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TOPIC HIGHLIGHT

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Treatment of gastric cancer

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Abstract

The authors focused on the current surgical treatment of resectable gastric cancer, and significance of peri- and post-operative chemo or chemoradiation. Gastric cancer is the 4th most commonly diagnosed cancer and the second leading cause of cancer death worldwide. Surgery remains the only curative therapy, while perioperative and adjuvant chemotherapy, as well as chemoradiation, can improve outcome of resectable gastric cancer with extended lymph node dissection. More than half of radically resected gastric cancer patients relapse locally or with distant metastases, or receive the diagnosis of gastric cancer when tumor is disseminated; therefore, median survival rarely exceeds 12 mo, and 5-years survival is less than 10%. Cisplatin and fluoropyrimidine-based chemotherapy, with addition of trastuzumab in human epidermal growth factor receptor 2 positive patients, is the widely used treatment in stage Ⅳ patients fit for chemotherapy. Recent evidence supports the use of second-line chemotherapy after progression in patients with good performance status

Key words: Gastric cancer; Surgery; Radiotherapy; Adjuvant chemotherapy; Palliative chemotherapy; Chemoradiation

Core tip: Surgery remains the only curative therapy of localized gastric cancer, while perioperative and adjuvant chemotherapy, as well as chemoradiation, can improve outcome. Cisplatin and fluoropyrimidine-based chemotherapy, with addition of trastuzumab in human epidermal growth factor receptor 2 positive patients, is the widely used treatment in stage Ⅳ patients. Second-line chemotherapy after progression in patients with good performance status represents a good option.

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INTRODUCTION

Gastric cancer is the 4th most commonly diagnosed cancer

and the second leading cause of cancer death worldwide. Gastric cancer generally remains asymptomatic for a long time and is early detected more commonly in Japan and South Korea, due, at least in part, to active screening programs. Despite increased incidence, Asian gastric cancer patients have a better prognosis than Western patients, probably due to an active screening program or to a more aggressive therapeutic approach. Surgery remains the only curative therapy, while perioperative and adjuvant chemotherapy, as well as chemoradiation, can improve outcome of resectable gastric cancer with extended lymph node dissection. No clear superiority of one strategy over another has emerged, all contributing to a gain of 15% in survival over surgery alone; thus, head-to-head comparisons would be required. Unfortunately, more than half of radically resected gastric cancer patients relapse locally or with distant metastases, or receive the diagnosis of gastric cancer when tumor is disseminated; therefore, median survival rarely exceeds 12 mo, and in metastatic setting, 5-years survival is less than 10%. Cisplatin and fluoropyrimidine-based chemotherapy, with addition of trastuzumab in human epidermal growth factor receptor 2 (HER2) positive patients, is the widely used treatment in stage Ⅳ patients fit for chemotherapy. Recent evidence supports the use of second-line chemotherapy after progression in patients with good performance status. Biological therapies are among the new frontiers of research in the treatment of gastric cancer; increased survival with trastuzumab in patients with HER2-positive and with ramucirumab in second line has been indeed recorded.

SURGERY

Ever since surgery has played a crucial role in the treatment of gastric cancer[1]. In the last decades, two new technical advances have revolutionized treatment methodology, namely endoscopic resection and minimally invasive access[2,3].

In Eastern countries, detection of early gastric cancer, *i.e.*, tumors confined to mucosa ($T1_a$) or submucosa ($T1_b$) with a low rate of nodal metastasis, has become increasingly common due to extensive screening programs; thus, early gastric cancer currently represents a large percentage of newly diagnosed tumors in Japan and South Korea[4]. Several years ago early gastric cancer was deemed to be radically treated with endoscopic resection, with no need for extensive abdominal manipulation. However, horizontal and vertical margin invasion, and particularly the risk of nodal involvement, had to be immediately considered to avoid true oncological disasters. Initially, endoscopic mucosal resection, or, even better, endoscopic submucosal dissection (ESD), were indicated as standard treatment for differentiated-type adenocarcinoma without ulcerative findings UL(-) (depth of invasion clinically diagnosed as $T1_a$ and diameter $\leqslant$ 2 cm). Accordingly, resection was judged as curative when all of the following conditions were fulfilled: en-bloc resection, size $\leqslant$ 2 cm, differentiated-type on histology, $pT1_a$, negative horizontal margin, negative vertical margin, and no lymphovascular infiltration [ly(-), v(-)][5]. The above rules (so called standard criteria) were followed for many years by endoscopists with excellent results[6]. However, more recently, remarkable improvements in technical management allowed to extend such indications to more advanced forms of early gastric cancer (expanded criteria). Currently, ESD is also indicated in differentiated, $\leqslant$ 3 cm, $pT1_a$, UL(+) tumors, or undifferentiated, $\leqslant$ 2 cm, $pT1_a$, UL(-) tumors, or differentiated, $\leqslant$ 3 cm, $pT1_b$ (but with submucosal invasion $\leqslant$ 500 μm from the muscularis mucosae)[5]. Although close follow-up surveillance remains essential, within these criteria ESD has recently been shown to be a feasible and effective method for treating early gastric cancer[2,7,8].

Minimally invasive access, namely laparoscopic gastric surgery, was initially devised for benign esophago-gastric diseases and is currently standard option for hiatal hernia repair and achalasia[9]. Due mainly to technical difficulties and oncological concerns, the laparoscopic access was initially confined to treatment of distal-sided early gastric cancer not requiring total gastrectomy and enlarged lymphadenectomy[10,11]. Following reports of satisfactory oncological adequacy for laparoscopic surgical treatment of colorectal cancer, the laparoscopic approach has been gradually extended to also include advanced gastric cancer requiring total gastrectomy with radical lymphadenectomy. Although data are still controversial, a number of studies have shown laparoscopic approach in the treatment of advanced gastric cancer to be feasible, safe, and oncologically adequate[3,12]. Recently, robot-assisted gastrectomy has been shown to offer potential advantages over conventional laparoscopy with regard to lymphadenectomy and digestive restoration[13].

Whatever the approach (open or laparoscopic), there is no doubt that surgery remains the only potentially curative treatment for all $T1_b$ to T4 gastric cancers, and after failure of endoscopic resection[14]. The most important and still debated issues are represented by extent of resection and role and extension of lymphadenectomy.

In case of gastric cancer involving the fundus and/or the body of the stomach, the vast majority of surgeons perform total gastrectomy since proximal gastric resection is flawed with a significant rate of postoperative complications[15]. On the contrary, controversy has long been in place about extension of resection and importance of histologic subtype (namely, intestinal or diffuse according to the Lauren's classification)[16] in case of cancer of the antrum. Several years ago total gastrectomy was hypothesized to offer oncological advantages over subtotal distal resection in terms of wider lymphadenectomy and effective removal of multicenter neoplastic foci, particularly frequent in histologically proven undifferentiated or diffuse subtype carcinomas[17]. However, at the end of the last century, two European trials showed no differences in overall survival rates between total and subtotal distal gastrectomy - provided extension of the proximal margin of the resection into healthy tissue, thus

ensuring adequate clearance of the margins - and correctly performed lymphadenectomy (see below)[17,18] in the latter procedure. Currently, there is general agreement that subtotal distal resection should be considered the standard of care for cancer of the antrum. The Japanese Gastric Cancer Association (JGCA), formerly known as the Japanese Research Society for Gastric Cancer, has recently stated that "a proximal margin of at least 3 cm is recommended for T2 or deeper tumors with an expansive growth pattern (Types 1 and 2) and 5 cm is recommended for those with infiltrative growth pattern (Types 3 and 4)", thus finally ending a long-standing debate[5].

Controversy over the extent of lymphadenectomy in the treatment of gastric adenocarcinoma has persisted for decades. There has been very little disagreement that at least a D1 lymphadenectomy (namely lymph node stations from 1 to 7 according to the JGCA's classification) should be performed[19]. However, in Japan, a D2 lymphadenectomy (namely D1 lymphadenectomy plus node stations 8a, 9, 10, 11d, 11p, and 12a) has been recommended as standard practice since the 1960s[20]; since Eastern surgeons strongly believe that a D2 lymphadenectomy significantly improves long-term results and overall survival rates[5]. On the contrary, in Western countries the majority of surgeons continue to perform a D1 (or even a D0, *i.e.*, a lymphadenectomy less than D1) resection. This is mainly due to the results of two European randomized trials carried out in the 1990s which failed to demonstrate a survival benefit for D2 over D1 lymphadenectomy[21,22]. However, these two studies have been strongly criticized for significant differences between the two groups analyzed. Indeed, almost 50% of patients in the D2 group did not undergo resection of 12a node station. In addition, patients undergoing splenectomy and/or pancreatectomy as part of a D2 resection had high rates of post-operative morbidity and mortality, thus confounding the results and obscuring statistical differences between the two groups[14,23]. However, a large number of subsequent retrospective studies has shown a correlation between better outcome and lymphadenectomy extended beyond the boundaries of a D1 resection, with dismal long-term survival rates when positive nodes are found beyond the boundaries of a D2 resection, thus suggesting progression of gastric adenocarcinoma to a systemic disease when spreading is beyond D2 nodes[24]. Furthermore, the Dutch D1D2 trial[25], after a median follow-up of 15 years, reported on a significant benefit of D2 lymphadenectomy over D1 lymphadenectomy in terms of locoregional recurrence and survival. D2 lymphadenectomy fulfills the AJCC Cancer Staging Manual, which recommends a minimum of 16 lymph nodes be examined, results in lower rates of loco-regional recurrence[26], and, ultimately, improves overall survival[23,27]. It is particularly evident when splenectomy and/or pancreatectomy are spared (so-called D1+ lymphadenectomy) thus decreasing post-operative complications rates[5]. A recent meta-analysis including 12 randomized controlled trials involving 3573 patients, with survival analyses from 1332 patients, has shown no significant differences in overall survival between D1 and D2. However, subgroup analysis of patients without splenectomy and/or pancreatectomy indicated a clear trend for longer overall survival and a significant better disease-free survival rate for D2 compared to D1 patients[14]. These data strongly suggested that D2 lymphadenectomy with spleen and pancreas preservation should be recommended as the standard surgical approach to resectable gastric cancer.

In Western countries a substantial percentage of gastric cancer patients presents with unresectable disease. In such cases, the role of non-curative gastric resection, excluding the cases with signs of gastric outlet obstruction or uncontrolled bleeding, remains controversial[28]. On the one hand, resection allows reduction of tumor burden and cancer-related complication rates, but it is associated with significant perioperative mortality and morbidity and may delay start of chemotherapy[29]. On the other hand, simple operative exploration without resection may expose patients to severe tumor complications[30]. Pending large, randomized, prospective studies, no definitive evidence supporting either one strategy exists. However, all single series provide evidence for chemotherapy to improve survival rates and to decrease the incidence of tumor-related complications[31].

Peritoneal carcinosis is the most common type of recurrence in advanced gastric cancer, particularly in undifferentiated or with infiltrating growth pattern tumors[32]. When possible, complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) have been shown to be the best option for a disease that is otherwise incurable[33]. Recently, in high risk gastric cancers, that is, tumors suspected to have serosal invasion and/or poor histologic differentiation, analysis of liquid from peritoneal lavage has been suggested to be crucial to individuate free tumor cells in the abdominal cavity in order to tailor more effective treatments[34]. This is a new fascinating frontier in the management of gastric cancer[35]. Preliminary results of potentially curative gastric resection of the primary tumor and HIPEC in patients without overt peritoneal carcinosis despite detection of free tumor cells in the peritoneal lavage are encouraging[36,37].

The last challenge in the treatment of gastric cancer is represented by liver metastases. Until few years ago their detection was considered synonymous with generalized neoplastic disease, thus contraindicating curative treatment[38,39]. There is no doubt that gastric cancer shows a very aggressive biology with high and early propensity to spread through lymphovascular vessels and peritoneal serosa, thus liver-only deposits are an uncommon event[40]. However, even when this occurs, better survival rates have been demonstrated to be achievable with aggressive treatment. Curative hepatic resection of liver-limited metastases, particularly single liver metastases less than 5 cm in size, has been associated with significantly superior 5-year overall survival and median survival rates than those obtained with sys-

Table 1 Meta-analyses of adjuvant chemotherapy for resectable gastric cancer

Ref.	Year	Trials (*n*)	Patients (*n*)	OR/HR for death (95%CI)
Hermans *et al*[71]	1993	11	2096	0.88 (0.78-1.08)
Earle *et al*[57]	1999	13	1990	0.80 (0.66-0.97)
Mari *et al*[56]	2000	21	3658	0.82 (0.75-0.89)
Panzini *et al*[58]	2002	17	3118	0.72 (0.62-0.84)
Janunger *et al*[61]	2002	21	3962	0.84 (0.74-0.96)
Zhao *et al*[72]	2008	15	3212	0.90 (0.84-0.96)
Liu *et al*[73]	2008	19	4599	0.85 (0.80-0.90)
GASTRIC group[62]	2010	17	3838	0.82 (0.76-0.90)

temic chemotherapy alone[41,42]. Radiofrequency ablation may represent a valid alternative to surgical resection in liver metastasis with Ø ≤ 3 cm or for patients unfit for major hepatic surgery[43]. Finally, delivery of high doses of cytotoxic agents to liver tumors through the hepatic artery with minimal systemic side effects may be an effective strategy for control of multiple liver metastases or in order to shrink liver deposits prior to subsequent surgical resection or radiofrequency ablation[44].

ADJUVANT THERAPIES

Although complete resection of cancer (R0) and extended lymph node dissection (D2) are the only curative treatments for gastric cancer, a high rate of locoregional as well as distant recurrences has been reported. The site of recurrence is locoregional in 19%-42% of cases, peritoneal in 21%-72%, and distant in 18%-49%. A survival benefit has been observed from the addition of chemotherapy or chemoradiotherapy to surgery alone, while no benefit has been obtained with adjuvant radiotherapy alone[28,45-47].

Adjuvant chemotherapy

In the last decades, several phase Ⅲ trials have investigated the role of adjuvant chemotherapy *vs* surgery alone, but conflicting results have been obtained. These differences can be explained by the large heterogeneity of patients enrolled, the small number of series, the different surgical accuracy, and the different chemotherapy regimens used[48-54]. We also investigated in a randomized, multicenter, phase Ⅲ trial the efficacy and safety of epirubicin, leucovorin, 5-fluorouracil and etoposide combination (ELFE regimen) as adjuvant therapy for radically resected gastric cancer patients. After a 5-year follow-up, the ELFE regimen was not shown to improve overall survival when compared to surgery alone[55].

In order to obtain more reliable results, several meta-analyses (Table 1) and two recent phase Ⅲ trials have been carried out, conclusively establishing a statistically significant benefit for chemotherapy in terms of overall survival and recurrence rate[56-62].

A recent meta-analysis performed by the GASTRIC group[62], including 3838 patients from 17 different trials of adjuvant chemotherapy, concluded for a modest but statistically significant benefit with the use of adjuvant post-operative chemotherapy with respect to surgery alone (HR = 0.82; 95%CI: 0.76-0.90, P = 0.001). The estimated median survival was 4.9 years (95%CI: 4.4-5.5) in the surgery-only group *vs* 7.8 years (95%CI: 6.5-8.7) in the group of treated patients. However, no standard CT regimen has been defined in this setting.

Mono-chemotherapy with fluoropyrimidines has been tested in the Asian ACTS-GC trial by Sakuramoto *et al*[63] 1059 stage Ⅱ-Ⅲ gastric cancer patients were randomized to receive S-1, an oral fluoropyrimidine containing tegafur, gimeracil and oteracil potassium, as post-operative therapy (two oral doses of 40 mg per square meter per day for 4 wk followed by 2 wk of rest for 1 year), or surgery alone. A statistically significant advantage in terms of 3-year survival was observed in the chemotherapy arm (80.1%, 95%CI: 76.1-84.0) *vs* the surgery arm (70.1%, 95%CI: 65.5-74.6), with a good tolerability for S-1 and a low incidence of G3-4 toxicities (anorexia 6%, nausea 3.7%, diarrhea 3.1%). A similar advantage was also recorded in the following 5-year survival analysis (72.6% *vs* 61.4%, HR = 0.65; 95%CI: 0.53-0.81). However, these results were limited by patient selection, thus needing to be confirmed in a more heterogeneous population. Furthermore, the use of S-1 in Western countries could be limited by pharmacokinetic factors. Tegafur (5-fluorouracil pro-drug) pharmacokinetic is indeed limited by polymorphisms in cytochrome P-450 2A6, and, consequently, 5-fluorouracil plasma concentrations are more likely to be elevated in patients from Western countries[64].

Furthermore, in the CLASSIC phase Ⅲ trial led by Bang *et al*[65], 1035 patients with stage Ⅱ-ⅢB gastric cancer were randomly assigned to receive adjuvant chemotherapy with 8 cycles of capecitabine (1000 mg per square meter twice daily for 2 wk in a cycle of 21 d) plus oxaliplatin (130 mg per square meter every 21 d), so called XELOX, or surgery alone. After a median follow-up of about 34 mo, 3-year disease-free survival rates were 74% and 59% in the surgery plus chemotherapy and surgery only group, respectively (HR = 0.56; 95%CI: 0.44-0.72, P < 0.0001). Grade 3 or 4 toxicities were recorded in 56% of patients in the chemotherapy arm (nausea 65.7%, neutropenia 60.5%, anorexia 59.3%). At the 15th ESMO World Congress in Gastrointestinal Cancer (July 2013), data from the 5-year follow-up of the CLASSIC trial demonstrated a 34% reduction in the risk of death in the XELOX arm, higher than the reduction previously reported after three years of follow-up[66].

Adjuvant XELOX might represent a valid strategy in curable gastric cancer Asian patients. Currently, there is no doubt on the survival benefit derived from adjuvant chemotherapy in radically resected gastric cancer for stage ⩾ T2 or N+ according to United States, European, and Italian guidelines[67-69], although further phase Ⅲ trials are required to assess which regimen is optimal for both Western and Eastern populations.

The utilization of HIPEC as adjuvant setting in patients at high risk for carcinomatosis is very interesting.

The results of various clinical studies indicated that HIPEC could potentially allow for a better prognosis in patients who underwent resection for advanced gastric cancer playing a role in the prevention of peritoneal local-regional recurrence despite R0 resection. However because of small number of trials, further study about this matter are warranted[70].

Adjuvant chemoradiation

Considering the high rate of local recurrence in gastric cancer, combined treatment with radiation therapy and sensitizing 5-fluorouracil or capecitabine has been compared with chemotherapy or surgery alone in several trials.

The addition of post-operative radiation to adjuvant chemotherapy has been firstly studied in a prospective randomized trials by Dent *et al*[74], Moertel *et al*[75], and the British Stomach Cancer Group[45]. Data from this studies did not show a survival benefit for patients receiving adjuvant therapy, however, because of their small accrual, heterogeneous cohort, unstandardized surgery and radiotherapy, and 5-fluorouracil dosage, it is difficult to draw conclusions from these studies.

An important role was played by the Gastrointestinal Cancer Intergroup phase Ⅲ Trial (INT 0116)[26]: 566 patients were randomized to receive surgery alone or adjuvant chemoradiation consisting of 5-fluorouracil (425 mg per square meter daily) plus leucovorin (20 mg per square meter daily) for 5 d and radiation (4500 cGy of radiation, 180 cGy per day, given 5 d per week for 5 wk), followed by 2 cycles of 5-fluorouracil (425 mg per square meter daily for 5 d) plus leucovorin (20 mg per square meter daily for 5 d) for one month. After a median follow-up of 5 years, the chemoradiation group achieved a significant advantage in overall survival (36 mo *vs* 27 mo, $P < 0.005$) and in progression-free survival (HR = 1.52; 95%CI: 1.23-1.86, $P < 0.001$). The advantage in the chemoradiotherapy-treated group has been recently confirmed at the 10-year follow up (disease free survival HR = 1.51; $P < 0.001$; overall survival HR = 1.32; $P < 0.004$)[76]. Local recurrence occurred in 29% of patients in the surgery alone group and in 19% in the chemoradiation group; regional relapse was reported in 72% of patients in the surgery alone group and in 65% of the patients in the chemoradiation group; distant metastases were observed in 18% of relapsing patients in the surgery alone group and in 33% of patients in the chemoradiation group. Of note, treatment was burdened by high toxicity, with the most common G3 toxicities being hematologic (54%) and gastro-intestinal (33%). Although this treatment approach is considered to be standard therapy in the United States, it has not gained wide acceptance in Europe because of concerns about abdominal chemoradiation toxicity and the quality of surgery performed; indeed, 54% of enrolled patients received a sub-optimal lymph-node dissection (D0-D1). In order to clarify this issue, a subgroup analysis published in 2002 revealed that the survival benefit of adjuvant chemo-radiotherapy remained similar in the D0 and D1 lymph-node dissection groups, while survival benefits in the D2 dissection group were doubtful. Therefore, radiation therapy can be useful to compensate inadequate surgery, by improving local control of disease and reducing local relapses (19% *vs* 29%)[77,78].

The results of the phase Ⅲ ARTIST trial have been recently published[79]. 458 patients with D2 resected gastric cancer were randomly assigned to receive adjuvant XP (capecitabine 2000 mg per square meter on days 1 to 14 and cisplatin 60 mg per square meter, repeated every 3 wk) or XP/XRT/XP (capecitabine 2000 mg per square meter on d 1 to 14 and cisplatin 60 mg per square meter, repeated every 3 wk followed by 45 Gy radiations plus capecitabine 1650 mg per square meter for 5 wk followed by 2 additional cycles of XP). With a median follow-up of 53.2 mo, the adjuvant chemoradiotherapy arm did not obtain a significant advantage over the chemotherapy alone arm, with 3-year disease-free survival rates of 78.2% and 74.2% in the XP/XRT/XP arm and in the XP arm ($P = 0.0862$), respectively. Of note, in a subgroup analysis of 396 patients with positive pathologic lymph nodes, a statistically significant prolonged disease-free survival was recorded in the chemoradiation arm (estimated 3-year disease-free survival rate of 77.5%) as opposed to the XP-alone arm (3-year disease-free survival: 72.3%, $P = 0.0365$). This improvement in disease-free survival was mainly due to radiation-induced decreased regional lymph node recurrence. Most common G3-G4 toxicities in chemo- and chemoradiation arms were respectively: neutropenia (40.7% and 48.4%), nausea (12.4% and 12.3%), and vomiting (3.5% and 3.1%). In the ARTIST-2 trial this promising role of chemoradiotherapy *vs* chemotherapy alone in patients with node positive gastric cancer is still being evaluated.

Recently, Zhu *et al*[80] have published data from a trial carried out in the Chinese population. Specifically, 380 patients with D2 resected gastric cancer were randomized to receive adjuvant chemotherapy alone *vs* adjuvant chemoradiation therapy with intensity-modulated radiotherapy (IMRT). A significant difference in DFS in patients with positive nodes and in the whole population as well was observed. The marked effect on disease-free survival in this trial as opposed to the ARTIST trial was probably due to inclusion of patients with more advanced disease, especially in terms of lymph nodes involvement, and to the use of IMRT.

These results still need to be reproduced in the Western population and will be defined by the ongoing CRITICS trial (see below)[81].

The employment of a triplet in a chemoradiation regimen has also been recently investigated by the Intergroup Trial CALGB 80101 (presented as abstract at the 2011 ASCO Annual Meeting)[82]. From April 2003 to May 2009, 546 patients with resected gastric or gastro-esophageal cancer patients were randomized to receive 1 cycle of 5-fluorouracil (425 mg per square meter daily) plus leucovorin (20 mg per square meter daily) for 5 d/mo, followed by 45 Gy (1.8 Gy/d) and concurrent 5-fluorouracil (200 mg per square meter daily CI throughout radiotherapy), followed by 2 additional cycles of 5-fluorouracil/leucovorin (arm A) or 1 additional cycle of ECF (epirubicin 50 mg per square meter on day 1, cisplatin 60 mg per square meter on day 1, and 5-FU 200 mg per square meter CI d 1-21) followed by 45 Gy (1.8 Gy/d) and concurrent 5-fluorouracil (200 mg per square meter daly CI throughout radiation therapy), followed by 2 cycles of reduced dose of ECF (epirubicin 40 mg per square meter on day 1, cisplatin 50 mg per square meter on day 1, and 5-FU 200 mg per square meter daily C.I. d 1-21) (arm B). Median survival was 37 mo in arm A and 38 mo in arm B (HR = 1.03, 95%CI: 0.80-1.34, $P = 0.80$). Three-year overall survival was 50% in arm A and 52% in arm B, respectively. 3 year-DFS was 46% in arm A and 47% in arm B. Grade 4 toxicities were: 40% arm A *vs* 26% arm B ($P < 0.001$). Specifically, neutropenia (53% *vs* 48%), diarrhea (15% *vs* 7%), and mucositis (15% *vs* 7%) for arms A and B, respectively, were the most frequent.

We also assessed, in a pilot study published three years ago, the safety of adjuvant chemoradiotherapy in patients with stage Ⅲ or Ⅳ radically resected gastric cancer. Treatment with FOLFOX regimen plus radiotherapy was safe, and, after a 3-year follow-up, both disease-free and overall survival rates were shown to be substantially better than those observed in untreated patients[83].

Finally, European and Italian guidelines encourage use of adjuvant chemoradiotherapy in patients with high risk of local relapse (stage T2 with histopatological risk factors, T3-4, N+) and in patients not receiving adequate lymphadenectomy (< D2) or are R1 after surgery[68,69].

Necessarily, the planning of radiotherapy fields requires experience and a quality control system. Radiotherapy is influenced by its confirmation in 3D (3D-CRT) or IMRT, and these technologies have been shown to reduce toxicities. A total radiation dose of 45 Gy is set to run in 25 fractions of 1.8 Gy. The delimitation of volumes must meet the guidelines established by RTOG and EORTC and include tumor bed, celiac lymph nodes, and para-aortic nodes.

NEOADJUVANT (PERIOPERATIVE) TREATMENT

Neoadjuvant chemotherapy for gastric cancer aims at downstaging disease, increasing the rate of curative resection, and eradicating undetectable micrometastases. In addition, pre-surgical patients usually have better performance status and can tolerate treatments better.

This approach has been demonstrated to obtain downstaging of gastric cancer, increase in curative resections, and improvement of disease-free and overall survival in randomized clinical studies (MAGIC, FFCD 9703, and EORTC 40954). Currently, all guidelines recommend this approach for patients with locally advanced gastric cancer.

The use of radiation alone or in combination with chemotherapy in the preoperative setting is still controversial and more data from adequate powered randomized trial are needed.

Neoadjuvant chemotherapy

The role of neoadjuvant chemotherapy in gastric cancer, gastro-esophageal junction and lower esophageal adenocarcinoma has evolved in the past decade from disappointingly negative trials to a favorable one[61]. Indeed, in the first Dutch randomized controlled trial of neoadjuvant chemotherapy, 56 patients with apparently operable gastric cancer were randomized to receive preoperatively 4 cycles of 5-fluorouracil, doxorubicin and methotrexate (FAMTX) followed by surgery or surgery alone. The rate of curative resection favored the surgery alone group, and in the latest update, the median survival since randomization was 18 mo in the FAMTX group *vs* 30 mo in the surgery alone group ($P = 0.17$); moreover, preoperative chemotherapy was associated with a negative effect[84].

In Europe, perioperative chemotherapy has been promoted on the basis of the MAGIC[85] and FFCD9703[86] randomized trials. The former, performed in the United Kingdom, enrolled 503 patients with resectable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus cancer (25% had lower esophageal or gastro-esophageal junction cancer) to either perioperative chemotherapy and surgery (250 patients) or surgery alone (253 patients).

Chemotherapy consisted of 3 preoperative and 3 postoperative cycles of ECF: intravenous epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2) on day 1 and a continuous intravenous infusion of 5-fluorouracil (200 mg/m^2 per day for 21 d). Curative resection rates were 69.3% and 66.4% in the perioperative and in the surgery group, respectively. There was a greater proportion of stage T1 and T2 tumors and less advanced nodal disease in the perioperative group.

The perioperative chemotherapy group had a higher likelihood of overall survival (HR for death = 0.75; 95%CI: 0.60-0.93, $P = 0.009$; 5-year survival rate: 36% *vs* 23%) and progression-free survival (HR for progression = 0.66; 95%CI: 0.53-0.81, $P < 0.001$). Although 90.7% of patients completed preoperative chemotherapy, only 103 of 208 (49.5%) who completed preoperative therapy and surgery also received postoperative treatment.

A similar benefit emerged from the French FFCD 9703 trial, in which 224 patients were randomly assigned to 2 or 3 cycles of preoperative chemotherapy with infusional 5-fluorouracil plus cisplatin (CF) followed by

surgery and adjuvant CF chemotherapy, or surgery alone. Of note, 75% of all patients had adenocarcinoma of the distal esophagus or of the gastro-esophageal junction. The R0 resection rate was significantly better in the perioperative arm compared to the surgical resection alone arm (84% *vs* 73%, $P = 0.04$). Differences in the 5-year disease-free survival and the 5-year overall survival rate were 13% (34% *vs* 21%, $P = 0.0033$) and 14% (38% *vs* 24%, $P = 0.021$), respectively, in favor of neoadjuvant therapy.

Recently, the European EORTC 40954 trial[87] assessed the efficacy of preoperative cisplatin, 5-fluorouracil, and leucovorin in gastric and gastro-esophageal cancer patients. This study needed 282 events to detect with 80% power an improvement in median survival from 17 mo with surgery alone to 24 mo with neoadjuvant therapy. The trial was stopped early for poor accrual after 144 patients randomly assigned (72:72). The total of 52.8% patients had tumors located in the proximal third of the stomach, including AEG type Ⅱ and Ⅲ. The curative resection rate was 81.9% after neoadjuvant chemotherapy and 66.7% in the neoadjuvant and surgery alone arm ($P = 0.036$). The surgery-only group had more metastatic lymph nodes than the neoadjuvant group (76.5% *vs* 61.4%, $P = 0.018$). Postoperative complications were more frequent in the neoadjuvant arm (27.1% *vs* 16.2%, $P = 0.09$). After a median follow-up of 4.4 years and 67 deaths, a survival benefit could not be shown (HR = 0.84; 95%CI: 0.52-1.35, $P = 0.466$).

This trial showed a significantly increased R0 resection rate, but failed to demonstrate a survival benefit due to a low statistical power; there was a high rate of proximal gastric cancer including AEG and/or a better outcome than expected after radical surgery alone due to the high quality of surgery with resection of regional lymph nodes outside the perigastric area (celiac trunc, hepatic ligament, lymph node at *a. lienalis*; D2).

Radiation in perioperative therapy

The use of radiation alone as preoperative treatment remains unclear, due to limited numbers of randomized clinical trials evaluating the efficacy of radiotherapy alone.

Zhang *et al*[88] randomized a large sample size (370 patients) of gastric adenocarcinomas of cardia to surgery alone or radiotherapy for a total dose of 40 Gy and surgery. Tumor resectability and T2 cancer were more frequently observed in the radiation arm with a 11.0% decrease in T4 tumors. Five- and 10-year survival rates for radiation plus surgery and surgery alone groups were 30.1%, 19.7%, and 20.2%, 13.3%, respectively, while no significant differences were observed between the two groups in terms of surgical complications.

In another randomized trial with a longer follow-up (20 years), 51 patients per arm were randomly assigned to 20 Gy in 5 daily fractions followed by surgery or surgery alone. The 5-year and 10-year survival rates were 39.0% and 32.0%, and 30.0% and 18.0%, for preoperative radiotherapy and surgery alone groups, respectively ($P > 0.05$); however, after 20 years, the study failed to demonstrate a survival benefit for preoperative radiotherapy[89].

Of note, these two studies were started in the 1970s, when radiation used to be delivered by telecobalt or 8-MV photon, now rarely used.

Finally, in the meta-analysis of Fiorica *et al*[90], 9 randomized trials (4 preoperative and 5 postoperative trials) were evaluated. Preoperative radiotherapy was associated with a 3-year (HR = 0.57; 95%CI: 0.43-0.76, $P = 0.0001$) and 5-year (HR = 0.62; 95%CI: 0.46-0.84, $P = 0.002$) survival advantage. Although a trend in postoperative mortality in the preoperative treatment group was observed, this difference turned out not to be statistically significant (HR = 0.61; 95%CI: 0.24-1.57, $P = 0.31$). A recent meta-analysis confirmed a statistically significant benefit for resectable gastric cancer patients treated with radiation therapy, however, subgroup analyses for pre- and postoperative settings were not available[91].

Perioperative chemoradiation

Recently, a phase Ⅲ trial was carried out to investigate a possible survival benefit for preoperative chemoradiotherapy compared to chemotherapy alone in locally advanced gastroesophageal and gastric cancer patients.

In the German study PreOperative Chemotherapy or Radiochemotherapy in Esophagogastric Adenocarcinoma Trial[92], 119 patients were randomized to receive 5-fluorouracil, leucovorin, and cisplatin (PLF) followed by surgery or PLF followed by chemoradiation with cisplatin and etoposide and then surgery. Unfortunately, the trial was stopped prematurely due to poor accrual, thus limiting result interpretation. Nevertheless, response rate and tumor-free lymph node status were higher in the chemoradiation arm (cPR = 15.6% *vs* 2%, $P = 0.03$; ypN0 = 64.4% *vs* 36.7%, $P = 0.01$), although the 3-year survival benefit for the two groups did not reach statistical significance (47.4% *vs* 27.7%, $P = 0.07$).

Finally, the ongoing CRITICS trial (NCT00407186), in which patients with resectable gastric cancer are being treated with 3 cycles of preoperative epirubicin, cisplatin, and capecitabine (ECC) followed by surgery and then either another 3 cycles of ECC or concurrent chemoradiation (45 Gy, cisplatin and capecitabine) will help clarify the role of postoperative chemoradiotherapy[81].

METASTATIC DISEASE

In Western countries about two thirds of gastric cancer patients are diagnosed with locally advanced or metastatic disease. Median survival for these patients is around 10 mo, and less than 10% survive at 5 years. Furthermore, even after curative resection, about 50%-60% of patients relapse locally or with distant metastases. A PS > 2, liver metastases, peritoneal metastases, and alkaline phosphatase > 100 are considered unfavorable prognostic factors[93].

A meta-analysis by Wagener *et al*[94] demonstrated efficacy of chemotherapy compared with best supportive

care. Specifically, data from three randomized clinical trials favored chemotherapy in terms of quality of life and survival of patients with a good performance status (HR = 0.39; 95%CI: 0.28-0.52). Several trials and a meta-analysis also confirmed an advantage with regard to quality of life and survival when advanced gastric cancer patients were treated with combination chemotherapy with respect to single agent[95,96].

In the late 80's the FAM regimen (5-fluorouracil 600 mg/m^2 on days 1, 8, 29 and 36, adriamycin 30 mg/m^2 on days 1 and 29, and mitomycin C 10 mg/m^2 on day 1) became a widely used treatment[97,98], only to be later replaced by FAMTX (methotrexate 1500 mg/m^2, followed after 1 h by 5-fluorouracil 1500 mg/m^2 on day 1. Leucovorin rescue at 15 mg/m^2 after 24 h, orally, every 6 h for 48 h, and adriamycin 30 mg/m^2), according to the results of a randomized phase Ⅲ trial including 213 patients. The response rate of FAMTX was 41% *vs* 9% ($P < 0.0001$); survival with FAMTX was also superior (42 wk *vs* 29 wk, $P = 0.004$). There were no major differences in toxicity[99,100].

In Asian countries, cisplatin plus infusional 5-fluorouracil or capecitabine or S-1 is currently standard practice on the basis of a favorable Japanese trial[101]. The combination of cisplatin plus S-1 was also tested in metastatic gastric cancer in Caucasian patients[102,103] against cisplatin plus infusional 5-fluoruracil. Despite a slight better median survival for cisplatin/S-1, no statistical differences were found (8.6 mo *vs* 7.9 mo, HR = 0.92; 95%CI: 0.8-1.05, $P = 0.20$). Safety was significantly better in the cisplatin/S-1 group, however, the dose of cisplatin was lower (75 and 100 mg/m^2 in experimental and standard group, respectively).

The REAL Ⅱ trial by Cunningham *et al*[104] confirmed non-inferiority of capecitabine to infusional 5-fluorouracil (HR = 0.86; 95%CI: 0.80-0.99) and established non-inferiority of oxaliplatin to cisplatin (HR = 0.92; 95%CI: 0.80-1.10) in two-by-two comparisons. On day 1 of every 3-wk cycle, patients in all study groups received an intravenous bolus of epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2) in both the ECF and ECX groups, while oxaliplatin (130 mg/m^2) was administered intravenously in the EOF and EOX groups. 5-fluorouracil (daily dose of 200 mg/m^2) and capecitabine (twice daily doses of 625 mg/m^2) were given throughout treatment in the appropriate groups. Median survival times in the ECF, ECX, EOF, and EOX groups were 9.9, 9.9, 9.3 and 11.2 mo, respectively; 1 year-survival rates were 37.7%, 40.8%, 40.4%, and 46.8%, respectively. In a secondary analysis, overall survival was longer with EOX than with ECF, with a HR of 0.80 for death in the EOX group (95%CI: 0.66-0.97, $P = 0.02$). Progression-free survival and response rates did not differ significantly among the regimens. The EOX regimen was associated with the highest median survival. Response rates were 47.9% for EOX, 46.4% for EOF, 42.4% for ECX, and 40.7% for ECF (no significant differences among the four treatment arms). Oxaliplatin-based regimens were generally well tolerated, with inferior incidence of severe neutropenia, alopecia, and nephrotoxicity, and higher incidence of severe peripheral neuropathy and diarrhea.

Furthermore, in a meta-analysis including the REAL Ⅱ and MLI17032 trials, a longer survival and a higher response rate was observed with capecitabine (HR = 0.87) compared with infusional 5-fluorouracil-containing chemotherapy[105].

In United States docetaxel is the drug of choice to add to cisplatin and 5-fluorouracil, based on V325 phase Ⅲ trial results[106], in which 445 advanced gastric cancer patients were randomized to receive docetaxel 75 mg/m^2 (day 1) plus cisplatin 75 mg/m^2 (day 1) and 5-fluorouracil 750 mg/m^2 per day continuous infusion (days 1 to 5; DCF), or once every 4 wk cisplatin 100 mg/m^2 (day 1) and 5-fluorouracil 1000 mg/m^2 per day continuous infusion (days 1 to 5; CF). The addition of docetaxel to CF significantly improved time to progression (5.6 mo *vs* 3.9 mo), survival (9.2 mo *vs* 8.6 mo), and overall response rate (37% *vs* 25%), despite the poor prognosis of the selected population, when compared with the CF-treated population. However, an increased rate of neutropenia (29% incidence of febrile neutropenia) was recorded. For this reason, the DCF regimen could be recommended for patients with good performance status[107].

Conversely, epirubicin, cisplatin, 5-fluorouracil (ECF) is the favorite three-drug regimen in Europe on the basis of two randomized studies[108,109] and a meta-analysis[96]. ECF showed a higher overall response rate (45% *vs* 21%, $P = 0.0002$), a longer median time of survival (8.9 mo *vs* 5.7 mo, $P = 0.0009$) and a better median failure-free survival duration (7.4 mo *vs* 3.4 mo, $P = 0.00006$) when compared with FAMTX. A better quality of life with the ECF regimen was also recorded.

HER2 is overexpressed in 10%-25% of gastric cancer. Recently, the international phase Ⅲ ToGA trial[110] randomized 594 HER-2 positive metastatic gastric cancer to receive capecitabine (1000 mg/m^2 orally twice a day for 14 d followed by a 1-wk rest), or 5-fluorouracil (800 mg/m^2 per day by continuous intravenous infusion on d 1-5 of each cycle) plus cisplatin (80 mg/m^2 on day 1 by intravenous infusion) with or without trastuzumab (8 mg/kg intravenously on day 1 of the first cycle, followed by 6 mg/kg every 3 wk). The addition of trastuzumab to chemotherapy improved significantly overall survival compared with chemotherapy alone (13.8 mo *vs* 11.1 mo, HR = 0.74, $P = 0.0046$) as well as progression free survival (6.7 mo *vs* 5.5 mo, HR = 0.74, $P = 0.0002$). A greater survival benefit was detected in an exploratory subgroup analysis of patients HER2 2+ and FISH positive, and HER2 3+ and FISH positive (16.0 mo *vs* 11.8 mo, HR = 0.65). Also, response rate and time to progression were significantly improved by the addition of trastuzumab.

Thus, trastuzumab, in association with platinum and 5-fluorouracil or capecitabine, is now widely considered the standard of care for first line therapy of patients diagnosed with HER 2 positive gastro-esophageal junction

Table 2 Milestone phase Ⅲ trials in metastatic gastric cancer

Ref.	Regimen	*n*	Response rate	Overall survival	DSF/PFS/TTP	G3-G4 toxicity
Cullinan *et al*[122], 1985	FAM	350	-	-	-	-
	5-FU					
Wils *et al*[100], 1991	FAMTX	213	41%	42 wk		4%
	FAM		9%	29 wk		3%
					Median TTP: 12	
Kim *et al*[123], 1993	FAM	117	51%	No difference	21.8	-
	PF		26%		9.1	
	5-FU					
					PFS	
Webb *et al*[108], 1997	FAMTX	256	21%	5.7	3.4	-
	ECF		45%	8.9	7.4	
Vanhoefer[124], 2000	ELF		9%	7.2		No toxicity G 3- 4
	PF		20%	7.2		
	FAMTX		12%	6.7		
					TTP:	
Van Cutsem *et al*[106]	CF	224	37%	9.2	3.9	69%
V325 trial, 2006	DCF	221	25%	8.6	5.6	59%
Cunnigham *et al*[104]	ECX	250	42.4%	11.2	ECF: 40.7 and	Neutropenia most frequent in
REAL II, 2008	EOX	244	47.9%		similar in all groups	ECX and ECF regimen 51.5%
	ECF	263	40.7%	9.9		and 41.7% *vs* 29.9% and 27.6%
	EOF	245	46.4%			
					PFS:	
Koizumi *et al*[101]	S-1	150		11	4.0	Neutropenia:
Spirit trial, 2008	CDDP + S-1	149		13	6.0	59% *vs* 16%
						Anemia: 38% *vs* 6%
						Anorexia 45% *vs* 9%
					TTP	
Ajani *et al*[102]	CDDP+	508	32%	7.9	5.5	
FLAGS, 2010	5-FU	521	29%	8.6	4.8	
	CDDP + S-1					
Bang *et al*[110]	CDDP + 5-FU/Cap	290		11.1		
ToGA, 2010	CDDP + 5-FU/Cap +					Neutropenia
	Trastuzumab	294		13.8		88%
						79%

FAM: 5-fluorouracil, adriamycin, mitomycin; 5-FU: 5-fluorouracil; FAMTX: 5-fluorouracil, adriamycin, metrotexate; PF: Cisplatin, 5-fluorouracil; ECF: Epirubicin, cisplatin, 5-fluorouracil; ELF: Etoposide, leucovorin, 5-fluorouracil; CF: Cisplatin, 5-fluorouracil; DCF: Docetaxel, cisplatin, 5-fluorouracil; ECX: Epirubicin, cisplatin, capecitabine; EOX: Epirubicin, oxaliplatin, capecitabine; EOF: Epirubicin, oxaliplatin, 5-fluorouracil.

and gastric cancer. Table 2 summarizes the results of the main phase Ⅲ trials of chemotherapy for advanced gastric cancer.

Despite the promising results obtained in phase Ⅱ trials, addition of HER 1 inhibitors cetuximab and panitunumab to chemotherapy failed to increase overall and progression free survival of metastatic gastric cancer patients in the phase Ⅲ randomized trials EXPAND[111] and REAL Ⅲ[112]. Disappointing results were also obtained with the anti-angiogenetic antibody bevacizumab used in combination with platinum-based chemotherapy[113,114].

Recently a phase Ⅲ LoGic trial[115] of first line capecitabine and oxaliplatin did not reach its primary endpoint, with a hazard ratio (HR) for OS of CapeOx + L compared to CapeOx + P of 0.91 (95%CI: 0.73-1.12, $P = 0.35$); median 12.2 mo *vs* 10.5 mo, respectively. Prespecified subgroup analyses showed significant improvements in OS in Asian pts (HR = 0.68) and those under 60 years (HR = 0.69). There was no association between IHC and OS. though certain subgroups showed improvement. Further clinical and molecular analyses will be presented. The results of the phase Ⅲ TYTAN[116] trial conducted in Asia indicate that HER2-targeted therapy, Lapatinib, has the potential to prolong patient survival when used in the second-line setting in HER2-positive advanced gastric cancer, but only in individuals who test HER2 positive by immunohistochemistry (IHC 3+).

The role of a second line has been recently clarified. Randomized clinical trials[117-119] and a meta-analysis[120] demonstrated improved overall survival and quality of life with irinotecan or docetaxel chemotherapy *vs* best supportive care.

Finally, at the latest ASCO Meeting, ramucirumab, a fully human immunoglobulin G1 monoclonal antibody highly specific for the extracellular VEGF-binding domain of VEGFR-2, was demonstrated to have a significant antitumor activity in a range of malignancies, according to results in clinical trials. The REGARD trial for gastro-esophageal and gastric adenocarcinoma demonstrated ramucirumab to significantly improve overall survival and progression-free survival *vs* BSC, with a median overall survival increasing from 3.8 to 5.2 mo ($P = 0.0473$)[121]. This translated into a 22% reduction in the risk of death with ramucirumab.

Ramucirumab has also been evaluated in combination with paclitaxel in the phase Ⅲ RAINBOW trial, but results are still pending.

CONCLUSION

Depending on the site and extent of cancer, surgery is the only potentially curative treatment for all T1b-T4 gastric cancers, and extended lymphadenectomy (D2) should be recommended as standard of care in resectable gastric cancer, while endoscopic submucosal resection followed by close surveillance is the preferred option for early stage cancer. Surgical treatment of liver-limited metastases and hyperthermic intraperitoneal chemotherapy for peritoneal carcinosis are fascinating frontiers.

Furthermore, a survival benefit for postoperative chemotherapy, chemoradiotherapy, and perioperative chemotherapy in case of pathologic T > 2 and/or node-positive gastric cancer patients has been established, and chemotherapy should contain 5-fluorouracil and cisplatin or their analogs capecitabine and oxaliplatin. Neoadjuvant chemoradiation should be implemented with caution.

Finally, in select metastatic gastric cancer patients, chemotherapy is better than best supportive care only, with cisplatin-5-fluorouracil or capecitabine as the most widely used drugs. Addition of anti-HER2 antibody trastuzumab to first-line chemotherapy for patients overexpressing HER2 receptor and addition of the anti VEGFR-2 antibody ramucirumab in second line improves overall survival and progression-free survival when compared to chemotherapy alone.

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