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**Multimodal treatment of gastric cancer in West: Where are we going?**

Marrelli D *et al*. Multimodal treatment in gastric cancer

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**Abstract**

The incidence of gastric cancer is decreasing worldwide, above all for intestinal histotype of the distal third. On the contrary, proximal location and diffuse Lauren histotype have been reported to be generally stable over time. In the West, no clear improvement in long-term results was observed in clinical and population-based studies. Results of treatment in these neoplasms are strictly depending on tumor stage. Adequate surgery and extended lymphadenectomy are associated with good long term outcome in early stages; however, results are still unsatisfactory in advanced stages (III and IV), where additional treatments could provide a survival benefit. This implies a tailored approach to gastric cancer. The aim of this review is to summarize the main multimodal treatment options in advanced resectable gastric cancer. Perioperative or postoperative treatments, including chemotherapy, chemo-radiotherapy, targeted therapies, and hyperthermic intraperitoneal chemotherapy have been reviewed, and the main ongoing and completed trials have been analyzed. An original tailored multimodal approach to non-cardia gastric cancer has been also proposed.

**Key words:** Gastric cancer; Epidemiology; Chemotherapy; Radiotherapy; Hyperthermic intraperitoneal chemotherapy; Targeted therapy

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**Core tip:** In advanced gastric cancer the multimodal treatment is currently an option of choice in the West. Adequate surgery and extended lymphadenectomy, together with modern chemotherapy, radiotherapy, targeted therapies, and a combination of all could possibly improve survival in advanced stages of gastric cancer. A tailored multimodal approach is strictly necessary in the light of treatment results and recent epidemiological trends, which indicate a relative increase of more aggressive forms, such as proximal location and diffuse Lauren histotype in the West. The main ongoing and completed clinical trials regarding multimodal approach to gastric cancer have been reviewed, and an original tailored multimodal protocol to non-cardia gastric cancer has been proposed.

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**CHANGING EPIDEMIOLOGY OF GASTRIC CANCER**

Despite the reported declining incidence, gastric cancer (GC) is one of the most common causes of death for neoplasm in the world[1-3].

It represents the fourth most common cancer after lung, breast and colon-rectum, and the second most common cancer-related cause of death after lung cancer. Geographic variability of GC is also well known: highest incidence rates are observed in East Asia, Central Asia, Eastern European Countries, and Pacific coast of South and Central America, whereas the lowest incidence rates are found in Northern Europe and Northern America[3]. Even within the same State, wide geographic incidence variability can be observed: in Italy, mortality is high in Central Area, above all along the Central Appennine mountains, and very low in Southern Italy[5,6]. Even if in partly obscured by population aging, a decreasing incidence of GC has been reported worldwide in the past decades. This epidemiological trend has been attributed to several factors, such as the increased consumption of vegetables and fruit instead of cured meat, and changed methods of food conservation (refrigeration, instead of salt preservation)[7]. The decreased prevalence of *Helicobacter pylori* infection had also a role. However, decreasing rates were more evident in high-risk areas, whereas in low-risk areas they fell slowly, with a trend to become stable over time[5,6,8,9].

Certain subtypes of GC demonstrate different epidemiological features. Tumors located in the distal third of the stomach showed the most evident decrease in incidence rate, whereas proximal tumors are stable or even increasing[10,11]. This trend has been confirmed in some recent specific studies: incidence decreased among males and females, but the proportion of cardia tumours remained stable over time; five-year survival worsened over time for patients with non-cardia tumours, whereas the risk of death decreased for patients with a cardia tumour[12].

Different epidemiological trends in the intestinal (IT) and diffuse (DT) Lauren histotypes were also observed. The declining incidence of GC has been linked to the decreasing number of IT; on the contrary, the incidence of DT is generally stable throughout the world[10,13-15]. As most proximal tumors are IT, it is important, when evaluating epidemiological trends, to subset data according to histotype and location. In a recent study from the Italian Research Group for Gastric Cancer (GIRCG), a decreasing number of IT of the distal stomach was observed; on the contrary, IT located in the proximal third, and DT, at any location, were stable over time[9]. As a consequence, the DT neoplasms showed a relative increase with time (Figure 1).

Recent studies also reported different trends of GC incidence in young age; declining rates were observed for subjects 40–84 years of age, whereas for younger cohorts, incidence rates increased over time[16]. Recent reports from Europe also confirmed these findings[17]. The higher prevalence of DT in young age may contribute to explain the epidemiological trends described for specific histotypes of GC.

As for GC prevention, two potential strategies may be proposed. A primary prevention is possible due to eradication of Helicobacter pylori, and a secondary prevention by detection of GC in mass screening[4].

Primary prevention is based on the fact that H. pylori is the strongest known factor associated with distal IT. The infection is possible to eradicate using antibiotics in association with an antisecretory agent. It is proposed to offer a prophylactic eradication for high-risk individuals, or in high-risk areas.

The secondary prevention- a mass screening is performed in countries with the highest incidence of GC. In Japan or South Korea the screening programs seems to be effective, with the higher rate of early GC detection, improved 5-year survival, and improved proportion of localized GC at diagnosis[4,17]. The main offered methods are- barium X-Ray, combination of barium digital radiography together with serum pepsinogen testing, and an endoscopy with photofluorography. However, a mass screening is hard to promote and organize in low-risk areas, where few but more advanced GC cases, mainly with proximal location or DT, are generally observed in clinical practice[4].

**CLINICAL IMPLICATIONS OF THE CHANGING EPIDEMIOLOGY**

The above mentioned epidemiological trends could have important clinical implications. Indeed, the overall number of newly diagnosed GC cases is decreasing, but the relative percentage of proximal locations and DT is increasing. Proximal tumors, including those involving the esophago-gastric junction (EGJ), have been demonstrated to be associated with higher clinical aggressiveness and worse prognosis in several studies[9,19-21]. As such, the relative increase in the proportion of proximal tumors could lead to general decrease of survival probability.

Another important consequence of epidemiological trends is the relative increase of the DT tumors (Figure 2). Besides histomorphometrical characteristics, IT and DT histotypes show evident differences in epidemiological, clinical and molecular features[22]. It is more common in males and older patients, whereas DT usually affects younger patients with a lower male-female ratio. Environmental factors seem to be involved in pathogenesis of IT, as it usually follows the sequence chronic atrophic gastritis, intestinal metaplasia, and dysplasia; on the contrary, DT usually originates from healthy gastric mucosa or non-atrophic gastritis and is more related to genetic factors. A characteristic of the DT is also the greater biological aggressiveness. The risk of lymph node metastasis is higher in the DT, as compared with the IT, at the same T stage. Indeed, the DT is a strong risk factor for lymph node metastasis in early gastric cancer[23], but an increased risk is also present in more advanced pT stages. In the Figure 3, the correlation between lymph node metastasis and Lauren histotype, stratified for pT stage, has been evaluated in 2090 non-cardia GC from the GIRCG database. The incidence and the number of lymph node metastases resulted notably higher in the DT, as compared with the IT at the same pT stage. Furthermore, the DT is also a risk factor for lymph node metastases in extra-regional nodal stations (such as para-aortic nodes)[24,25].

These features could notably affect the indications to more extended lymphadenectomy and neo-adjuvant treatments in the DT, due to the higher probability of lymph node involvement. On the other hand, clinical diagnosis, by radiological imaging, of lymph node metastasis may be more difficult in the DT; it has been reported that in this histotype the size of involved nodes may be smaller than the commonly used cut-off values[22].

Besides the lymph node involvement, DT tumors also show a greater propensity to peritoneal spread. Indeed, several studies demonstrated the higher risk of peritoneal recurrence in DT, above when the serosa is involved[22,26].

In a GIRCG follow-up study, the 5-year risk of peritoneal recurrence has been calculated to be 69% in DT with serosal involvement, *vs* 20% of the IT cases at the same pT stage. It has been demonstrated that the clinical impact of extended surgery, including D2/D3 lymphadenectomy, is of low value in serosally exposed forms at risk of peritoneal recurrence[27,28].

The chance of cure in patients with peritoneal recurrence of GC is very low: in a GIRCG follow-up study, 5-year survival probability in 221 patients with metachronous peritoneal carcinomatosis (PC) was only 3% (Figure 4)[29]. As such, prevention of peritoneal recurrence, more than treatment after its occurrence, may be the only potential chance of cure in high-risk cases[30].

The DT, in a late phase, could evolve into a diffuse infiltration, thickening and stiffening of the gastric wall with reactive fibrosis, also named gastric linitis plastica. This is a subset of GC with a large propensity to diffuse infiltration, massive lymph node metastasis, and peritoneal seeding[31]. The rate of radical resection in this form of GC is lower than 30%, and, even after an R0 resection, the five-year survival probability does not overcome 5%. Interestingly, some population-based studies from Europe, along with the decreased incidence of GC, reported a significant increase of gastric linitis plastica with time[32]. These data are consistent with previously mentioned epidemiological trends.

All these features of GC may be also at the basis of epidemiological and survival data reported in large studies from European Countries. Recent data from 49 cancer registries in 18 European countries (EUROCARE-4 working group), reported a notable survival increase in Europe over the period 1988–1999 for several cancer sites, in particular for prostate, colon-rectum and breast. However, for stomach cancer the increase was very small (from 22% to 24%), despite potential time-related improvements in diagnosis, surgical and medical treatment[33]. Interestingly, survival improvement was higher for men (4.1%) than women (1.4%). Authors explained these data with the declining incidence of cancers of the distal stomach, than those arising in the cardia or fundus, which are usually diagnosed in older patients, at advanced stage, and with diffuse/signet ring morphology. Other population-based and clinical studies reported similar results. In the previously mentioned French study, the global prognosis of GC did not improve significantly over a 12-year period of observation[32]. Recent studies from the Nederlands also confirmed the decreasing incidence of GC but stable survival rates over time[34].

These data seem to be consistent with the findings of a previous GIRCG study: along with the decreasing number of distal IT tumors and the relative increase of DT forms with time, a lacking improvement of cancer-related survival probability and a significant increase of peritoneal recurrence after surgery was observed[9]. In particular, survival rates decreased in the more recent period in the group of patients with serosal involvement, in females and in distal tumors, whereas an increasing trend was observed in proximal tumors. All these data may fit with the hypothesis that the relative increase of DT tumors may have contributed to the lacking or small improvement of treatment results of GC in Western Countries.

**TREATMENT OF EARLY FORMS**

Surgical treatment with adequate lymphadenectomy could offer a high probability of cure even in Western patients. Survival rates in early stages reported from specialized Western centers are very similar to those obtained in series from Japan and Korea[21,27,35].

Selected forms of early gastric cancer can be treated by endoscopic mucosal resection or endoscopic submucosal dissection, in accordance with the standard criteria described by the Japanese Gastric Cancer Association (JGCA), with acceptable results even in the West[36,37]. The resection is judged as curative when all of the following conditions are fulfilled: en-bloc resection, tumor size not greater than 2 cm, histology of intestinal-differentiated-type, pT1a, negative horizontal (lateral) margin, negative vertical margin, and no lymphovascular invasion.

Although endoscopic approach to early forms is increasing in specialized centers in the West, it is still far from become a clinical standard. Early forms not treatable by endoscopic resection should be submitted to surgical resection with lymphadenectomy. According to the JGCA treatment guidelines[36] a D1 lymphadenectomy may be adequate in early forms with clinically negative lymph nodes. However, we should underline that a proportion of early forms in the West are DT, which is associated with a higher risk of lymph node metastases and greater lymph node spread, above all when submucosa is involved. Furthermore, in the West endoscopic resections, which can be considered as treatment but also staging procedures, are performed much less frequently than in East Asia, and the clinical diagnosis of lymph node metastasis by imaging procedures has still a low accuracy[38]. As such, the Italian guidelines advice a standard D2 lymphadenectomy in early forms of GC[39]. Only in selected cases (high-risk patients, early forms with favourable pathological characteristics, not treatable by endoscopic resections) more limited procedures should be considered (D1 plus).

Early forms of GC could also be treated by minimally-invasive (laparoscopic or robotic) approach, which demonstrated non-inferior oncological results than open surgery in recent studies[40,41]. However, it should be emphasized that oncological criteria regarding resection margin and lymph node dissection need to be carefully followed in minimally-invasive procedures.

**TREATMENT OF ADVANCED RESECTABLE FORMS**

In advanced resectable forms of GC, it is now well established that an adequate surgical treatment is a key-point to obtain acceptable long-term results. As for the extent of resection, subtotal gastrectomy offers low postoperative morbidity and mortality risk, and better quality of life, without affecting long-term oncological results, when an adequate resection margin can be obtained (R0 resection)[42]. A proximal margin of at least 3 cm is recommended for T2 or deeper tumors with an expansive growth pattern, and 5 cm is recommended for DT and tumors with infiltrative growth pattern. In all other cases, a total gastrectomy should be the preferred procedure. In early forms, a resection margin of 2 cm may be enough[39]. Total gastrectomy with splenectomy should be also recommended for tumors located along the greater curvature. Splenectomy should be performed only when a macroscopic involvement of lymph nodes at the splenic hilum is present.

The extent of lymphadenectomy is crucial. Even if some randomized studies failed to demonstrated a significant advantage on overall survival, a re-evaluation of the Dutch trial showed a reduced cancer-related survival in the long term and a higher incidence of late recurrence of GC in patients submitted to limited (D1) lymphadenectomy[41].

A crucial condition is that good early postoperative results in terms of morbidity and mortality should be ensured. This is consistent with the reports of observational non-randomized studies from specialized centers[44,45].

Nowadays, D2 lymphadenectomy is generally accepted as the standard approach in most national guidelines[39,46]. The correct procedure of lymphadenectomy involves the removal of nodal stations from 1 to 12, with some variations depending upon the extent of gastric resection[36]. Special attention should be paid upon to the complete removal of infra-pyloric nodes (station 6), right paracardial nodes (station 1), left gastric artery nodes (station 7), celiac axis (station 9), hepatic artery (station 8a), splenic artery (station 11), and hepatoduodenal ligament nodes (station 12a).

More extended lymphadenectomies (D2+) could be performed, in selected cases at risk of metastasis to posterior (station 8p, 12p, 12b, 13), mesenteric (station 14) or para-aortic (stations 16a2, b1) lymph nodes, in specialized centers and in the setting of clinical studies[22,23]. In particular, proximal tumors or DT are particularly prone to metastasize to distant nodes, and in our opinion they may benefit from a super-extended lymphadenectomy[25,28]. However, it should be emphasized that in more advanced stages (UICC TNM stages IIIA and more) results of surgical approach, even with adequate lymphadenectomy, are still unsatisfactory in Western patients[35]. As such, additional treatments should be planned to improve long-term survival probability in these forms.

**MULTIMODAL TREATMENT OF GASTRIC CANCER**

The neoadjuvant treatment seems to be a good option in advanced GC. The term advanced should be understood as a T3, T4 and/or N+ and/or with positive peritoneal cytology. In this case the majority of patients who are diagnosed in this stadium might get benefits from perioperative treatment.

Even though dietary changes and usage of antibiotics in fight with chronic Helicobacter pylori infection helped in steadily fallen down of new cases of GC, still the progress in GC treatment is limited[47]. Surgery is still the only treatment with curative intent in locoregional disease. From oncological point of view the issue is to resect the cancer with negative resection margin (R0), and with adequate lymph node dissection. The biggest problem especially in West is diagnosis of the patients with locally advanced disease. Advanced stage of the disease is associated with much higher rate of locoregional recurrence. That led to introduce additional treatments with multimodal concept in preoperative, perioperative and postoperative time. Nowadays we can observe differences in multimodal treatment of GC according to different places of the world. In Asia the most commonly used treatment is adjuvant chemotherapy, in USA the favored treatment is chemoradiotherapy (CRT), and in Europe neoadjuvant approach is mostly used. Nowadays some of these approaches change.

The GC still has a poor survival in advanced stages (less than 30% 5-year survival probability in stage III). As Cunningham *et al*[48] and Ychou *et al*[49] proved an advantage of starting multimodal treatment with preoperative chemotherapy over surgery alone this seems to be a good treatment option. In trial presented by Schumacher *et al*[50] the neoadjuvant therapy improved R0 resection rate even though it did not improve overall survival (OS). In the study by Stahl *et al*[51] neoadjuvant CRT showed higher rate of complete responders, and in the study by van Hagen *et al*[52] an improved OS was observed.

In Asian countries in contrast the highest interest lies in postoperative oral chemotherapy, which was associated with improved OS compared with surgery alone[53,54]. However, these results were not reproduced in Western countries.

In United States after presenting the result of trial by MacDonald *et al*[55] in 2001 CRT is used routinely.

***Neoadjuvant chemotherapy***

Neoadjuvant approach is currently recommended across Europe based on Magic trial and FNLCC/FFCD trial[48,49]. Another benefit of neoadjuvant chemotherapy (NC) discussed by Ott *et al*[56] for potentially resectable gastric cancer are higher rate of R0 resection achieved by downstaging of a primary tumor, and probable effect on micrometastases and isolated tumor cells in lymph nodes. This author underlines also that neoadjuvant setting is also more often proposed to younger and in general good health status patients.

In Magic trial the chemotherapy consisted of 3 cycles of i.v. epirubicin, cisplatin and 5-FU preoperatively and 3 cycles after operation[48]. NC was not associated with worse postoperative complications and 30-days mortality than surgery alone. So the argument that neoadjuvant setting may be more dangerous for patients was overthrown. From the main results 5-year survival rate was 36% *vs* 23% in favor of perioperative chemotherapy arm. Also statistically significant were OS and progression free survival (PFS). As only 49.5% of patients got the full perioperative chemotherapy treatment, this was one of the main issues criticized by some investigators. This issue was investigated in the study by Mirza *et al*[57] where it was checked for patients using the same regimen as in Magic trial. Benefit of full perioperative regimen was observed on DFS, but not on OS. The conclusion might be that administrating adjuvant part of this regimen postpone tumor recurrence rather that help in prevention.

The trial FNLCC/FFCD proved beneficial effect of perioperative chemotherapy for gastric and esophageal adenocarcinoma[49]. In preoperative period, 2 or 3 cycles of i.v. cisplatin and 5-FU were administered, and after surgical approach the chemotherapy was continued just in case of response to treatment or in stabilization. A higher rate of R0 resection in NC in comparison with surgery alone was observed, as well as improved OS and DFS. The 5-year survival rates were 38% *vs* 24% in favour of NC.

In a meta-analysis by Ronellenfitsch *et al*[58] OS was 9% better after neoadjuvant setting. This effect is seen 18 mo after surgery and lasted at least 10 years. R0 resections are achieved 1.4 times more often after neoadjuvant treatment. Importantly, side effects of neoadjuvant setting like postoperative morbidity or mortality as well as prolonged hospital stay were not increased significantly than in surgery alone arm. Another interesting aspect is that no benefit of neoadjuvant setting for elderly patients is seen. The biggest benefit for OS was observed in subgroup of patients with EGJ. One of the unanswered questions is the age of patients recruited to the trial. The median age of EGJ patient is 70, and over this age patients were in majority rejected from the trials. This issue is currently under investigation by a German group proposed by Spoerl. Another subgroup of patients with high interest is the signet ring cell carcinoma. They seem to do not benefit from neoadjuvant treatment[59]. The response rate differs also as we analyze subgroups of patients according to pathological features. In DT a good pathological response was only observed in 14.5% of patients[60].

In Asian countries also the concept of neoadjuvant treatment begins to play an important role. Currently several trials (JCOG 0210, JCOG 0501, JCOG 1002, and PRODIGY) are under investigation. Also in Italy a GIRCG phase II trial recruits patients with non-cardia GC who received an accurate pretreatment clinical staging with diagnostic laparoscopy and peritoneal washing, in all cases followed by standard D2 gastrectomy. This trial was aimed to answer whether preoperative or perioperative chemotherapy plays a role in advanced GC treatment (NCT01876927).

***Neoadjuvant chemoradiotherapy***

As NC proved to be safe preoperative treatment, the addition of radiotherapy in preoperative treatment has gained interest. The German POET trial compared NC vs CRT with locally advanced EGJ cancers[51]. In one arm 2 courses of cisplatin, 5-FU and folicid acid (FA)-(PLF) with afterwards 3 weeks of combined CRT (30Gy in 3 wk with cisplatin/etoposid), followed by surgery were administered, *vs* 2.5 courses of PLEF with surgery. This trial was closed early, and showed no significant difference in survival - 33.1 *vs* 21.1 mo in favor of CRT, but with higher mortality in CRT arm- 10.2% *vs* 3.8% (*P* = 0.26). Results regarding 3-year survival showed an improvement from 28% to 48% in CRT arm.

In study by Burmeister on 75 patients, the addition of radiotherapy increased the rate of pathological complete remission (13% *vs* 0%, *P* = 0.02), and reduced the rate of R1 resection (0 *vs* 4%, *P* = 0.04)[61]. Analyzing 5-year overall survival and progression-free survival, only a trend was observed in favor of CRT, without statistical significance (OS 45% *vs* 36%, *P* = 0.6).

In the CROSS trial from the Netherlands, patients with esophageal and EGJ cancers were assigned to CRT arm (carboplatin, paclitaxel and 41.4 Gy of radiotherapy in 23 fractions) followed by surgery, *vs* surgery alone[52]. The surgery alone arm showed R0 resection in 69% of patients with a median survival time of 24.2 mo, whereas in the neoadjuvant CRT arm the R0 resection was achieved in 92% (*P* < 0.001), with complete pathological response rate up to 29% of patients; however, it is noteworthy that in case of squamous cell carcinoma the complete response rate was better (49%) than adenocarcinoma (23%). The median survival time was 49.4 months (*P* = 0.003), and 5-year survival improved from 34% to 47%. Postoperative complications rate and in-hospital mortality were similar in both arms (4%). Neoadjuvant regimen also reduced locoregional recurrence rate (34% to 14%; *P* < 0.001), and the probability of PC (14% to 4%; *P* < 0.001). Distant metastases also showed a difference between both arms (35% *vs* 29%, *P* = 0.025). This treatment protocol is now recommended for neoadjuvant CRT in patients with EGJ adenocarcinoma in United States. Currently ongoing TOPGEAR trial investigates CRT *vs* CT in EGJ and stomach cancers. In CT arm 3 courses of ECF are given preoperatively, and in CRT arm 2 courses of ECF followed by 45 Gy, or a radiation with concurrent 5-FU. Patients in both arms receive 3 courses of ECF after surgery. Results of this study are awaited.

A meta-analysis by Sjoquist *et al*[62] reviewed trials with localized gastroesophageal adenocarcinoma with preoperative CRT and chemotherapy alone. The hazard ratio for OS was 0.75.

***Adjuvant chemotherapy***

Analyzing data from different Countries, results of adjuvant chemotherapy after gastrectomy in Western studies are less convincing than Asian studies.

In a study by Japanese group (ACTS-GC trial), oral fluoropyrimidine (S-1) was given after surgery for 1 year, and results were compared with surgery alone. The 5-year OS was 70.1% *vs* 61.1%[53,54]. This trial was stopped earlier because of significantly better OS in S-1 group. It needs to be underlined that very high rates of OS in both arms are due to excellent surgery, as D2 lymphadenectomy was proved in 100% of cases. The problem in translating this trial into White population is that Tegafur, present in S-1 a precursor of 5-FU, is transformed in the body by cytochrome p450 to 5-FU. The probably difficulties observed in White population is due to the polymorphism of CYP2A6 gene, and following complications[63]. In FLAGS trial, the comparison of cisplatin+S-1 and cisplatin+5-FU in palliative manner showed significantly better tolerance in patients with the addition of S-1[64].

In the CLASSIC trial, adjuvant chemotherapy with capecitabine and oxaliplatin after curative D2 gastrectomy was compared with surgery alone[65]. This Asian trial proved significant improvements in 3-year disease-free survival (74% *vs* 59%, *P* < 0.0001), and OS (83% *vs* 78%, *P* = 0.0493). This trial was also stopped earlier as the benefit of using this chemotherapy schema was proved. In the chemotherapy arm, oxaliplatin peripheral neuropathy occurred in 56% of patients, but only in 2 % of cases the grade was 3/4. It seems that this regimen might be an alternative to S-1 schema. A meta-analysis on 17 trials of adjuvant chemotherapy after gastrectomy showed a small but statistically significant benefit for 5-FU based chemotherapy[66]. Adjuvant chemotherapy increased OS by 6%, and reduced the risk of death by 18%. A meta-analysis by Zhang *et al*[67] showed that four chemotherapy regimens may be effective. First, FU+mitomycin C+adriamycin; second, 5FU+mitomycin C; third, tegafur; and fourth, mitomycin C. Other proposed regimens seem to be not so effective: FU+ BCNU, FU+ methyl –CCNU, FU+ cisplatin, FU+ anthracyclines, and FU + mitomycin c+ cytarabine. Another meta-analysis by GASTRIC group (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) showed statistically significant improvement in OS after 5-FU based chemotherapy[66]. The same group in another meta-analysis on advanced GC concluded that experimental arms of chemotherapy are responsible for modest improvement in OS and DFS (HR 0.88 and 0.81). The median survival was below 1 year and none of the new regimens might be used as a standard[68].

***Adjuvant chemoradiotherapy***

After presenting the results of INT-0116 trial by MacDonald *et al*[55] adjuvant CRT plays an important role in GC treatment. The problem of additional radiotherapy is the increased toxicity rate. Grade 3/4 hematologic toxicity occurred in 54%, and gastrointestinal toxicity in 33%. The toxic effect was also responsible for stopping the treatment in many cases. In patients with diffuse histology the addition of radiotherapy did not get additional benefit. The biggest concern is about radiation of large portion of gastrointestinal mucosa. Current studies are focused on using three-dimensional conformal and intensity-modulated radiation therapy, and also new more safe radiotherapy techniques[69-71]. In the phase II trial with 3D-CRT/IMRT the toxicity grade 3 or 4 for nausea and vomiting (14.5%), decreased appetite (11.8%), leukopenia/neutropenia (9.1%) and fatigue (6.4%) was observed and that proved to be a safe procedure[71]. We will have to mention that in MacDonald trial an increased number (but not statistically significant) of secondary malignancies after additional CRT were reported[55]. The biggest challenge is to prove whether addition of radiotherapy into the regimen is better than chemotherapy alone. This issue was analyzed in ARTIST trial[72]. No difference in 3-year DFS was observed between those two arms, but analyzing subgroups with lymph node metastases, 3-year DFS was improved in CRT arm (77.5% *vs* 72.3%; *P* = 0.0365). This was also seen when adjusting for tumor stage. No difference in case of local or distal recurrence rate was observed. No OS was given in 3-year analysis. Next trial- ARTIST-II will investigate the influence of chemotherapy or CRT in lymph-node positive patients. The interesting aspect is that in INT-0116 trial, D2 resection was performed in only 10% of cases, whether in majority of Asian studies it is closely or gets 100%. Indeed, local recurrences were observed in 29% of cases in INT-0116 trial, *vs* 2.8% in Japanese ACTS-GC trial. It seems that the addition of radiotherapy confers a potential benefit to patients with suboptimal surgical approach. This was proved by a Dutch study, showing a reduction in local recurrences after RCT in patients with D1 resection, whereas this effect was not seen in the D2 resection group[73].

The problem of GEJ region radiotherapy must be described shortly but in other paragraph. The main difficult is that these patients are subgroups in esophageal cancer trials and in GC trials. Some of these problems were mentioned above in case of neoadjuvant setting like in CROSS trial results[52]. After surgery of GEJ, additional RCT is based on INT-0116 trail (about 20% of patients in this trial had GEJ position)[55]. In current AJCC staging the GEJ tumors are staged as esophageal not as gastric one. The only trial exclusively for GEJ tumors was done in Germany analyzing neoadjuvant CRT *vs* chemotherapy alone; higher rate of complete pathological response (15.6% *vs* 2%), and a trend towards improved 3-year survival (47% *vs* 28%, *P* = 0.07) in favor of neoadjuvant CRT were observed[51].

The German trial also tried to identify those patients who benefit from neoadjuvant therapy using PET-CT[74]. The MUNICON study tried to predict response after 2 wk of NC in GEJ cancers. Patients non-responders to chemotherapy were directed to surgery, sparing them from unnecessary toxicity, as well as performing surgery earlier. We must also highline that GEJ tumors are in majority FDG (fluorodeoxyglucose) sensitive, but in 30% they do not uptake FDG[75]. The solution might be usage radioisotopes as fluorothymidine for GC[76]. The most important studies from multimodal GC treatment are presented in the table (Table 1).

***Targeted therapies***

The new drugs that may be used in targeted therapies may probably play an increasing role in modern treatment of GC. Epidermal growth factor receptor (EGFR) is overexpressed in vast majority of GC. The trials that used anti-EGFR antibody cetuximab (EXPAND trial), and panitumumab (REAL3 trial) failed to improve survival in GC patients[77,78]. In case of panitumumab in REAL3 trial the drug was proven to even worsening survival of treated patients[78]. Another antibody tested in adjuvant setting in gastric cancer is Bevacizumab against vascular endothelial growth factor A (VEGF-A). In AVAGAST trial addition of this antibody into treatment did not improve OS when added to standard chemotherapy[79]. Overexpression of human epidermal growth factor receptor-2 (HER-2/neu) is present in over 20% of patients with GC. An antibody against this receptor –Trastuzumab, proved significant improvement in OS in metastatic gastric and GEJ cancers in ToGA trial[80]. On oral version- Lapatinib is currently investigating in trial for HER-2 Positive GC (LOGIC). Currently we wait for the results of ongoing trial using molecular targeted drugs in gastric cancer- LOGIC (using Lapatinib), TYTAN (using Lapatinib), RAINBOW (using Ramucirumab), GRANITE-1 and GRANITE-2 (using Everolimus). We have also to mention that currently many drugs are tested in phase I and II trials, just like finished II phase trial based on Apatynib with promising results[81,82]. From molecular point of view the biggest interest lies in drugs that will be effective on VEGR2, c-MET, FGFR1, 2, HER2, HER3, and members of the PI3K/AKT/mTOR pathway.

***HIPEC***

In advanced cases PC of gastric origin is a condition with very poor prognosis with mean survival range of 2.2-8.8 mo and no 5-year survival probability[30]. Surface of peritoneum is a preferential site of GC dissemination. Currently a lack of efficient systemic therapy is available and that pushed many clinicians to fight with this localized disease by intraperitoneal administration of cytotoxic agents (intraperitoneal chemotherapy -IPEC). Other possible delivery options have been described, like peri-operative normothermic intraperitoneal chemotherapy (NIPEC), hyperthermic intraperitoneal chemotherapy (HIPEC), post-operative intraperitoneal chemotherapy (EPIC), and delayed post-operative intraperitoneal chemotherapy (DIPEC)[83]. As Spratt in 1980 proposed HIPEC with additional cytoreductive surgery, this new therapeutic option began to play an important role in advanced GC[84]. The advantage of HIPEC in comparison with other ways of delivering intraperitoneal chemotherapy is an effect of hyperthermia on cytostatic drug as well as direct cytotoxic effect of heat[30]. The neoadjuvant treatment as well as adjuvant one showed a potential benefit in decreasing rates of PC[85]. First IPEC studies showed that patients receiving chemotherapy intraperitoneally with mitomycin C, but also cisplatin and fluorouracil proved better OS after curative resection of locally advanced gastric cancer[86]. After first report by Fujimoto *et al*[87] regarding HIPEC in patients with secondary PC, other departments used that technique in PC of GC origin. In one of the biggest study on 107 patients treated with HIPEC, Yonemura *et al*[88] proved that patients that underwent complete resection had better 5-year survival than those with residual disease (13% *vs* 2%). The completeness of resection was an independent prognostic factor[89,90]. The French multiinstutional study on 159 patients showed that radical resection and HIPEC are associated with 5-year survival rate of 23%[83]. However, it should be emphasized that only a small rate of patients submitted to complete macroscopic cytoreduction (R0 or R1) had a chance of survival probability in that study.

Another issue is PC after radical gastrectomy. Peritoneal surface is the place of most common type of the recurrence after GC surgery. After curative resection, PC may occur in 20%-50% of cases, and rises up to 80% in cases with positive peritoneal cytology[91,92]. The biggest problem is that adjuvant intravenous chemotherapy or radiotherapy did not improve survival in patients at high risk of PC. Only intraperitoneal chemotherapy may prevent the development of PC, and addition of hyperthermia synergistically with some drugs increases the depth of penetration into the tissue[30].

At least two meta-analysis are available on issue of intraperitoneal chemotherapy. The first by Xu *et al*[93] in 11 randomized clinical trials, which in 7 was seen comparison of surgery +HIPEC *vs* surgery alone. IPEC showed to be superior after curative surgery *vs* surgery alone, and also combination of HIPEC or addition of activated carbon particles was proved to be significantly better than other drugs combination. Second meta-analysis by Yen *et al*[94] reviewed all clinical trial with IPEC. From 13 trials, 4 of them investigated the efficacy of HIPEC, 5 NIPEC, 2 EPIC, and 2 combined effect of HIPEC and EPIC, and finally 2 trials reported combined effect of DIPEC. All data form 1648 patients showed a significant difference in survival of patients treated with HIPEC, or HIPEC together with EPIC. A trend toward survival improvement was observed by NIPEC. No benefit was seen by using EPIC or DIPEC. In our opinion, the addition of HIPEC may provide a survival benefit in patients at high risk of PC after gastrectomy, as patients with diffuse-mixed type, serosal invasion, or positive peritoneal cytology. The HIPEC is an effective treatment in patients with free cancer cells and microfoci of a cancer, and becomes more and more less effective as the tumor mass is bigger, and the disease is disseminated[30]. Currently the new trial is ongoing to prove the effectiveness of HIPEC during curative gastrectomy in case of positive peritoneal cytology (GASTRICHIP trial). This new perspective can probably help in wider usage of HIPEC to prevent further PC.

***Metastatic gastric cancer***

GC is often diagnosed as an advanced disease especially in Western countries where no screening for early diagnosis is used. The surgical resection of all pathological tissues is essential for curative treatment, and in advance disease in majority cases it is not possible. Still palliative chemotherapy in case of stage IV gastric cancer is a treatment of choice. Because of improvement of modern chemotherapy, better response, and usage of surgical techniques, survival of stage IV gastric cancer improved during last decades. The biggest question is who will benefit from more aggressive treatment especially keeping in mind that extended survival has to be important as well as patients’ quality of life (QoL)[95]. The role of surgery even in primarily incurable disease increases because some patient who responds well on chemotherapy might be restaged by a surgeon and eventually planned for a surgery. Unfortunately, the outcome measured in most studies is only limited to survival outcome. The real surgical palliation should be defined as a treatment that is referred as one to relief symptoms or that improve QoL[96]. Surgical resection that does not follow to resect all pathological masses should be named as noncurative rather than palliative. In the SEER database from 23830 patients with stage IV disease, surgery was offered to 45.7% of patients. Overall the median survival was only 4 months. In case of any surgical approach this treatment had survival advantages over others. In the study by Li *et al*[97] on a group of 253 synchronous GC metastases, 5-year survival was 6.5% for patients with resection *vs* 0% without surgery. Multivariate analysis proved that patients with liver metastases, peritoneal dissemination, and those without resection get worse. The survival difference between groups with or without resection was only seen with those who had single site peritoneal dissemination. The Cochrane review found that the usage of chemotherapy improved survival over best supportive care in patients with incurable GC[98]. The authors also stated for usage of combination chemotherapy over single agent approaches. After a modern multimodal treatment the improvement in tumor response again raises a question about surgical approach. In Japan study on 28 patients that replied good for S-1 based chemotherapy, 93% rate of R0 resection was observed. In 4 patients a complete response was seen, and the median survival was 29 mo, with 34% of 5-year survival[99]. In the French FREGAT study the palliative gastrectomy was done because of solid organ metastases (5.6%), localized PC (4.6%), diffused PC (2.3%) or incomplete tumor resection (12.8%)[100]. Median survival of patients with resection was better than non-resection group (11.9 *vs* 8.5 mo, *P* < 0.001). Multivariate analysis proved that factors associated with survival were: ASA score II-IV, localized PC, diffuse PC, signet ring histology. Patients with ASA I-II and incomplete resection without metastasis nor PC, one site solid organ metastasis without PC, or localized PC without signet ring cell histology, showed the highest benefit from surgical approach. This subgroup of patients had median survival from 12 to 18.3 mo. Analyzing surgical treatment in case of distant metastases we must also mention about treatment of liver metastases of gastric cancer origin. No trials were performed on this field, and a recent review by Grimes *et al*[101] was based on 17 retrospective studies. The solitary disease patients had better OS than metachronous one and patients with metachronous disease had better prognosis than synchronous. Hepatectomy in these patients is a safe procedure with about 2% perioperative mortality, and morbidity from 17% up to 60%. The authors state that metachronous metastatic disease limited only to the liver, with surgical possibility of resection, should be consider on clinical trial.

In the latest GIRCG study on synchronous hepatic metastases in case of GC it is clearly seen that clinical criteria may be used to select candidates for a curative surgery. The effect of surgical approach has an impact on survival especially when adjuvant chemotherapy is added[102].

***Multivisceral resection of advanced forms***

The role of multivisceral resection, in the setting of locally advanced GC, has been evaluated in several studies; most of them reported a higher risk for perioperative morbidity and mortality, with limited objective benefit in terms of survival, but a potential advantage of extended resection for some subgroups[103]. In a recent GIRCG study, 206 patients with a clinical T4b carcinoma were evaluated[104].

One hundred twelve underwent a combined resection of the adjacent organs for clinically T4b stage. Postoperative mortality and complication rates were acceptable, and overall 5-year survival rate was 27.2%. The completeness of resection and lymph node invasion resulted as independent prognostic parameters at multivariate analysis. At present, even if a chance of cure with extended surgical approach could be obtained in subgroups of patients with invasion of adjacent organs, modern multimodal approach to these forms should include neoadjuvant treatment, followed by extended surgery in responders. The addition of HIPEC should be considered.

**CONCLUSION**

Results of treatment in specialized Western centers are good in early stages (I-II), but still unsatisfactory in more advanced stages of GC (IIIB and more), above all when compared with Eastern series. Treatment options have been changed in recent years from a standard to a tailored approach. Different individualized procedures can range from endoscopic resection, D2 with open or minimally invasive approach, to neoadjuvant therapy followed by extended surgery (Figure 5). In more advanced stages, a combined approach with the inclusion of HIPEC may represent a new frontier for multimodal treatment of resectable GC. It should be also emphasized that a tailored treatment of GC involves necessarily an appropriate pre-treatment clinical staging of the disease. Clinicians should be aware to face, in the future, fewer GC cases, but with higher biological aggressiveness, due to the relative increase of proximal and DT tumors. The high propensity of DT to lymph node metastasis and peritoneal dissemination makes multimodal treatment, in particular including NC and HIPEC, a modern and necessary approach to this still fatal disease.

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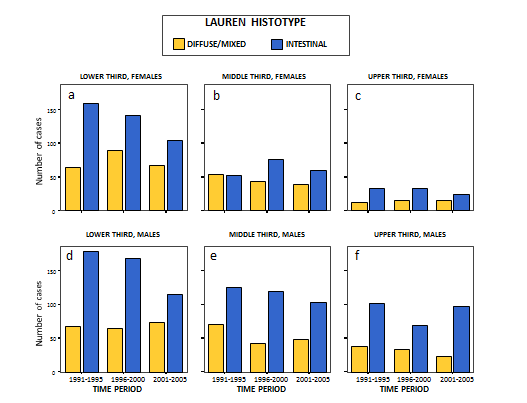
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**Table 1 Main trials regarding adjuvant and neoadjuvant therapy for gastric cancer reported in literature**

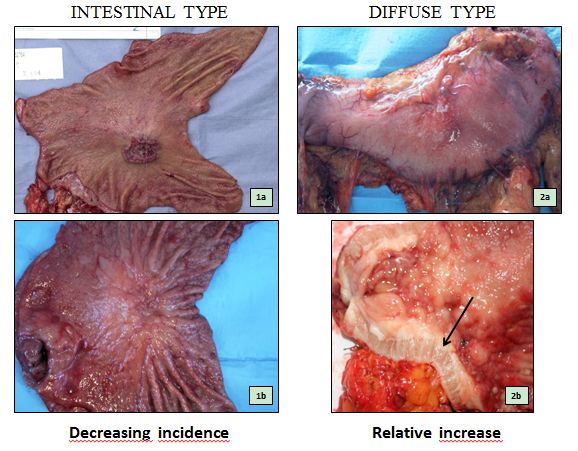
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| --- | --- | --- | --- | --- | --- |
| **Trial name** | **Therapy** | **Treatment arms** | **Tumor position** | **OS *P* vaule** | **PFS/DFS *P* vaule** |
| Neoadjuvant CT | | | | | |
| MAGIC[48] | CT | Perioperative  Res. *vs* mult | GC + EGJ | 0.009 | < 0.001 |
| FNLCC/ FFCD 9703[49] | CT | Perioperative  Res. *vs* mult | GC + EGJ | 0.021 | 0.003 |
| EORTC 40954[50] | CT | Preoperative  Res. *vs* mult | GC + EGJ | 0.466 NS | 0.2  NS |
| Neoadjuvant CRT | | | | | |
| POET[51] | CRT | Preoperative  CRT *vs* mult CT | EGJ (I, II, III) | 0.07  NS (3 yr) | 0.06  NS (3 yr) |
| CROSS[52] | CRT | Preoperative  Res. *vs* mult CRT | Esophagus + EGJ I, II, III | 0.003 | < 0.001 |
| Adjuvant CT | | | | | |
| ACTS-GC[53,54] | CT | Postoperative  Res. *vs* mult | Not given | 0.002 | < 0.001 |
| CLASSIC[65] | CT | Postoperative  Res. *vs* mult | GC + EGJ | 0.049  (3 yr) | < 0.0001  (3 yr) |
| Adjuvant CRT | | | | | |
| INT 0116[55] | CRT | Postoperative  Res. *vs* mult | GC + EGJ | 0.005 | < 0.001 |
| ARTIST[72] | CRT | Postoperative  Res. *vs* mult | GC | Not given | 0.0824  NS (3 yr) |

CT: Chemotherapy; CRT: Chemoradiotherapy; GC: Gastric; EGJ: Esophageal gastric junction; OS: Overall survival; PFS/DFS: Progression-free survival/disease-free survival; Res: Surgical resection alone; Mult: Multimodal treatment.

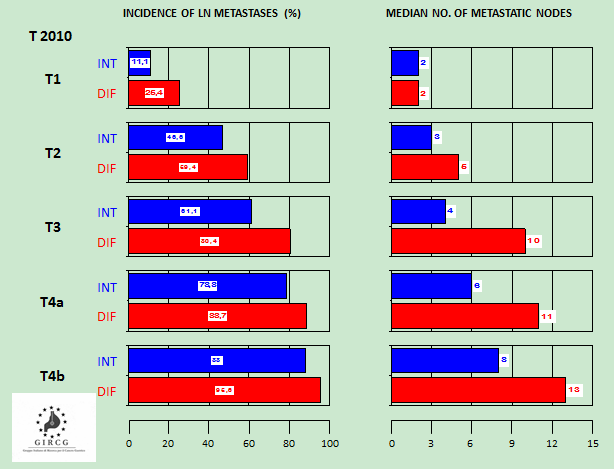
**Figure 1 Changing number of patients in three subperiods, stratified according to tumor location and Lauren histotype (GIRCG database).**



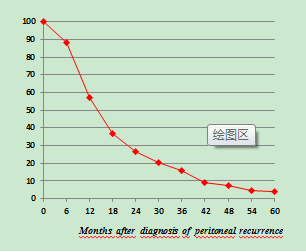
**Figure 2 Images of intestinal (1a and 1b) and diffuse type (2a and 2b) tumors of the stomach.** The arrow in 2b indicates the infiltrative growth of the diffuse histotype in the gastric wall.



**Figure 3 Incidence of lymph node metastases according to Lauren histotype stratified for pT stages (GIRCG database).**



**Figure 4 Survival rate of patients with peritoneal recurrence of gastric cancer.**



**Figure 5 Proposal of a tailored multimodal approach in resectable non-cardia gastric cancer.** JGCA: Japanese Gastric Cancer Association; NAC: Neoadjuvant chemotherapy; HIPEC: Hyperthermic intraperitoneal chemotherapy.

