposed [79]. The recent European phase III CRITICS trial, which randomized between NAD chemotherapy and gastrectomy followed by post-operative chemotherapy or post-operative chemoradiotherapy, demonstrated no survival benefit from adding radiotherapy to perioperative chemotherapy after D1 + or D2 lymph node dissection. This trial also documented a high rate (> 40%) of grade 3–4 adverse events during postoperative treatment in both arms, and concluded that future studies should focus on optimizing preoperative treatment strategies [80].

In Western countries, according to the ESMO guidelines, patients undergoing upfront surgery should be considered for the administration of adjuvant chemoradiotherapy in addition to adjuvant chemotherapy [8, 9]. In the NCCN guidelines, the standard postoperative regimen after < D2 gastrectomy is postoperative chemoradiotherapy and the standard after D2 lymphadenectomy is XELOX chemotherapy [8]. In the Korean guidelines, the adjunct of chemoradiotherapy is a possible addition to postoperative chemotherapy, especially in patients with node-positive disease, and is strongly suggested for patients with less than D2 lymphadenectomy [11].

5c) Conversion surgery: conversion surgery describes "a surgical treatment aiming at an R0 resection after chemotherapy for tumors that were originally unresectable or marginally resectable for technical and/or oncological reasons". In the original proposal for conversion surgery,

this treatment was considered feasible only for patients with hepatic or extraregional nodal metastases, excluding patients with peritoneal carcinomatosis [81]. In Japan, most studies on conversion surgery focused on the treatment of extensive node metastases (ELM). In particular, the phase II JCOG0405 investigated the role of preoperative chemotherapy with S1 plus cisplatin followed by radical surgery in patients with ELM, reporting a R0 resection rate of 82% and a 3-year survival rate of 59% [82]. Instead, the phase II JCOG1002 investigated the addition of docetaxel to the S1 plus cisplatin regimen, but the response rate and long-term survival benefits were not satisfactory [83]. A phase II trial (JCOG1704) investigating the preoperative triplet docetaxel–oxaliplatin–S1 in patients with ELM is being planned [84]. In Europe, conversion therapy was investigated in the phase II FLOT3 trial. This trial stratified patients with operable (M0) patients, limited metastatic disease (distant nodes, < 5 liver lesions, no visible carcinomatosis), or extensive metastatic disease. All patients received perioperative FLOT. Patients with limited metastatic disease who received NAD chemotherapy and proceeded to surgery (60% of patients with limited disease and 15% of the entire study population) had better survival than patients not undergoing gastrectomy (median OS 31.3 months vs 15.9 months) [85]. Based on these results, the ongoing Phase III RENAISSANCE/FLOT5 trial aims to evaluate the effects of upfront chemotherapy with 4 cycles of FLOT/FLOT + Trastuzumab followed by randomization to undergo (1) curative gastrectomy/esophagectomy and resection of metastatic lesions or local ablation procedure versus (2) chemotherapy prosecution, in the limited metastatic setting [21].

5d) Molecular therapy: available molecular drugs currently approved for the treatment of GC are trastuzumab, ramucirumab, regorafenib, pembrolizumab and nivolumab.

The use of Trastuzumab (anti-HER2 antibody) as a first-line agent for HER2 positive patients in the metastatic or recurrent setting is approved worldwide after the results of the ToGa trial [5]. Instead, its use in the neoadjuvant setting for HER2 + patients is being investigated in the three-arm phase II INNOVATION trial (standard preoperative CT vs. preoperative CT plus trastuzumab vs. preoperative CT plus trastuzumab and pertuzumab-a HER dimerization inhibitor) [86]. In the conversion setting, the phase II JCOG1301 trial is comparing S1 plus cisplatin plus trastuzumab to S1 plus cisplatin alone for patients with HER2 + GC with ELM [87].

The VEGF-A inhibitor Bevacizumab has no current role in the treatment of GC, after the non-significant results in the neoadjuvant (UK Medical Research Council ST03 [88]) and palliative first-line (AVAGAST and AVATAR trials [89, 90]) settings.

The use of ramucirumab (anti-VEGFR2 antibody) in the second-line setting, alone or in combination with weekly paclitaxel, was associated with increased overall survival in the REGARD and the RAINBOW trials, respectively [6, 7]. In the neoadjuvant setting, ramucirumab is being investigated in the RAMSES/FLOT7 study that compares FLOT vs. FLOT/Ramucirumab for Perioperative Therapy of Gastric or GEJ Cancer (RAMSES) [22].

Regorafenib, an oral multi-tyrosine kinase inhibitor, demonstrated increased progression-free survival in first-line resistant GC in the phase II INTEGRATE trial [91]. It is currently being evaluated in the randomized phase III trial INTEGRATE II (NCT02773524; arm 1: regorafenib, arm 2: placebo).

The PD1–PDL1 immune checkpoint inhibitors (anti-PD1 antibodies) pembrolizumab and nivolumab have been recently investigated in the third-line setting in the cohort 1 of the phase II KEYNOTE-059 trial (pembrolizumab) and in the phase III ATTRACTION-2 trial (nivolumab vs. placebo) [92]. Results of the cohort 1 of the KEYNOTE-059 trial documented a Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST) objective response rate of 11.6% (30/259 patients), with a complete response in 2.3% (6/259 patients). The median response duration (absence of progressive disease) was 8.4 months. The objective response rate and response duration were comparable in PDL1-positive and -negative patients, but PDL1-positive patients had a [93]. Results of the ATTRACTION-2 trial documented a significant increase in median overall survival in the nivolumab arm. The post hoc subgroup analysis did not document a significant difference in survival between PDL1-positive and PDL1-negative patients [94]. Pembrolizumab was investigated in the second-line setting in the phase III KEYNOTE-061 trial (pembrolizumab vs. paclitaxel in patients with PDL1 CPS > 1). In this trial, the difference in overall survival between the two arms was not significant (one-sided $p = 0{\cdot}0421$) but pembrolizumab showed a better safety profile [95]. Pembrolizumab was investigated in the first-line setting in the cohorts 2 and 3 (cohort 2—combination therapy of pembrolizumab, cisplatin and 5-fluorouracil or capecitabine, cohort 3—monotherapy) of the KEYNOTE-059 trial. The results demonstrated a RECIST objective response rate of 60.0% and 25.8% in cohorts 2 and 3, respectively [96]. In the adjuvant setting, the role of nivolumab is currently being investigated in the phase III ATTRACTION-5 (NCT03006705) trial, comparing S1 or XELOX plus either nivolumab or placebo in patients with pStage III G/EGJ cancer after D2 or > D2 lymphadenectomy. In the neoadjuvant setting, the role of pembrolizumab in adjunct to perioperative therapy is being investigated in the phase III KEYNOTE-585 (NCT03221426) trial, which compares preoperative cisplatin plus 5-FU or S1 or FLOT plus pembrolizumab (arm 1) or cisplatin plus 5-FU or S1 or FLOT plus placebo (arm 2) in patients with resectable GC [23].

In the ESMO guidelines, the use of ramucirumab is currently approved as a second-line treatment in metastatic or recurrent GC [9]. In the NCCN guidelines, ramucirumab is approved in the second-line setting, the use of pembrolizumab is approved in the second-line setting in patients with MSI/dMMR and in the third-line setting in patient with CPS ≥ 1 [8]. In the Korean and Japanese guidelines, ramucirumab is the second-line standard of treatment and nivolumab is the drug of choice in the third-line setting [10, 11].

5e) Regional therapies: regional therapies including intraperitoneal chemotherapy have been considered in the prophylactic, cytoreductive or conversion setting due to the specific tropism of GC to the peritoneum, which sometimes is its exclusive route of diffusion [24].

In the prophylactic setting, previous Western RCTs did not prove a benefit for HIPEC [24–26], while some promising results were detected in Japanese RCTs [27, 28]. It was advocated that the negative results of the Western RCTs were due to inappropriate selection of included patients [24]. However, a recent meta-analysis including mostly Eastern RCTs failed to prove a significant role of prophylactic HIPEC in increasing survival and diminishing the risk of peritoneal recurrence in the RCT arm, even if a tendency toward significance was documented [97]. A recently reported Chinese randomized case–control study showed a significantly higher 3-year DFS rate (93 vs 65%) and lower peritoneal recurrence rate (23 vs 3%) for prophylactic HIPEC versus standard resection [98]. In Europe, the GASTRICHIP trial, a phase III multicenter RCT, is currently testing the survival benefit of HIPEC as an adjunct to perioperative therapy and D1/D2 gastrectomy in stage II–IV patients GC at high risk of peritoneal diffusion (GC involving the serosa and/or with lymph node involvement and/or with positive cytology) [99]. The recently registered GOETH trial (NCT03917173) will evaluate the survival benefit of CO_2 HIPEC as an adjunct to surgery in stage II–IV patients with high risk of PC (cT3–4 or *N* + perforation or positive cytology) [100].

HIPEC has been investigated in the cytoreductive setting as well. Two phase II trials investigating HIPEC in adjunct to gastrectomy in patients with limited peritoneal stage IV disease are currently ongoing in the US (NCT02891447 and NCT03092518). In Europe, the phase I–II trial PERISCOPE I evaluated the safety and feasibility of a procedure combining gastrectomy, cytoreductive surgery (CRS) and HIPEC with oxaliplatin followed by docetaxel. Its results were reported in 2018 and confirmed the safety and feasibility of the intraperitoneal administration of these drugs, combined with a stringent post-operative care protocol [101]. The Phase III RCT PERISCOPE II is currently ongoing [102]. PERISCOPE II aims to compare the administration of palliative systemic chemotherapy only versus gastrectomy, CRS and HIPEC after neoadjuvant chemotherapy in patients with Stage IV disease limited to the peritoneum (with positive cytology or limited peritoneal disease—PCI < 7). The GASTRIPEC trial (NCT02158988) is comparing CRS + HIPEC with CRS alone in patients with gastric cancer and synchronous peritoneal carcinomatosis undergoing perioperative chemotherapy. In Korea, a phase Ib/II trial on upfront CRS + HIPEC is ongoing (NCT02995850).

Finally, HIPEC has been investigated in the setting of conversion surgery. In the US, Badgwell et al. conducted a phase II trial to investigate laparoscopic HIPEC as an adjunct to chemotherapy in 19 stage IV patients (with positive cytology or occult peritoneal carcinomatosis). They reported that the procedure was safe, feasible, and repeatable and that patients had median OS of 20.3 months [103]. A following paper from the same group reported that laparoscopic HIPEC allowed for conversion surgery in 11 (25%) of 44 stage IV cases after negativization of the positive cytology [104]. In Japan, a specific form of regional conversion therapy is the Neoadjuvant Intraperitoneal and Systemic bimodal chemotherapy (NIPS) proposed by Yonemura et al. since 2006 [105]. This group recently reported a complete cytoreduction rate of 57.4% after laparoscopic HIPEC + NIPS followed by CRS and HIPEC in stage IV patients. In this study, patients undergoing this combined treatment had a median survival of 19.2 months and a 2-year survival rate of 41% [106].

So far, the Korean, the ESMO or the NCCN guidelines do not consider the use of CRS and/or HIPEC in the multimodal treatment of GC outside of clinical trials [8, 9, 11]. In the novel Japanese guidelines, there is consideration for cytoreductive HIPEC or NIPS in patients with positive cytology or peritoneal micrometastasis. Bimodal chemotherapy (intraperitoneal and systemic) is also considered in the palliative setting [10, 107].

In conclusion, the indications for the administration of the different multimodal treatments, according to the GC presentation and stage, are expanding. Patients who were once exclusive candidates to palliative chemotherapy are now considered for induction treatment and, possibly, conversion surgery. The most feared type of GC recurrence, peritoneal carcinomatosis, may be preventable and is currently considered for surgical approach in selected cases. Many GC treatments are available on different fronts (systemic, locoregional), even though our capacity of characterizing GC in terms of sensitivity to the different treatments and in terms of biological behaviour is still limited. In the next years, the development of studies based on molecular signatures is expected to allow for the refinement of the strategies for the administration of the different targeted treatments in the neoadjuvant, adjuvant, palliative and conversion setting (Tables 4 and 5).

Table 4 Recent phase II/III trials evaluating targeted therapy

Title	Authors/PI	Status	Publication Year	Country	Phase	Population	Intervention	Control	Results
ToGa	Bang Y-J	Completed	2010	KO	III	Advanced HER2-positive gastric andEG junction cancer	Trastuzumab + CT ($n=298$)	CT alone ($n=296$)	Median OS: 13.8 months v 11.1 months
INNOVATION	Wagner AD	Ongoing	2019	DE	II	Localized HER2-positive gastric and EG junction adenoca	Arm A: standard preop CT alone (FLOT, CAPOX or FOLOFOX)	Arm B: preop CT/trastuzumab Arm C: preop CT/trastuzumab/pertuzumab	
JCOG1301	Kataoka K	Ongoing	2015	JP	II	Advanced HER2-positive gastric or EG junction adenoca with extensive lymph node metastasis (ELM)	S1/cisplatin/trastuzumab	S1/cisplatin	
AVAGAST	Ohtsu A	Completed	2011	JP	III	Advanced gastric cancer	Bevacizumab/capecitabine/cisplatin	Placebo/capecitabine/cisplatin	Median OS: 12.1 v 10.1 months ($p=0.1002$) Median PFS: 6.7 v 5.3 months ($p=0.0037$) ORR: 46.0% v 37.4% ($p=0.0315$)
AVATAR	Shen L	Completed	2015	CH	III	Inoperable locally advanced or metastatic gastric or EG junction cancer	Bevacizumab/capecitabine/cisplatin ($n=100$)	Placebo/capecitabine/cisplatin ($n=102$)	Median OS: 10.5 v 11.4 months ($p=0.56$) Median PFS: 6.3 v 6.0 months ($p=0.47$)
REGARD	Fuchs CS	Completed	2014	US	III	Advanced gastric or EG junction adenoca	Ramucirumab ($n=238$)	Placebo ($n=117$)	Median OS: 5.2 v 3.8 ($p=0.047$)
RAINBOW	Wilke H	Completed	2014	DE	III	Previously treated advanced gastric or EG junction adenoca	Ramucirumab/paclitaxel ($n=330$)	Placebo/paclitaxel ($n=335$)	Median OS: 9.6 v 7.4 months ($p=0.017$)
RAMSES/FLOT7	Al-Batran SE	Ongoing	2016	DE		Resectable locally advanced gastric or EG junction adenoca	FLOT/Ramucirumab	FLOT	
INTEGRATE	Pavlakis N	Completed	2016	AU/NZ/KO/CA	II	Advanced gastric or EG junction adenoca	Regorafenib ($n=97$)	Placebo ($n=50$)	Median PFS: 2.6 v 0.9 months ($p<0.001$)
INTEGRATE II	Pavlakis N	Ongoing	2017	AU/NZ/KO/CA	III	Refractory advanced gastric or EG junction cancer	Regorafenib	Placebo	

Table 4 (continued)

Title	Authors/PI	Status	Publication Year	Country	Phase	Population	Intervention	Control	Results
KEYNOTE-059	Fuchs CS	Completed	2018	US	II	Previously treated advanced gastric or EG junction cancer	Pembrolizumab ($n=259$)		Objective response rate: 11.6% (complete response in 2.3%) Median response duration: 8.4 months - in PD-L1-positive tumors: 15.5% and 16.3 months - in PD-L1-negative tumors: 6.4% and 6.9 months
ATTRACTION-2	Kang Y-K	Completed	2017	KO	III	Advanced gastric or EG junction cancer refractory to, or intolerant of, two or more previous regimens of CHT	Nivolumab ($n=330$)	Placebo ($n=163$)	Median OS: 5.26 v 4.14 months ($p<0.0001$) 12-month OS rates: 26.2% v 10.9%
KEYNOTE-061	Shitara K	Completed	2018	JP	III	Previously treated, advanced gastric or EG junction cancer	Pembrolizumab ($n=196$)	Paclitaxel ($n=199$)	Median OS: 9.1 v 8.3 months ($p=0.0421$) Median PFS: 1.5 v 4.1 Grade 3–5 treatment-related adverse events: 14% v 35%
ATTRACTION-5	Terashima M	Ongoing	2017		III	Unresectable advanced or recurrent gastric/EG junction cancer refractory to or intolerant of standard therapy	S1 or XELOX + nivolumab	S1 or XELOX + placebo	
KEYNOTE-585	Bang Y-J	Ongoing	2019	KO	III	Localized gastric or EG junction adenoca	Preoperative cisplatin/5-FU or S1 or FLOT + pembrolizumab	Preoperative cisplatin/5-FU or S1 or FLOT + placebo	

Table 5 Recent phase II/III trials evaluating regional therapies

Title	Authors/PI	Status	Publication Year	Country	Phase	Population	Intervention	Control	Results
GASTRICHIP	Glehen O	Ongoing	2014	FR	III	Gastric cancer involving the serosa and/or lymph node involvement and/or with positive cytology at peritoneal washing	Surgery + HIPEC with oxaliplatin	Surgery	
GOETH	Di Giorgio A	Ongoing	2019	IT	III	Gastric carcinoma at high risk of developing peritoneal carcinomatosis	Surgery + CO_2 HIPEC	Standard surgery	
NCT02891447	Badgwell B	Ongoing	2016	US	II	Gastric adenoca with carcinomatosis or positive cytology	Surgery + HIPEC		
NCT03092518	Davis JL	Ongoing	2017	US	II	Gastric cancer with positive peritoneal cytology	Surgery + HIPEC		
PERISCOPE I	van der Kaaij RT	Completed	2017	NE	I/II	Gastric cancer with positive peritoneal cytology and/or limited peritoneal carcinomatosis	CT + Gastrectomy/ cytoreductive surgery (CRS)/ HIPEC with oxaliplatin–docetaxel		
PERISCOPE II	Koemans WJ	Ongoing	2019	NE	III	Gastric cancer with peritoneal dissemination	CT + Gastrectomy/ CRS/ HIPEC	Chemotherapy	
GASTRIPEC	Beate Rau MBA	Ongoing	2014	DE	III	Gastric and EG cancer with synchronous peritoneal carcinomatosis	CRS/HIPEC	CRS	
NCT02995850	Hyung WJ	Ongoing	2016	KO	Ib/II	Gastric cancer with peritoneal metastasis	Upfront CRS/HIPEC		
NCT02092298	Badgwell B	Completed	2017	US	II	Gastric or EG adenoca with positive peritoneal cytology or radiologically occult peritoneal carcinomatosis	CT + laparoscopic HIPEC with mitomycin C–cisplatin ($n = 19$)		Complication rate for HIPEC: 11% (4 of 38 procedures) 30-day mortality rate: 0% Median OS from the first laparoscopic HIPEC: 20.3 months

New technologies, data-driven-based research and educational updates

a) New surgical technologies

In the last years, thanks to the technological advances, augmented-reality and image-guided surgery have become new instruments of the precision surgery approach in abdominal surgery. Many augmented-reality and image-guided surgery strategies aiming to enhance the surgical performance are being developed, even if most still have to find a definite practical application and clear indications [19, 108]. The use of 3D imaging, thanks to its new technological developments, has gained attention as a possible instrument for GC surgery. Recently, the results of a phase III RCT (NCT02327481) comparing the operative times and the safety and efficacy of 3D laparoscopic gastrectomy versus 2D laparoscopic surgery were reported. No differences between the two groups regarding the operation time was detected. The intraoperative blood loss in the 3D group was slightly less than in the 2D group (61 ± 83 mL vs. 82 ± 119 mL, $p = 0.045$). The costs of the two types of operations were comparable [109].

Thus far, the most relevant surgical technology that has found a widespread practical use in the treatment of GC is the use of near infrared imaging (NIR) after injection of indocyanine green (ICG). NIR imaging allows the visualization of fluorescence in the NIR wavelength (700–1000 nm), thanks to the use of excitation light sources and devoted filters. Specific laparoscopic systems for NIR imaging are commercially available and NIR imaging can be integrated in the robotic platforms. ICG is a fluorophore emitting 800–840 nm of light. It can be used as a vital dye and be observed by the naked eye, but is better visualized with NIR imaging systems, allowing for the visualization of the biliary tract, the anatomic segments of the liver, the perfusion of the tissues and the lymphatic anatomy [19, 110]. In GC surgery, NIR is mainly applied as a navigation tool for tumor localization, and sentinel or radical lymph node dissection (Fig. 1). Indeed, the perti-tumoral injection of ICG, performed one day before or at the time of surgery, allows to identify the location of the tumor, its lymphatic drainage and the anatomy of its draining lymph nodes [19].

The use of ICG as a tracer for sentinel node detection has been investigated by many Eastern studies. In 2018, one Japanese study investigated the ICG method as a safer alternative to the radioisotope method in aiding sentinel node detection. Results reported safety and high efficacy of ICG-guided sentinel node dissection (92% of "radioisotopic hot nodes" were removed with this technique) [111]. A 2018 systematic review and meta-analysis investigated the diagnostic value of NIR- and ICG-guided GC sentinel lymph node mapping. Thirteen clinical studies (evaluating 971 patients) were included. The results indicated high sensitivity, specificity and accuracy for the ICG sentinel node method: 0.94 (95% CI 0.80–0.99), 1.00 (95% CI 0.60–1.00) and a ROC area under the curve (AUC) of 1.00 (95% CI 0.99–1.00), respectively [112]. The SENORITA trial (NCT01804998) is the only phase III RCT active on this topic. This study has a non-inferiority design, is conducted on patients with T1N0M0 GC ≤ 3 cm, and compares the survival outcomes of patients undergoing laparoscopic stomach-preserving surgery with sentinel node dissection vs standard surgery (with D1 + dissection) [113].

Another application for NIR plus ICG is the lymph node mapping during radical surgery for advanced GC. In 2017, a pilot study on the use of ICG during robotic gastrectomy was published. Its results reported no significant difference between patients undergoing robotic gastrectomy with ($n = 14$) or without ($n = 65$) ICG regarding the operative time, the total number of retrieved nodes and the operative blood loss. However, the ICG group had a greater number

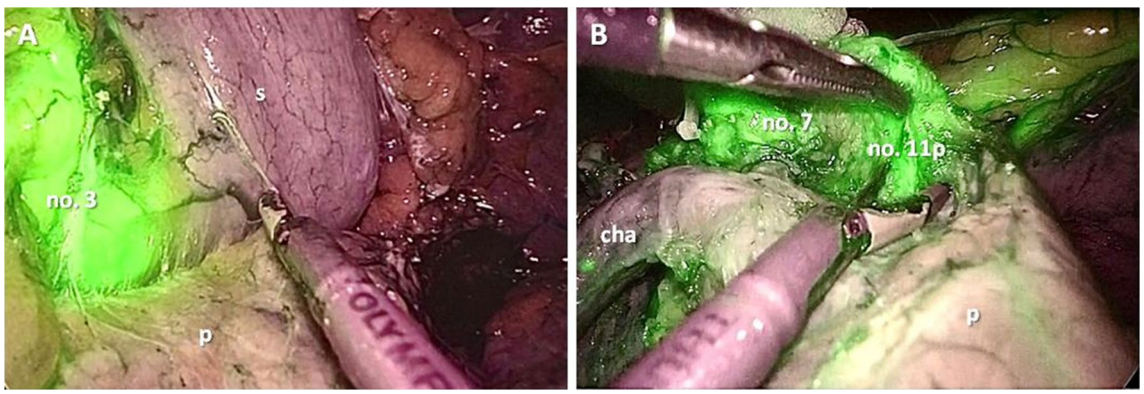

Fig. 1 Image-guided surgery by indocyanine lymphography during D2 gastrectomy. *s* stomach, *p* pancreas, *cha* common hepatic artery, *no. 3* nodes of the 3 station, *no. 11p* nodes of the 11p station, *no. 7* nodes of the 7 station

of nodes retrieved at the greater curvature side of the low body (station 4d) and at the infrapyloric region (station 6) [114]. In 2018, the results of another feasibility study were reported. In this study, the removal of ICG-stained tissues not included in the preliminary dissection (D1 + /D2) in patients undergoing laparoscopic pylorus preserving gastrectomy and laparoscopic distal gastrectomy allowed for the removal of extra nodes from station 6 [115]. The results of a Korean prospective single-arm study were recently reported. This study followed prospectively 40 patients undergoing robotic radical gastrectomy and conducted a propensity-score matching analysis pairing this group with an historical control. The results reported the safety and feasibility of ICG injection, and a greater mean number lymph nodes retrieved in the ICG group (48.9 vs 35.2; $p < 0.001$), due in particular to a greater number of station 2, 6, 7, 8, and 9 nodes [116]. Last, the result of a recent European propensity score-matched study comparing 37 patients undergoing robotic gastrectomy with ICG lymph node mapping versus 37 patients undergoing robotic gastrectomy without ICG confirmed the better outcome of ICG in terms of node retrieval, reporting a higher mean total number of harvested nodes in the ICG group (50.8 vs 40.1, $p = 0.03$) [117]. Ongoing trials investigating the role for ICG in lymph node mapping are the prospective trial Fluorescence Image-Guided Lymphadenectomy in Robotic Gastrectomy (IG-MIG) (NCT03931044) and the phase II RCT Indocyanine Green Tracer Using in Laparoscopic Gastrectomy with Lymph Node Dissection (ICGTinLG) (NCT03050879).

Other applications for ICT-guided surgery are being investigated. One preliminary study investigated the role for intravenous ICG in identifying the infra-pyloric artery, detecting an overall positive predictive value (PPV) of 80% for this technique [118]. Another study reported on the use of intravenous ICG to detect possible ischemia at the anastomosis sites. In this study, the anastomotic vascular perfusion was assessed with an intraoperative score of fluorescence activity. The technique was feasible, but the few complications occurred (1 leak, 1 stenosis) did not relate with the ICG score [119].

b) Large-scale databases, big data and artificial-intelligence (AI)-based research

With the rapidly expanding volume of health data collection, it is foreseen that a new chapter of oncologic research will be based on data-driven strategies, including the collection of Big Data and the application of AI-based analytic strategies (Fig. 2) [120, 121]. Thus far, the analysis of a large, multicentric dataset of 25,000 patients conducted by Sano et al. [122] by conventional statistics leads to the substantial changes of the stage grouping in the 8th edition of the TNM. However, contemporary, a machine-learning analysis of another large dataset from six continents from the Worldwide Esophageal Cancer Collaboration (WECC) led to the development of the new classification for tumors of the esophagus and esophagogastric junction [123]. Many National and International Datasets collecting information

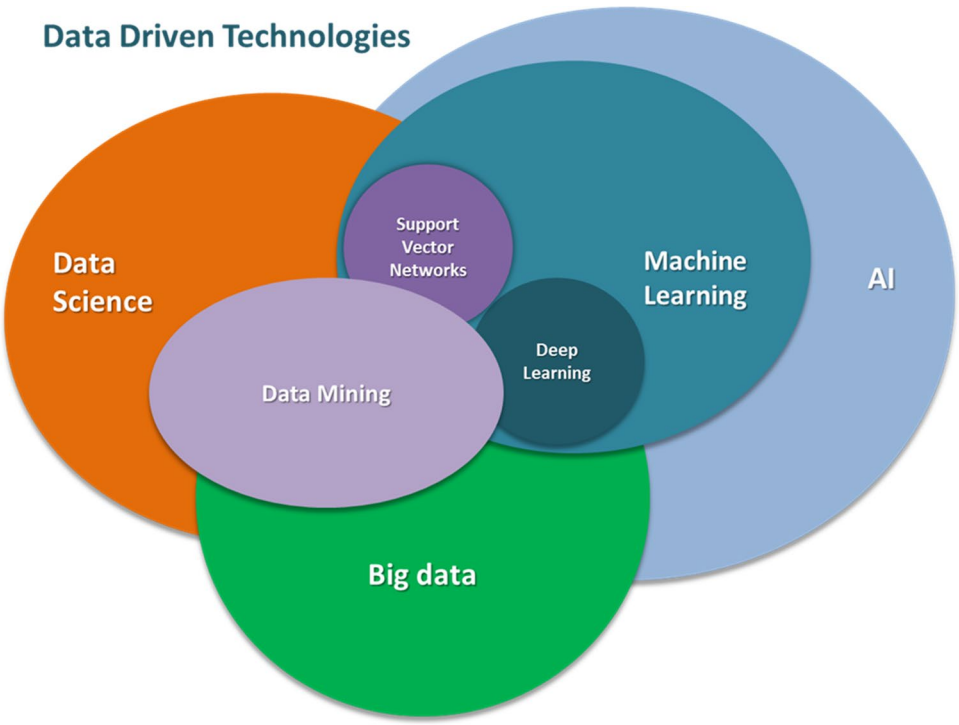

Fig. 2 Data-driven technologies

on the epidemiology and prognosis of GC patients exist [1, 124, 125] and worldwide, the development of comprehensive datasets and biobanks is ongoing [126–128].

"Big data" have been defined in many way, among which "data sets that are so large or complex that traditional data sets processing applications are inadequate" [129]. The use of Big Data Analysis is extremely appealing and has many potential advantages in oncology. Apart from the intuitive advantages of having a large sample size, Big Data analysis has also the advantage of including patients who are often under-represented in RCTs. Contrarily, possible disadvantages are represented by data validity, missing data, incomplete data capture due to the unavailability of diagnosis codes for certain clinical situations, and by the regulation of individual privacy [130]. Many of the techniques used to manage and analyze Big Data are derived from AI-based methods, which are capable of dealing with large amount of data. AI-based methods include machine-learning methods, namely, AI techniques that use statistical methods to enable machines to improve with experience. Machine learning methods, in turn, include support-vector machine (SVM) networks, namely, supervised learning models with associated learning algorithms that analyze data used for classification and regression analysis, and deep learning methods, namely, a subset of machine-learning methods that make the computation of multi-neural network feasible [129]. Due to the nature of big data and the possible residual and/or unmeasured confounding after machine-learning-based analytics, studies using these approaches usually require an accurate study design, the use of various statistical adjustment methods and the use of supervised AI-learning activity [129, 130].

The use of AI has been recently applied to the detection of early gastric cancer in endoscopic images. Indeed, a Japanese group developed a deep learning convolutional neural network (CNN) that could automatically detect gastric cancer in endoscopic images [131]. A second Korean study validated an AI-based algorithm demonstrating its superior sensitivity in detecting upper gastrointestinal cancers compared to that of non-expert endoscopists [132]. A Chinese group developed and validated a deep learning algorithm for determining EGC invasion depth. The model demonstrated 76% sensitivity and 96% specificity in identifying "SM2 or deeper" cancers and achieved significantly higher performance than that of the endoscopists [133]. A further application of deep learning CNNs was tested for the histopathological classification of GC, finding a satisfactory overall classification accuracy of 0.6990 (ROC AUC) [134]. Other studies have focused on increasing the possibility of cancer prediction, developing machine-learning methods able to identify the best biomarkers for GC cancer individuation [135–137]. Moreover, new insights on the origin and progression of GC have been given, thanks to AI-based methods that were employed to scan the whole genome of 212 gastric cancer tumors in a Singapore Institute. This analysis identified new cancer-associated mutation hotspots located throughout the genome, providing evidence that mutations in the non-coding DNA may cause cancer by altering the 3D genome structure [138].

Another field of research is represented by the improvement of the current prognostic and predictive models. In 2017, results of a Korean study comparing a prognostic model created with a deep learning strategy showed a better performance than a prognostic model developed using Cox regression [139]. In 2018, another Korean study demonstrated that a deep learning survival recurrent network (SRN) had a ROC AUC of 0.81 at 5 years from gastrectomy and was more powerful in predicting the survival rates of GC patients than the TNM staging [140]. Last, a SVM prediction model was used to identify genes related with GC recurrence, defining a 65-gene classifier that was able to recognize high and low risk of recurrence GC cases with high sensitivity and specificity [141]. Radiomics has been defined as a specific type of data mining, that extract and analyzes quantitative image features from medical imaging in order to improve the clinical decision making [142]. Most of the recent radiomic studies use machine-learning statistical techniques for analysis. In 2019, the results of a study testing the performance of a model that stratified a radiomic signature and significant clinicopathological risk factors (T stage, N stage, and differentiation) reported significant prognostic superiority of this model over a clinical nomogram alone. The model showed a remarkable consistency between predicted and actual survival [143]. Other radiomic studies used SVM models to identify preoperatively an adverse pathological status for GC that demonstrated a greater correlation with prognosis than the TNM8 [144], and to identify the presence of lymph node metastases with a model that performed significantly better than the radiologists [145]. Another study tested the performance of machine learning-based clinical decision-support models for predicting the extent of lymphadenectomy (D1 vs. D2) in local advanced GC, obtaining a 0.965 area under the ROC curve and an overtreatment reduction going from 21.7% (121/557) treating all patients with D2 dissection, to 0.7–0.9% (4–5/557) using the machine-learning approach [146]. In the predictive setting, machine-learning strategies have been used to predict the efficacy of adjuvant therapy in certain categories of patients based on their pathologic and immunopathological characteristics [147, 148]. Preliminary studies have also focused on identifying factors associated with the efficacy of neoadjuvant therapy [149] and on identifying new targetable biomarkers for molecular therapy [150].

c) Standardization of GC surgery and educational aspects

Quality assurance has being regarded as the current main challenge for surgeons [152]. The standardization of the surgical treatments is being advocated in surgical oncology, due to the poor quality of the surgical RCTs and to the fact the unstandardized surgical practices have a high risk of distorting the results of the RCTs, especially those focusing on neoadjuvant and adjuvant therapy (as occurred in the first trials on multimodal therapy in GC [53, 54]). Quality assurance is being promoted by many international initiatives, the most recent of which has been the inauguration of the new platform SURGCARE, a collaborative project between the European Society of Surgical Oncology (ESSO) and the Japanese Clinical Oncology Group (JCOG) [151, 152]. In GC, due to the increasing specific evidences and to the shift towards precision medicine (and precision surgery dictated) by trial results and new guidelines [10], the standardization of GC treatment and the establishment of a standard expertise level have been advocated. This request include the multimodal aspects of therapy, the surgical technical expertise, with special attention for the application of mini-invasive techniques, the surgical management in a broader sense, including the performance of ex vivo lymph node dissection, the establishment of a registry of complications and of medical database inclusive of follow-up [153]. Most studies have reported reduced morbidity and mortality and better oncological outcomes in high-volume centers; however, the results are still controversial, especially in regards of the effect of the hospital versus the surgeon volume [154–157].

Reports on the number of cases needed for a surgeon to reach the plateau of the learning curve for radical gastrectomy have been discordant, ranging from 15 to 100 procedures in previous studies and including heterogeneous reports in terms of type of the learning curve (based on complications, operative time or oncologic survival) [158, 159]. In particular, in 2016, a multicenter Korean study conducted on 3284 patients operated by nine surgeons between 2001 and 2006 evaluated the association between surgeon experience and survival. The results reported that the survival learning curve for D2 gastrectomy is long, including at least 100 operations to reach a plateau. Moreover, it detected the lowest survival rate in patients treated by surgeons with an experience of 50–100 cases [159]. The survival curve of more challenging techniques, as laparoscopic total gastrectomy, has been evaluated in comparison with open surgery. In one Korean study, the learning curve for laparoscopic total gastrectomy performed by a single surgeon, already experienced in open total gastrectomy, reached the plateau at around 54 cases [160].

In light of these results, some concern has been expressed for the training for GC surgery in Western countries, especially training occurring outside high-volume centers, where the number of patients with GC is limited and the access to the surgical procedures for GC during the surgical residency even more limited.[161–163]. To overcome the limit given by the number of cases, the role of mini-invasive surgery has been promoted. Indeed, mini-invasive procedures are easier to record and share when compared with open ones. Recorded procedures allow surgeons to perform a thorough self-examination of their surgical technique as they can review the surgical procedure, and give access to operations performed by experts to young surgeons-in-learning [162]. Moreover, the use of web seminars and internet study has been advocated [164]. Until the learning curves are not fully standardized and clear evidence on the training requirements is not obtained, it seems reasonable to promote the surgical training for GC, especially the training for mini-invasive gastrectomy, only in experienced centers [161, 165].

Conclusions

In recent years, the treatment of GC there has evolved within different fields. The optimization of the perioperative management associated with gastrectomy has been implemented on large scale according to the ERAS principles, even though the full application of these principles is still controversial. The long-time-awaited results of many trials investigating the role for preoperative and postoperative management have been published, changing the clinical practice with new standards for neoadjuvant and adjuvant therapy. Targeted medicine is becoming a reality, and novel investigations focused on the efficacy of various targeted treatments are currently ongoing. The surgical treatment is evolving towards a precision-driven approach, thanks to enhancers of the surgical performance (3D, robotics, image-guided surgery). Modern platforms increase the possibility for further targeting of the different treatments, promote the use of data-driven technologies and open new possibilities for surgical learning. In the next years, these innovations are expected to substantially change the traditional approach to GC treatment.

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Compliance with ethical standards

Conflict of interest None.

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