Cancer Management and Research

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REVIEW

Optimal management of resected gastric cancer

This article was published in the following Dove Press journal:
Cancer Management and Research

Riccardo Giampieri
Michela Del Prete
Luca Cantini
Maria Giuditta Baleani
Alessandro Bittoni
Elena Maccaroni
Rossana Berardi

Oncology Clinic, AOU Ospedali Riuniti, Università Politecnica delle Marche, Ancona, Italy

Abstract: Although advances in medical treatment for gastric cancer (GC) have been made, surgery remains the mainstay of cure for patients with localized disease. Improvement in surgical modalities leads to increased chance of cure for resected patients, but a non-negligible number of patients eventually relapse. On this basis, it has been hypothesized that the addition of complementary systemic or local treatments (such as chemotherapy and radiotherapy) could help in improving patients' survival by reducing the risk of recurrence. Several studies have tried to identify the best approach in localized GC: some of them have assessed the role of perioperative chemotherapy [CT] with different drug combinations, while others have focused on the benefit obtained by addition of radiotherapy, whose role is still under investigation. In particular, the role of chemoradiotherapy, both in adjuvant and neoadjuvant settings, is still uncertain. In the last few years, several clinicopathological and molecular factors have been investigated and identified as potential prognostic markers in GC. Many of these factors could have influenced the outcome of patients receiving combined treatments in the abovementioned studies. Patients have not been generally distinguished by the site of disease (esophageal, gastric and junctional cancers) and surgical approach, making data difficult to be interpreted. The purpose of this review was to shed light on these highly controversial topics.

Keywords: gastric cancer, chemotherapy, radiotherapy, adjuvant, neoadjuvant, prognostic factors

Introduction

Although the incidence of gastric cancer (GC) has progressively decreased over the past decades, this neoplasm still represents the fifth most common malignancy in the world and the third leading cause of cancer death in both sexes worldwide.[1] Surgical resection plus adequate lymphadenectomy remains the best chance of a cure. Despite the improvement in surgical techniques, ~40%–60% of patients eventually relapse and recurrence usually occurs within 2 years.[2] Therefore, in addition to standard R0 surgical resection, improvements in complementary therapies such as chemotherapy (CT) and radiotherapy are needed to increase cancer-specific outcome. Unfortunately, most of trials conducted in the perioperative setting have not taken into account the role of several clinicopathological and molecular factors that could have influenced patients' outcome.

The aim of this study was to review the principal evidence and the late-breaking trials available on this topic, highlighting how certain clinicopathological parameters could help estimate the proper risk of relapse of GC patients. We have discussed the rationale of adjuvant, perioperative CT and combined treatment (chemoradiotherapy

Correspondence: Riccardo Giampieri
Clinica Oncologica, AOU Ospedali Riuniti, Università Politecnica delle Marche, via Conca 71, 60126 Ancona, Italy
Tel +39 71 596 3834
Fax +39 71 596 4192
Email riccardo.giampieri81@gmail.com

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Dovepress
http://dx.doi.org/10.2147/CMAR.S151552

[CRT]), underlining the importance of a proper multidisciplinary evaluation in offering the best treatment choice to these patients.

Methods

To identify published studies pertaining to our subject, we systematically searched electronic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Excerpta Medica dataBASE (EMBASE) and the Cochrane Database of Systematic Reviews. There were no language restrictions although articles in English were preferred. Articles published between 2001 and 2017 were included in the search. Two investigators (RG and MDP) performed the search independently, and their results were compared and combined.

Prognostic factors in GC

Clinical prognostic factors

The prognosis of resected GC patients is determined by several clinicopathological factors, including radical resection (R0) of the primary tumor,[3,4] tumor size,[5] tumor location (poorer prognosis for proximal GC compared to distal GC)[6] and histopathology (better prognosis for intestinal-type GC compared to diffuse-type GC, according to Lauren's classification).[7] Regarding age, recent data have shown how certain molecular features, including overexpression of p53 ($p<0.001$), overexpression of human epidermal growth factor receptor 2 (HER2; $p=0.006$) and microsatellite instability (MSI; $p=0.006$), were less frequent in younger patients. Cancer-related mortality resulted higher in the younger population ($p=0.048$), but this difference was not significant after adjusting for the stage of cancer, meaning that stage is the most important predictor of prognosis.[8] By contrast, Kang et al[9] mentioned age as an independent factor influencing early recurrence of pT2-4a stage GC.

Some patients' characteristics have been also reported as prognostic factors in GC,[10] particularly the prognostic nutritional index (PNI), which is calculated based on the serum albumin concentration and total lymphocyte count in the peripheral blood. Even though this factor has been proposed to assess the perioperative nutritional status and the surgical risk in patients undergoing gastrointestinal surgery, an association between PNI and a higher risk of postoperative complications in GC has been suggested, and a lower PNI has been found in patients with more advanced tumor features, such as deeper depth of invasion and positive lymph node metastases, even if the optimal cutoff value of PNI to predict the outcome remains unclear.[11–13]

According to a series of 455 patients presented by De Franco et al,[14] perineural invasion emerged as an independent prognostic factor, especially in the group of patients with Lauren's intestinal histotype (hazard ratio [HR]: 1.99; 95% confidence interval [CI]: 1.24–3.19; $p=0.005$). Perineural invasion defined as infiltration of carcinoma cells into the perineurium or neural fascicles, showed an association with other histopathological characteristics of aggressiveness, such as tumor–stroma ratio, another marker of poor prognosis that is currently investigated.[15]

TNM staging

The most recognized system to predict prognosis in GC is the pathological stage, defined by the Classification of Malignant Tumours (TNM staging).

In particular, the locally advanced GC, defined as T4 (tumor perforating the sierosa or invading adjacent structures), has been associated with poor prognosis and increased postoperative mortality and morbidity. Difficulty in reaching an R0 resection could explain the shorter survival rate observed in T4 GC.[16] Multiorgan resection (MOR) of pT4 GC should be reserved to certain patients without adverse prognostic factors.[17]

The prognostic role of lymph node resection in GC is well established, and several trials reported an improved survival for patients who underwent D2 lymphadenectomy compared to D1.[18–22] The Union International for Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) TNM staging proposed a dissection of 15 or more nodes for an optimal staging and also the Japanese Gastric Cancer Association (JGCA) staging system adopted numeric classification instead of anatomic nodal classification 2010. Recently, the Seventh UICC N staging system has been demonstrated to be superior to the previous UICC editions and the Japanese N staging for a prognostic prediction of GC.[23] The survival benefit of extensive lymphadenectomy (>15 or >25 lymph nodes) in node-negative GC increases by pathological T stage. Among patients with T2–T4 (locally advanced) N0 disease, the percentage of locoregional relapse was higher in those with <25 harvested lymph nodes.[24] Similarly, in the node-positive group, new data stressed that retrieval of >25 lymph nodes improves long-term outcomes without affecting patient safety, raising some doubts on the established cutoff of 15 lymph nodes.[25]

Lymph node ratio (LNR) has been identified as a prognostic factor. In a recent paper,[26] the optimal cutoff of LNR >0.25 was associated with the highest likelihood of identifying patients with worse prognosis.

Anyway, a node-negative state (pN0) does not guarantee long-term survival without recurrence. The prognostic role of

micrometastases in regional lymph nodes (defined as tumor cell clusters <2.0 mm in size, not detected by conventional pathologic examination) in pN0 tumors has been recently investigated.[27] Immunohistochemical staining techniques have been applied for detecting regional lymph nodes micrometastases and have been incorporated in the TNM staging system. According to the Seventh UICC/AJCC system, lymph node micrometastases should be reflected in the node staging of the disease: if the number of macrometastatic nodes is <15, detection of only one micrometastasis could change the N stage. With these premises, the current staging system would state that lymph node micrometastases have the same prognostic value as lymph nodal macrometastases: there is still much debate on this matter, and thus, the notion of a negative prognostic role of lymph nodal micrometastases remains controversial.

Serum tumor markers

Serum tumor markers are widely used in early diagnosis, disease monitoring and assessment of treatment effects in GC, but their prognostic role has not been fully determined. The positive rates of serum biomarkers such as CEA, CA19-9 and CA72-4 have been strongly related to TNM staging and prognosis of resected GC patients,[28] as indicated in a meta-analysis by Xiao et al.[29] A recent Asian study performed among 573 resected GC patients[30] showed that elevated preoperative CEA, CA19-9, CA24-2 and CA72-4 were significantly associated with pathological types ($p<0.05$) and TNM staging ($p<0.05$). In a multivariate analysis, high preoperative CA72-4 and CA24-2 served as prognostic factors for GC and were useful to find early tumor recurrence and metastasis.

Finally, Shimada et al[31] recently performed a literature review on circulating tumor markers in a series of published papers on GC patients: interestingly, only in 187 publications concerning the subject of GC patients (before the end of November 2012), tumor markers were described and only in 19/187 publications, the values of all three relevant tumor markers (CEA, CA19.9 and CA72-4) could be found. Despite these limitations, the review suggested a strong prognostic negative role for patients having a rise in the values of these tumor markers, suggesting early signs of relapse (predominantly in the liver or peritoneum).

Inflammatory biomarkers

Emerging evidence indicates that inflammation plays a critical role in the initiation and progression of different tumor types, including GC, resulting in changes in the levels of circulating white blood cells. The inflammatory response to tumor may contribute to tumor growth, progression and metastasis through several mechanisms, including upregulation of inflammatory mediators, aberrant activation of immune regulatory cytokines, suppression of apoptosis and DNA damage. Those biomarkers in the peripheral blood that can exhibit the status of inflammation are considered as potential prognostic markers.

In particular, the neutrophil-to-lymphocyte ratio (NLR) is a marker for systemic inflammatory response, derived from the absolute neutrophil and lymphocyte number in full blood counts. Various studies examined the clinical use of NLR to predict GC patient outcomes, even if the optimal cutoff value is still inconsistent.[32] A recent systematic review including several retrospective studies reported an association between increased NLR and worse overall survial (OS), suggesting that NLR may be a useful, inexpensive and noninvasive pretreatment prognostic factor.[33] As concerns resected GC, an elevated preoperative NLR has been associated with tumor progression and poor prognosis after surgical resection.[34–36]

Further prospective studies are required to assess the prognostic value of NLR in GC.

Molecular prognostic factors

In the last few years, due to the increasing level of understanding of the molecular basis of carcinogenesis, several molecular targets have been investigated and identified as potential prognostic markers in GC.

HER2

Despite a well-established role of HER2 status in the treatment of metastatic GC with trastuzumab, the clinical significance and prognostic value of such overexpression is not fully understood,[37,38] partially due to the heterogeneity of the criteria used for HER2 assessment. The overall direction of some meta-analyses suggests HER2 as a poor prognostic factor,[39,40] except for the meta-analysis by Gu et al,[41] which enrolled only studies where the HER2 status was assessed by using the same eligibility criteria of the TOGA trial and reported that relapse-free survival (RFS) and OS were not related to HER2 expression. A few studies evaluated the role of HER2 status in resected GC and showed conflicting results. A recent Japanese study[42] reported an HER2-positive ratio of 8.1% for curatively resected GC, suggesting that the presence of HER2 positivity might be less frequent in resectable GC than in metastatic cases. Most of HER2-positive tumors in that study were of the intestinal type according to Lauren's classification, consistent with previous reports. Another recent study including 1,148 resected GC patients

showed a significant poorer survival in HER2-positive patients than in HER2-negative patients, both for intestinal and diffuse type (HR: 1.59, 95% CI: 1.24–2.02, $p<0.001$), suggesting that HER2 overexpression could be a prognostic factor in any stage of resectable GC.[43] Conversely, a recent study by Fisher et al[45] among 254 stage I–III GC patients after curative resection reported an HER2-positive ratio of 10.6% but no association between HER2 status and survival.[44] Hsu et al evaluated HER2 expression in 1036 GC patients who underwent curative surgery; 6.1% of patients showed HER2 positivity that was more often related to differentiated histology. However, HER2 positive expression did not seem to have an independent prognostic role.[46]

Terashima et al[38] analyzed outcome for patients enrolled in the ACTS-GC trial,[47] stratified by HER2 (and EGFR) expression. HER2-positive expression did not seem to influence OS regardless of treatment received, with patients submitted to tegafur/gimeracil/oteracil (S-1) therapy vs observation (Obs) having better prognosis both in the HER2-positive (5-year OS, respectively, 69.9% vs 58.8%) and HER2-negative (5-year OS, respectively, 74.2% vs 62%) expression. A trend toward an overall worse OS was seen in patients with HER2-positive status, albeit not statistically significant ($p=0.46$).

Taken together, these findings seem to suggest that HER2 overexpression occurs in the early phase of gastric carcinogenesis and that HER2 status may not influence the outcomes of early stage/resected GC patients.

E-cadherin

The prognostic impact of E-cadherin downregulation in GC has been assessed for years with heterogeneous results. Functional loss of E-cadherin is implicated in the pathogenesis and metastasization of GC, promoting altered signaling between cancer cells and extracellular-matrix components and subsequent impairment of these pathways.[48] Lack of E-cadherin activity can be caused by several molecular mechanisms, such as somatic and germline mutations of CDH1 gene[49] or epigenetic factors, such as DNA methylation, loss of heterozygosity (LOH), promoter hypermethylation or activation of E-cadherin transcriptional repressors (Snail and Slug).

The prognostic role of reduced E-cadherin expression in GC has been widely explored but remains controversial. A recent meta-analysis, combining the outcomes of more than 4000 GC patients from 26 studies, reported a significant correlation between low expression of E-cadherin and poorer OS and clinicopathological features, indicating that TNM stage, depth of invasion, lymph node and distant metastasis, grade of differentiation and E-cadherin might be independent prognostic factors.[50] Another study by Corso et al[51] performed an analysis of somatic CDH1 mutations, LOH and promoter hypermethylation in 246 patients with sporadic GC (negative for CDH1 germline mutations): patients with CDH1 structural alterations displayed a significantly poorer survival rate than negative patients or patients with epigenetic CDH1 alterations. Moreover, patients with CDH1 epigenetic alterations had more often diffuse histotype tumors and more frequently displayed lymph node metastases. A recent translational study assessed the correlation of several biomarkers, including E-cadherin, with the outcome of resected GC patients, finding a correlation between abnormal E-cadherin expression and more advanced disease stage and poor outcome.[52] Loss of normal E-cadherin expression in GC after curative surgical resection has also shown a correlation with the presence of peripheral blood micrometastases, poor survival and some clinicopathological features (TNM stage, lymph node metastasis and poor tissue differentiation).[53]

Further studies are still needed for a wide application of this biomarker in clinical practice.

Vascular endothelial growth factor (VEGF)

VEGF is a major inducer of angiogenesis and vessel permeability, binding to its receptors expressed on vascular endothelial cells. VEGF plays an important role in cancerogenesis through neovascularization. VEGF overexpression in serum and tissue has been suggested as a poor prognostic factor in various tumor types, including GC, and as a marker for tumor recurrence or reduced survival.[54] Recently, a meta-analysis by Chen et al[55] found a significant link between high VEGF expression and poor survival of resected GC Asian patients, confirming its prognostic significance.

VEGF-A, VEGF-C and VEGF-D expressions have also been studied in GC, resulting in controversial results. Most of these studies included a relatively small sample size to draw definitive conclusions.[56,57]

MSI

MSI results from alterations in genes responsible for DNA repair, such as *MLH1* and *MSH2*. MSI can be considered as a prognostic marker, as GC patients who are positive for MSI (MSI high) have certain features, such as tumors located in the antrum and an intestinal phenotype with an expansive growth pattern.[58,59] Several studies investigated the prognostic significance of MSI in GC, with some of them reporting an association between MSI-high status and better prognosis.[60]

A recent large analysis by Kim et al,[61] collecting data from 1276 patients with stages II and III GC who underwent curative gastrectomy, evaluated the prognosis of MSI-high GC patients compared to MSI-low and microsatellite stable tumors, according to CT and other clinicopathologic features. MSI-high tumors were associated with a good prognosis in resected GC patients when treated with surgery alone, but the benefit of MSI-high status was attenuated by CT.

Hence, the role exerted by MSI in GC has been discussed but not definitely clarified, and further investigations are needed.

Inflammatory biomarkers, tumor markers and molecular markers are listed in Table 1.

Management of resected GC

Although surgical resectability represents the most important factor in localized GC patients, disease relapses are rather common and usually occur in the first 2–3 years after surgery.

It has been hypothesized that the addition of other systemic or local treatments (such as CT or radiotherapy) could help in improving patients' survival by reducing the risk of recurrence.

Adjuvant CT

There is a standard consensus worldwide regarding the use of adjuvant CT in resected GC patients, as means to reduce the risk of locoregional and distant relapse, particularly in

Table 1 Summary of molecular prognostic factors listed in the review

Molecular factor	Prognostic role	Trials	Effect
CEA, Ca19.9, Ca72.4, Ca24.2 (high levels)	Poor prognosis	28	Association with TNM stage, grade, sex, distant metastases, ascites ($p<0.001$)
		29	Poorer OS HR: 1.36, 95% CI: 1.24–1.48, $p<0.001$
		30	Association with pathological types and TNM staging ($p<0.005$)
		31	Early signs of relapse
NLR (high NLR vs low NLR)	Poor prognosis	32	mOS: 7.8 vs 10.8 months, HR for death: 2.61, 95% CI: 1.77–3.84, $p<0.0001$ mPFS: 4.8 vs 7.6 months, HR for progression: 2.51, 95% CI: 1.71–3.70, $p<0.0001$
		34	5-year survival: 57% vs 82%, $p<0.001$
		35	Median survival: 36 vs 60 months
		36	Worse OS and DFS
HER2 (positivity)	Controversial	38	No association with OS and RFS
		39	Significant association with OS HR: 1.56, 95% CI: 1.05–2.07, Z: 6.03, $p=0.000$
		40	Poor OS for patients with EGFR and HER2 high levels HR: 1.66, 95% CI: 1.35–2.02 HR: 1.43, 95% CI: 1.09–1.88
		41	No association with OS and RFS OS – HR: 0.97, 95% CI: 0.84–1.12, $p=0.63$ RFS – HR:1.08, 95% CI: 0.84–1.37, $p=0.55$
		43	Worse prognosis for HER2-positive patients HR: 1.59, 95% CI: 1.24–2.02, $p<0.001$
		44–46	No prognostic value in curatively resected patients
E-cadherin (normal vs abnormal expression)	Poor prognosis	50	HR: 1.62, 95% CI: 1.34–1.96
		52	6-year RFS: 47.1% (95% CI: 40.9%–54.1%) vs 22.8% (95% CI: 14.1%–37.2%) 6-year OS rate 51.0% (95% CI: 44.5%–58.4%) vs 37.5% (95% CI: 29.0%–48.3%)
VEGF (overexpression)	Poor prognosis	55	Poor 5-year OS (RR: 2.45, 95% CI: 2.11–2.83, $p=0.000$)
MSI (MSI-H vs MSI-L)	Controversial	58	No prognostic role. Better DFS for MSI-L treated with 5-FU-based adjuvant CT
		60	Better 5-year OS rate (68% vs 47.6%, $p=0.030$) and 3-year DFS rate (71.8% vs 55.2%, $p=0.076$) in patients who underwent curative surgery
		61	Better prognosis in curatively resected GC treated with surgery alone. The benefit is attenuated by CT. HR: 0.49, 95% CI: 0.26–0.94, $p=0.031$ (no CT) HR: 1.16, 95% CI: 0.78–1.71, $p=0.466$ (with CT)
		32	Better OS and PFS mOS: 14.2 vs 8.0 months, HR for death: 0.24, 95% CI: 0.16–0.35, $p<0.0001$ mPFS: 11.2 vs 5.0 months, HR for progression: 0.25, 95% CI: 0.17–0.33, $p<0.0001$

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; mOS, median overall survival; mPFS, median progression-free survival; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; RFS, relapse-free survival; VEGF, vascular endothelial growth factor; RR, risk ratio; MSI, microsatellite instability; MSI-H, MSI-high status; MSI-L, MSI-low status; 5-FU, fluorouracil; CT, chemotherapy; GC, gastric cancer; PFS, progression-free survival.

patients with a higher stage at diagnosis. Results of the most important adjuvant trials are summarized in Table 2. However, the management of adjuvant CT in clinical practice is usually complex. In particular, adjuvant therapy omission (ATom) is a rarely documented phenomenon and its impact on patients' prognosis is still unknown.

Datta et al[62] were able, in a recently published work, to identify some risk factors for ATom. The authors searched US National Cancer Database for patients with stages IB–III resected GC and developed a risk model for ATom, found in 53.7% of 4728 patients. Advancing age, comorbidity, underinsured/uninsured status, proximal tumor location and clinical T1-2 and N0 tumors were independent ATom predictors. Stratifying patients into low-, moderate- and high-risk categories, there was a predicted incremental risk of ATom (30% vs 53% vs 80%, respectively) and progressive delay to adjuvant therapy initiation (median time 51 vs 55 vs 61 days, respectively). Patients at moderate/high risk of ATom demonstrated an increased risk-adjusted mortality compared with low-risk patients (median overall survival [mOS] 26.4 vs 29.2 months, respectively).

Another problem when facing adjuvant CT in GC patients is the relatively low compliance due to frequent early discontinuation.

Kawazoe et al[63] analyzed early adjuvant discontinuation in GC patients who were receiving S-1 monotherapy. The HRs for relapse and death were significantly lower in the S-1-completed group compared with those in the S-1-discontinuation group (HR: 0.18, $p<0.001$ vs HR: 0.19, $p=0.002$, respectively). Multivariate logistic regression analysis revealed that S-1 discontinuation was significantly associated with an initial overdose of S-1, stage I cancer, creatinine clearance <66 mL/min and a side effect of nausea, thus suggesting that optimal management of patients at the first cycle of adjuvant CT is a factor influencing further completion of treatment.

Qu et al[64] reported the outcome for 237 patients who received adjuvant fluorouracil (5-FU)-based CT after radical D2 gastrectomy for stages IB–IIIC GC, stratified by number of cycles completed. OS rates were significantly better for patients who were able to receive six cycles or more of adjuvant CT. In particular, the estimated 3-year OS rates for the four-, six- and eight-cycle cohorts were 54.4%, 76.1% and 68.9%, respectively; the 5-year OS rates were 41.2%, 74.0% and 65.8%, respectively. Patients who received six cycles were more likely to have a better OS than those who received four cycles ($p=0.002$); however, patients who received eight cycles failed to show an additional survival benefit ($p=0.454$). At multivariate analysis, the number of CT cycles was associated with OS independently of clinical covariates ($p<0.05$).

Jo et al[65] analyzed the outcome for 94 elderly patients (>70 years old) with stages II–III GC who received adjuvant CT after a D2 dissection. In all, 55 (58.5%) patients received fluoropyrimidine-based adjuvant CT, whereas 39 patients received regular follow-up. The RFS of patients with adjuvant CT or regular follow-up only was 35.5 and 20.4 months, respectively ($p=0.030$). Multivariate analysis revealed that adjuvant CT is associated with longer RFS (HR: 0.50; 95% CI: 0.27–0.96). There was a trend toward an improved OS in the adjuvant CT group compared with the follow-up-only group ($p=0.242$), thus suggesting that elderly patients gain almost the same benefit from adjuvant CT as younger patients.

Jin et al[66] also reported the outcome for 360 elderly patients (>65 years old) who received adjuvant CT after a D2 dissection. Age, tumor location, lymph node involvement and tumor invasion were associated with the receipt of adjuvant CT. Adjuvant CT improved OS for non-metastatic elderly patients (HR: 0.60, 95% CI: 0.42–0.83, $p=0.003$). Significant survival benefits were found with adjuvant CT in stage III patients (HR: 0.67, 95% CI: 0.47–0.97, $p=0.033$) but not in stage I or II patients (HR: 0.52, 95% CI: 0.21–1.30, $p=0.161$).

Table 2 Summary of adjuvant trials listed in the review

Trial	Treatment schedule	Patients	HR (OS)	95% CI (*p*)	HR (RFS)	95% CI (*p*)
ACTS-GC[47]	1 year S-1 vs Obs	1059	0.68	0.52–0.87 (0.003)	0.62	0.50–0.77 (<0.001)
5-year follow-up[70]			0.67	0.54–0.83	0.65	0.54–0.79
CLASSIC[68]	6 months XELOX vs Obs	1035			0.56	0.44–0.72 (<0.001)
5-year follow up[69]			0.66	0.51–0.85 (0.0015)		
SAMIT[72]	S-1 vs UFT vs S-1→P vs UFT→P	1495				
S-1 vs UFT comparison					0.81[a]	0.70–0.93 (0.0048)
Sequential vs not-sequential					0.92[b]	0.80–1.07 (0.273)
ITACA-S[73]	FOLFIRI→DC vs 5-FU/FA	1106	1.0	0.85–1.17 (0.974)	0.98	0.82–1.18 (0.865)

Notes: [a]Non-inferiority, not proven; [b]superiority, not proven.

Abbreviations: HR, hazard ratio; OS, overall survival; CI, confidence interval; RFS, relapse-free survival; S-1, tegafur/gimeracil/oteracil; Obs, observation; XELOX, capecitabine plus oxaliplatin; UFT, paclitaxel followed by tegafur and uracil; P, paclitaxel; FOLFIRI, folinic acid, 5-fluorouracil and irinotecan; DC, docetaxel and cisplatin; 5-FU, fluorouracil; FA, folinic acid.

Park et al[67] analyzed the impact of delayed start of adjuvant CT on survival. In 840 resected D2 GC patients, the authors found an interval from surgery to CT start of <4 weeks in 337 (40.1%) patients (early group), 4–8 weeks in 467 (55.6%) patients (intermediate group) and >8 weeks in 36 (4.3%) patients (late group). The 5-year RFS was 55.7% in the early group, 54.4% in the intermediate group and 43.6% in the late group (p=0.076). The corresponding 5-year OS rates were 63.4%, 62.8% and 51.7% (p=0.037). On this basis, while early start of adjuvant treatment is not mandatory (before 4 weeks), it should be encouraged to start within 8 weeks from surgery.

Regarding what can be considered as an "optimal" regimen of adjuvant CT, guidelines suggest fluoropyrimidine-based CT; yet, strong data to support the use of CT doublet vs monotherapy is lacking, particularly due to the fact that many of the positive results of the use of adjuvant CT are obtained in trials where the comparator arm is made of simple Obs rather than a proper placebo.

One of the most influential trials supporting the role of adjuvant CT in resected GC patients is the CLASSIC trial,[68] which randomized 1035 Asiatic patients, who underwent D2 gastrectomy for stages II–IIIB GC, to receive adjuvant capecitabine plus oxaliplatin (XELOX) for 6 months or simple Obs. After a preplanned interim analysis at 34 months of median follow-up, the study met its primary end point, strengthening the role of adjuvant CT in this setting: a significantly improved disease-free survival (DFS) was seen in the CT group vs surgery-only group (respectively 74% vs 59%, HR: 0.56, 95% CI: 0.44–0.72, p<0.0001), even in spite of the relatively high incidence of G3 or higher toxicities in the CT arm (respectively 56% vs 6%). Noh et al[69] recently published the updated results for the 5-year follow-up: a significantly improved DFS was seen in favor of adjuvant CT vs Obs (respectively 68% vs 53%). In all, 103 (20%) patients died in the adjuvant group vs 141 (27%) patients in the Obs group (HR: 0.66, 95% CI: 0.51–0.85, p=0.0015). OS rate was 78% (95% CI: 74–82) in the adjuvant group vs 69% (95% CI: 64–73) in the surgery-only group.

In 2011, Sasako et al[70] reported the updated results for 5-year follow-up of the ACTS-GC randomized Phase III trial comparing adjuvant CT with S-1 vs surgery alone (standard D2 gastrectomy) in stages II–III GC:[47] The OS rate was 71.7% vs 61.1% (HR: 0.669, 95% CI: 0.540–0.828) and RFS was 65.4% vs 53.1% (HR: 0.653, 95% CI: 0.537–0.793), respectively, in the S-1 group vs surgery-only group.

Owing to the results of these two trials, the current standard in Eastern countries is to offer adjuvant therapy to patients with a resected stage II–III GC with either S-1 or XELOX. There are currently ongoing clinical trials in the East that are exploring the gain of a potential "fusion" of the two treatment schedules into one (for example, as in S-1 + oxaliplatin CT regimen).[71]

Combination CT has the advantage of exposing patients to more active drugs, potentially increasing the therapeutic index of adjuvant therapy, at the cost of increased toxicity. To lessen the burden in terms of toxicity, sequential treatment schedules have been tested.

The SAMIT trial[72] randomized 1495 patients between 2004 and 2009 to either adjuvant CT with paclitaxel followed by tegafur and uracil (UFT) vs S-1 or paclitaxel monotherapy followed by UFT vs paclitaxel monotherapy followed by S-1, with the aim of demonstrating the superiority of the sequential approach vs the standard treatment and non-inferiority of UFT vs S-1. The trial did not meet its primary end points, failing to show a significantly improved DFS in the sequential vs standard treatment arm (respectively 57.2% vs 54%, HR: 0.92, 95% CI: 0.80–1.07, p=0.273). UFT therapy did not reach the prespecified limit for non-inferiority (p=0.151) vs S-1 treatment (3-year DFS for S-1 vs UFT of 58.2% vs 53%, respectively; HR: 0.81, 95% CI: 0.70–0.93; p=0.0048). The authors concluded that S-1 monotherapy remains a standard of adjuvant CT in Eastern countries.

In the ITACA-S trial,[73] 1106 resected GC patients were enrolled between 2005 and 2009 and randomized to receive adjuvant CT with 5-FU/folinic acid (FA) or a sequential approach with folinic acid, 5-fluorouracil and irinotecan (FOLFIRI) followed by docetaxel and cisplatin. The primary end point was DFS. With a median follow-up time of 57.4 months, no differences were seen in terms of DFS (HR: 1.00, 95% CI: 0.85–1.17, p=0.974) and OS (HR: 0.98, 95% CI: 0.82–1.18, p=0.865).

Another way to overcome potential difficulties in the management of adjuvant treatment is to assess whether modified treatment schedules may be applied with the same efficacy: one example is the study by Tatebe et al[74] where a different schedule of S-1 administration is tested. The authors randomized 72 stage II–III resected patients to receive adjuvant S-1 as per label (group A, once daily for 4 weeks out of a 6 week cycle for 1 year overall treatment duration) or in a modified schedule (group B, alternate days continuously per 15 months), providing a significantly improved treatment completion rate in group B vs group A (91.8% vs 72.2%, respectively). In all, 3-year survival rate was 69.6% in group A and 87.3% in group B and 3-year RFS rate was 76.4% in group A and 73.1% in group B.

To conclude, most of the focus in adjuvant therapy comes from Eastern countries, where it is standard to perform adjuvant CT after R0 of stages IB–III GC. Regimens mostly used are based on fluoropyrimidines either alone (S-1 mainly) or in combination with oxaliplatin. The main problem with this approach is the relatively sub-par compliance to treatment (usually less than two-thirds of patients submitted to adjuvant CT complete preplanned CT program).

Perioperative CT

One of the main limitations of adjuvant CT is the rather low compliance to treatment: after extensive D2 or D1+ surgery, recovery times are usually rather long and the impact of adjuvant CT, usually performed for 6–12 months, takes its toll on patients. To overcome this problem, particularly in Western countries, a different strategy has been suggested: to perform a relatively short course of CT prior to surgery (neoadjuvant), followed by proper adjuvant CT after surgery. The most important studies supporting the neoadjuvant strategy are summarized in Table 3. The supposed benefits of performing neoadjuvant CT are that compliance in the preoperative phase is far greater than in the postoperative phase, there is a possibility of tumor shrinkage (thus allowing for a greater chance in R0 surgery) and there is a better selection of patients who would ultimately reach radical surgery, as supported by the rather dated MAGIC trial.[75]

Ychou et al[76] in the FNLCC ACCORD 07 FFCD 9703 trial assessed the role of perioperative CT in 224 GC patients, randomized to receive either cisplatin 100 mg/m^2 at day 1+5-FU 200 mg/m^2 daily (CF) in continuous infusion per 5 days for two to three cycles preoperatively, followed by surgery and then adjuvant CT with the same schedule for three to four cycles (for a total number of six cycles altogether). The OS rate was significantly improved by perioperative CT compared with surgery alone (38% vs 24%, respectively; HR: 0.69; 95% CI: 0.50–0.95, p=0.02). DFS was also significantly improved (HR: 0.65, 95% CI: 0.48–0.89, p=0.003). After a long accrual time (from 1995 to 2003), the study was closed due to difficulties in patient enrollment. The proportion of patients who underwent surgery in both groups was similar (96% vs 99%, respectively, for perioperative arm vs surgery) with a statistically significant difference in terms of non-resectional surgery in favor of the perioperative CT arm (6% vs 10%, respectively, p=0.002) and an improved R0 resection rate in patients enrolled in the perioperative arm (87% vs 74%, respectively). The proportion of patients experiencing surgical complications was not significantly different in the perioperative treatment arm, albeit there was a trend toward an increased morbidity (25.7% vs 19.1%, respectively, p=0.24). It should be noted that only 50% of patients treated with preoperative CT received further adjuvant CT after surgery.

Recently, Al-Batran et al[77] presented the results of the FLOT4 trial at the American Society of Clinical Oncology 2017 Annual Meeting. The trial randomized 716 gastric and gastroesophageal operable patients (cT2-4/cN-any/cM0 or cT-any/cN+/cM0) to receive preoperative CT with docetaxel 50 mg/mq day 1, 5-FU 2600 mg/mq day 1, leucovorin 200 mg/mq day 1 and oxaliplatin 85 mg/mq day 1 every 2 weeks (FLOT) for four cycles followed by surgery with radical intent and then by post-operative FLOX for cycles vs standard epirubicin, cisplatin and continuous infusion of 5-fluorouracil/capecitabine (ECF/ECX) CT for 3 cycles followed by surgery with radical intent and then ECF/ECX for other 3 cycles. The study met its primary end point (OS), and all secondary end points (progression-free survival, complete resection rate, surgical morbidity and mortality, CT-related toxicity) were also better in the experimental arm with FLOT. In particular, mOS for FLOT vs ECF/ECX was respectively 50 vs 35 months (HR: 0.77, 95% CI: 0.63–0.94, p=0.012), with a 3-year OS rate of 57% in the FLOT arm vs 48% in the ECF/ECX arm. Median progression-free survival (mPFS) was respectively 30 vs 18 months (HR: 0.75, 95% CI: 0.62–0.91, p=0.004), and the rate of R0 resections was significantly higher in the FLOT arm (84% vs 77%, respectively, p=0.011). As in other studies of perioperative CT, while 90% of patients enrolled in both arms were able to complete the planned preoperative CT, only a fraction of patients (46% in the FLOT arm and 38% in the ECF/ECX arm) were able to complete the

Table 3 Summary of neoadjuvant trials listed in the review

Trial	Treatment schedule	Patients	HR (OS)	95% CI (*p*)	HR (RFS)	95% CI (*p*)
MAGIC[75]	ECF→surgery→ECF vs surgery alone	503	0.75	0.60–0.93 (0.009)	0.66	0.53–0.81 (<0.001)
FFCD 9703[76]	CF→surgery→CF vs surgery alone	224	0.69	0.50–0.95 (0.02)	0.65	0.48–0.89 (0.003)
FLOT-4[77]	FLOT x4 vs ECF/ECX x3→surgery→FLOT x4 vs ECF/ECX x3	716	0.77	0.63–0.94 (0.012)	0.75	0.62–0.91 (0.004)

Abbreviations: HR, hazard ratio; OS, overall survival; CI, confidence interval; RFS, relapse-free survival; ECF, epirubicin, cisplatin and continuous infusion of 5-fluorouracil; CF, cisplatin and 5-fluorouracil; FLOT, oxaliplatin, docetaxel, leucovorin and continuous infusion of 5-fluorouracil; ECF/ECX, epirubicin, cisplatin and continuous infusion of 5-fluorouracil/capecitabine.

postoperative planned treatment. Severe (grade 3 or 4) toxicities observed more frequently in the FLOT arm compared to the ECF/ECX arm were diarrhea (10%), neutropenia (51%), infections (18%) and sensory changes (7%).

Although many of the studies seem to hint at a survival benefit for perioperative approach, some questions remain regarding the reproducibility of these results in clinical practice.

About the impact of toxicity of preoperative CT on surgery, from the trials presented, the number of patients who ultimately reach surgery is rather comparable with the number of patients who are resected immediately. Nevertheless, in everyday clinical practice, there are patients who in the case of severe toxicity from preoperative CT would never reach surgery, thus failing their only chance for a cure.

Robb et al[78] retrospectively analyzed the survival of 1293 patients (653 with gastroesophageal junction [GEJ] tumors, 640 with esophageal cancer) who received preoperative CT according to toxicity to treatment. Severe toxicity to neoadjuvant treatment (NTT) was associated with a higher postoperative mortality after resection of GEJ cancer (p=0.001) and more not-R0 resections (p=0.019). A significantly decreased number of patients receiving adjuvant treatment (p=0.012) and higher surgical morbidity (p=0.005) was also observed. Median survival was also reduced in patients who experienced NTT (p=0.018), which maintained its independent negative prognostic role on survival in the multivariate analysis (p≤0.007).

Other authors point out the relevant role of the adjuvant part of the complete perioperative treatment. In particular, while benefits coming from the preoperative part are rather well established, it is unclear whether completion of the adjuvant part of the perioperative treatment is linked to a better result. Mirza et al[79] retrospectively analyzed 66 patients who received NTT. A total of 31 (47%) patients also underwent adjuvant CT with a median of two cycles (range one to three). Patients who completed both treatment courses (both neoadjuvant and adjuvant) had significantly improved survival compared with those who received only neoadjuvant (p=0.04).

As reported by Davies et al,[80] tumor downstaging has been suggested to be an independent prognostic factor in resected GC. The authors reported the impact of response to preoperative CT on survival for 400 patients submitted to surgery for gastric or GEJ cancer after preoperative treatment. Patients experiencing downstaging to neoadjuvant CT had improved survival (HR: 0.43, 95% CI: 0.31–0.59, p<0.001). Tumor downstaging maintained its independent prognostic role even at multivariate analysis. The stage after neoadjuvant CT, rather than the stage before the start of neoadjuvant CT, was the strongest predictor of different outcomes.

To conclude, the neoadjuvant/perioperative treatment represents a strong option in locally advanced GC patients who are candidates for radical surgery: crucial points in this setting are the accurate selection of patients who would benefit most from this treatment approach and to increase the global awareness of this option to other medical personnel involved in patients' management (surgeons, general practitioners).

CRT

To reduce the probability of local recurrence for resected GC, other than CT, local treatments such as radiotherapy have been investigated both in adjuvant and neoadjuvant settings (the studies are summarized in Table 4).

The role of radiation therapy (RT) in the treatment of GEJ cancer is still uncertain, as the largest prospective trials do not distinguish GEJ cancer from either gastric or esophageal cancer.

The first study suggesting a potential role for adjuvant CRT was the INT0116 trial by Macdonald et al,[81] and is setting the current standard for adjuvant CRT in resected GC patients, as suggested in US guidelines. The study randomized 556 resected GC patients to receive adjuvant CRT with 5-FU/FA followed by 4500 cGy radiotherapy

Table 4 Summary of adjuvant and neoadjuvant CRT completed trials

Trial	Treatment schedule (adjuvant trials)	Points	HR (OS)	95% CI (*p*)	HR (RFS)	95% CI (*p*)
INT0116[81]	Surgery alone vs surgery→5-FU/FA+RT	556	1.35	1.09–1.66 (0.005)	1.52	1.23–1.86 (<0.001)
ARTIST[84]						
7-year update[85]	Surgery→XP+RT vs surgery→XP	458	1.13	0.77–1.64 (0.52)	0.74	0.52–1.05 (0.092)
Kim et al[86]	Surgery→5-FU/FA vs surgery→5-FU/FA+RT	90	NR	NR	54.6% vs 73.5%	NR (0.056)
Zhu et al[87]	Surgery→5-FU/FA vs surgery→5-FU/FA+IMRT	404	1.24	0.64–1.65 (0.122)	1.35	1.03–1.78 (0.029)
POET[90]	C/5-FU/FA+RT→surgery vs C/5-FU/FA→surgery	126	0.67	0.41–1.07 (0.07)	76.5% vs 59%	NR (0.06)
CROSS[91]	Carbo/P+RT→surgery vs surgery alone	366	0.65	0.49–0.87 (0.003)	0.49	0.35–0.69 (<0.0001)

Abbreviations: CRT, chemoradiotherapy; HR, hazard ratio; OS, overall survival; CI, confidence interval; RFS, relapse-free survival; 5-FU, fluorouracil; FA, folinic acid; RT, radiotherapy; XP, capecitabine plus cisplatin; IMRT, intensity-modulated radiotherapy; C, chemotherapy; Carbo, carboplatin; P, paclitaxel; NR, not reported.

at 180 cGy per day. mOS was significantly different in the surgery group compared with the CRT group (27 vs 36 months, respectively; HR: 1.35; 95% CI: 1.09–1.66; p=0.005). A significantly increased risk of relapse was also seen in the surgery arm vs the CRT arm (HR: 1.52, 95% CI: 1.23–1.86, p<0.001). Data were confirmed after 10 years of follow-up, as shown by Smalley et al,[82] who published an update report of survivals, showing a 1.32 HR for OS (95% CI: 1.10–1.60, p=0.0046) and 1.51 HR for RFS (95% CI: 1.25–1.83; p=0.001). A relatively high number of patients in the CRT arm experienced severe toxicity: 54% patients experienced NCI-CTC G3 or higher hematological toxicity and 33% showed severe gastrointestinal toxicity. Second malignancies were seen in 21 patients with radiotherapy vs eight patients with Obs (p=0.21), but this increase in toxicity was judged acceptable, given the magnitude of RFS and OS improvement. Note, most of the patients enrolled in the trial received suboptimal surgery. Only 10% of patients received a proper D2 resection, while 54% of them received a D0 resection. The relatively high number of patients who were then submitted to suboptimal surgery may explain the good performance of combined CRT in this group of patients.

About the role of adjuvant treatment in relation to surgery, a retrospective study conducted by Kim e al,[83] which analyzed 544 patients who underwent D2 lymphadenectomy followed by CRT, revealed a 20% reduction in the risk of death in the CRT group compared to the surgery-only group (446 patients), even if patients had received optimal D2 surgical resection. Compliance to treatment resulted in even higher (75.2%) reduction in the risk of death than that reported in the INT0116 trial (64%).

Another trial assessing the impact of adjuvant CRT in resected GC patients is the ARTIST trial,[84] which randomized 458 patients who underwent D2 resection to receive six cycles of adjuvant capecitabine plus cisplatin (XP) CT vs XP for six cycles plus an additional two cycles of XP in combination with radiotherapy. The compliance to the preplanned treatment schedule was acceptable, with 75.4% of patients completing XP vs 81.7% of patients in the XP+RT arm. No statistically significant differences were seen for DFS (p=0.0862). However, when considering the population of patients with node positive involvement (396/458, 86%), a statistically significant improvement in DFS was noted for patients randomized to XP+RT vs XP (p=0.0365), maintained in multivariate analysis adjusted for other risk factors (HR: 0.68, 95% CI: 0.4735–0.9952, p=0.0471).

Recently, Park et al[85] published the updated results of the ARTIST trial with 7-years follow-up time: DFS was comparable and not significantly different between the two treatment arms (XP vs XP+RT, HR: 0.74, 95% CI: 0.52–1.05, p=0.0922). Also no difference in terms of OS was seen in the general population (XP vs XP+RT, HR: 1.13, 95% CI: 0.775–1.647, p=0.5272). The interaction test showed that the effect of radiotherapy in improving survival was significantly different on the basis of histotype defined by Lauren's classification (interaction for DFS: p=0.04, interaction for OS: p=0.03) and LNR (interaction for DFS: p<0.01, interaction for OS: p<0.01). When analyzing only the population of node-positive GC patients, a significantly improved OS and DFS were seen. Particularly, as later assessed,[26] the ratio of metastatic lymph nodes to examined lymph nodes (*N* ratio) remained, on multivariate analysis, an independent prognostic factor for DFS. The HRs for the *N* ratio categories of 0%, 1%–9%, 10%–25% and >25% were 1, 1.061, 1.202 and 3.571, respectively. In patients having *N* ratio >25%, the 5-year DFS was greater (HR: 0.527, 95% CI: 0.307–0.904, p=0.020) in the XP+RT arm (55%) than in the XP arm (HR: 0.52, 95% CI: 0.307–0.904, p=0.020). On this basis, the authors planned a subsequent trial (ARTIST-2) that will assess the impact of adjuvant CRT in the selected population of D2-resected node-positive GC patients.

Kim et al[86] conducted a randomized Phase III trial on 90 patients who received adjuvant 5-FU based CRT vs only 5-FU adjuvant CT. Treatment was completed by 93.2% of patients in the CT arm and 87.0% of patients in the CRT arm. Overall intent-to-treat analysis showed that addition of RT to CT significantly improved locoregional RFS but not DFS. In subgroup analysis for stage III, CRT showed a trend toward improved DFS compared with CT, although it did not reach statistical significance (respectively 73.5% vs 54.6%, p=0.056).

Zhu et al[87] analyzed the impact of intensity-modulated radiotherapy (IMRT) applied to adjuvant CRT: 404 patients were randomized to receive adjuvant CT with 5-FU/FA vs adjuvant CRT with IMRT concomitantly with 5-FU/FA CT. mOS in the CT group was 48 vs 58 months in the group of patients who received both IMRT and CT (HR: 1.24, 95% CI: 0.94–1.65, p=0.122). IMRT was associated with increases in the median duration of RFS (36 vs 50 months, respectively; HR: 1.35; 95% CI: 1.03–1.78; p=0.029).

These results were summarized by Zhou et al[88] in a recent meta-analysis. A total of 960 patients from four randomized controlled trials (RCTs) were selected, pointing out that postoperative CRT after D2 lymphadenectomy significantly reduced locoregional recurrence rate (LRRR; risk ratio [RR]: 0.50, 95% CI: 0.34–0.74, p=0.0005) and improved disease-free survival (DFS; HR: 0.73, 95% CI: 0.60–0.89, p=0.002)

compared with CT. However, distant metastasis rate (DMR; RR: 0.81, 95% CI: 0.60–1.08, p=0.15) and OS (HR: 0.91, 95% CI: 0.74–1.11, p=0.34) were not affected by the type of treatment. The two groups did not show any differences in terms of grade 3–4 toxicity.

During the 2016 American Society of Clinical Oncology Annual Meeting, results of the CRITICS trial[89] were presented to answer the question whether CRT after neoadjuvant CT and adequate (D1+) surgery leads to improved OS in comparison with postoperative CT. Even though a similar rate of patients completed treatment according to protocol, no significant difference in OS was found between postoperative CT and CRT (5 year OS of 41.3% for CT and 40.9% for CRT, p=0.99). Toxicity was mainly hematological (grade 3 or higher: 44% vs 34%; p=0.01) and gastrointestinal (grade 3 or higher: 37% vs 42%; p=0.14) for CT and CRT, respectively.

Another potential application of CRT is in the neoadjuvant phase, due to the high probability of local control, particularly when tumor shrinkage, downstaging and downsizing could prove crucial in allowing for radical tumor resection. This type of approach is more frequently adopted for proximal lesions.

In the POET trial,[90] 126 patients with locally advanced gastric or GEJ tumor were randomized to receive either neoadjuvant CT followed by surgery or neoadjuvant CT followed by radiotherapy and surgery. The study failed to reach its preplanned accrual and was stopped prematurely. Despite a relatively comparable number of patients being submitted to complete tumor resection between the CRT arm vs CT arm (respectively 71.5% vs 69.5%), a significantly higher number of pathologically complete responses were seen in patients who had previously received CRT (15% vs 2.2%, respectively). A significantly higher number of node-free tumors were also observed in the CRT arm (64.4% vs 37.7%, respectively). There was a trend toward improved survival in the CRT arm vs CT arm (3-year OS rate respectively 47.4% vs 27.4%, HR: 0.67, 95% CI: 0.41–1.07, p=0.07). Postoperative mortality remained the most important limitation of this approach (10.2% vs 3.8% respectively for CRT vs CT, p=0.26).

The CROSS trial[91] investigated the role of neoadjuvant CRT in GEJ and esophageal tumors. Patients were randomized to receive neoadjuvant CRT with carboplatin and paclitaxel before surgery or to undergo surgery immediately. The primary end point of the study was met: a significantly improved OS was observed in the CRT group vs surgery-only group (respectively 49.4 vs 24.0 months, HR: 0.657, 95% CI: 0.495–0.871, p=0.003). This benefit in survival was obtained at the cost of an increased risk for hematological (leukopenia, thrombocytopenia in 50–60% patients) and gastrointestinal (esophagitis, anorexia in ~20% patients) toxicities. Although the study managed to meet its primary end point, it should be added that it enrolled mainly patients with tumors located in the esophagus (72%), with a minority of patients having a GEJ tumor (24%), preventing the applicability of these results to the setting of GC patients.

In the setting of resectable GC, the role of radiotherapy (preoperative, postoperative and intraoperative) was summarized in 2009 by Valentini et al[92] in a meta-analysis of 2025 patients that confirmed its impact on 5-year survival. Using an intent to treat analysis, the 5-year RR was 1.26 (95% CI: 1.08–1.48, NNT=17). The benefit was even higher in the preoperative setting (RR: 1.39, 95% CI: 1.13–1.73, NNT=10), but, once again, different approaches of surgery had been adopted and no definitive conclusions were reached.

To summarize the results of these studies, the studies suggest that adjuvant CRT may have a role, particularly in patients with suboptimal surgery or with noticeable lymph node involvement. In fact, recent data from CRITICS[89] have denied an additional benefit of adding postoperative radiotherapy in patients who underwent an adequate surgery with proper lymphadenectomy. The principal limitations of this option are linked to the need for a careful monitoring of patients who receive this treatment due to the relatively high incidence of potentially harmful side effects. Regarding the usefulness of neoadjuvant CRT, the relatively high incidence of toxicity with the increased risk of postoperative mortality may preclude its widespread use: referral of the patients to high-volume centers would be advisable. In addition, data from the TOPGEAR trial,[93] which is now ongoing, may help to understand whether addition of preoperative chemoradiation to perioperative epirubicin, cisplatin and continuous infusion of 5-fluorouracil (ECF) CT could improve patients' outcome compared to perioperative ECF CT alone.

Conclusion

Locally advanced GC has nowadays been recognized as a common form of presentation of this disease that, although curable only through surgery, requires multidisciplinary evaluation so as to offer additional treatment modalities able to increase the probability of survival, such as CT and RT. Indeed, even if different among various countries (Europe, Asia, US), survival gains obtained with pre-/postoperative CT/chemoradiation therapy have led to consideration of these treatment modalities as mandatory in the management of locally advanced GC patients. We believe that at least part of the reason for the confounding results of the different

trials that have been conducted and published on this matter might be traced back to the difficulties in estimating the proper risk of relapse for resected GC patients: an increasing number of factors, such as those treated in this review, both clinical and molecular, have been proposed as means to better calculate the prognosis of this group of patients. It is then hoped that these factors are taken into account when assessing the proper treatment strategy in the setting of everyday clinical practice. It is also hoped that a proper revision of the data of the published adjuvant and neoadjuvant trials in GC would be done by using, as means of stratification, these already well-described clinical and molecular features (such as histology, HER2 status, lymph node ratio, early adjuvant discontinuation and NTT).

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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