

Advanced gastric cancer: the value of surgery

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Summary. Gastric cancer is a common disease with high mortality. The definition of advanced gastric cancer is still debated. Radical surgery associated to appropriate systemic and intra-abdominal chemotherapy is the gold standard treatment. In presence of peritoneal carcinosis, reaching a complete cytoreduction is the key to achieve long-term survival. Adequate lymphadenectomy is also fundamental. Conversion therapy could be applied to selected IV stage patients. No definitive evidences exist regarding the oncological and surgical superiority of mini-invasive approaches over the classical open techniques. (www.actabiomedica.it)

Key words: advanced gastric cancer, chemotherapy, hipec, intraperitoneal, surgery, definition, metastasis, carcinosis

Introduction

Gastric cancer (GC) is the fifth cause of cancer death in the world. Some differences exist according to the geographic area. Eastern countries have a better prognosis in the treatment of these patients when compared to western. In Japan the survival for resectable GC is almost 70% (1), while in Europe and US the 5-year survival is almost 25% in advanced gastric cancer (AC) (2-6).

The TNM classification of the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) is widely used, even if with some criticisms (7-9).

However, precise definition of AC is still matter of debate. Some authors defined as AC the T3 and T4 cancers. As a counterpart, the vast majority considers advanced those tumors infiltrating beyond the submucosal layer that are not-early and not-metastatic even with N0 staging. Practically, AC could be considered the T2-T4b/N0-N3b/M0 according to the AJCC/

UICC TNM classification. In addition the proposal of esophagogastric junction cancers classification to replace the Siewert one raised many concerns. Recently the new TNM 8th classification of neoplastic diseases redefined the classification of the gastric and gastroesophageal junction cancers (GEJC) and formally included the GEJC among the gastric cancers (10). A meta-analysis confirmed the same biological behavior of the GEJC and the AC. The main difference is the anatomical diffusion due to the localization, to the different anatomy of the two regions and the consequent lymphatic drainage (11).

Extension of gastric resection

Radical surgery including adequate resection and lymphadenectomy is the only curative treatment either for early stage either for advanced but non-metastatic disease. Lymphadenectomy could be considered adequate with the retrieval of at least 16 lymph nodes (12).

The recommended oncologically correct proximal margins are: at least 3 cm for T2 or higher degree tumors with “expansive growth pattern” and at least 5 cm in “infiltrative growth pattern” diseases. The concept of adequacy of surgical resection has been defined as total gastrectomy for large tumors or for tumors of the lesser curve and in general in all those situations in which resection margins cannot be respected.

Lymphadenectomy

Besides the penetration of the serosa, the principal factors strongly related with prognosis are the lymph node (LN) involvement (13) and the clearance of lymph nodes (14-16).

As a matter of fact lymphadenectomy is important in staging and in increasing the long-term survival (5, 13). Eastern and western countries use different standard to regulate the extension of the lymphadenectomy. In “standard lymphadenectomy” (D1) almost 15-18 lymph nodes (LN) must be removed to have a proper staging. In “extended lymphadenectomy” (over-D1) the number of LN to remove is 31-35 to have a better staging of the N3 (according to the TNM) and to increase survival (17-20). In D2 lymphadenectomy at least 27 LN should be retrieved for optimal results (19). In Europe, the state-of-the-art in curative-intent surgery for AC is gastrectomy, D2 lymphadenectomy and omentectomy (5, 13, 15, 21-23).

Extent of lymphadenectomies

- *D1 lymphadenectomy* includes the peri-gastric stations (from station 1 to 7) (5, 24). When facing esophageal-gastric junction tumors also the infradiaphragmatic, paraesophageal and supra-diaphragmatic LN stations (19, 20, 110 and 111 LN stations) should be resected for D1 lymphadenectomy (5).
- “*D1 plus*” lymphadenectomy consists in the resection of the stations 8a, 9, and 11p too (25).
- *D2 lymphadenectomy* consists in the D1 resection associated to stations 10, 11d, and 12a (5, 25).
- *D3 lymphadenectomy* includes also the posterior (12p, 13, 14v) and para-aortic station (26).
- *Super-extender D3 lymphadenectomy* includes

splenectomy or distal pancreatectomy associated to D2 lymphadenectomy.

At least 16 LN should be retrieved for accurate pathologic evaluation. Some data suggested no increase in accuracy of pN staging with an increase of LN retrieval (27).

D1 vs D2 vs D3 lymphadenectomy

In T1a tumor not suitable for endoscopic resection and for differentiated and ≤ 1.5 cm cT1bN0 lesions *D1 lymphadenectomy* is indicated (25). A “*D1 plus*” lymphadenectomy has been reported as an alternative of D2 in high-risk cT1N0. *D2 lymphadenectomy* is indicated for potentially curable T2-T4 tumors, as well cT1N + tumors (25). Two randomized controlled trials (RCTs) (18, 28, 29) reported a superiority of the D1 compared with D2 lymphadenectomy. However, no other studies confirmed these results (22, 23, 30). The Italian Gastric Cancer Study Group (GIRCG) showed that D2 dissection without splenectomy and pancreatic resection is feasible and safe with similar results to D1 (22). Some data from a randomized trial (18, 31) showed an increased survival rate in patients who underwent D2 vs. D1, where gastric-cancer-related death and a regional recurrence were higher in D1. Another RCT (25) comparing the difference between D1 plus and D2 showed higher LN removal in D2 lymphadenectomy, no differences in LN ratio, no significant differences in median recurrence rate.

D3 lymphadenectomy is supposed to provide a better local control of disease in advanced gastric tumors with mixed-diffuse histotype (32). As in upper third GC 29% of para-aortic LN are involved compared to the 7% of middle and lower third GC ($p < 0.001$), the inclusion of para-aortic LN stations (16a, 16b) is important in upper third tumors, in larger tumors, or in tumor with station 7 involvement (33, 34). No benefit in survival rate is related to routine extended lymphadenectomy and removal of para-aortic LN (35, 36).

Super-extender D3 lymphadenectomy is strongly not recommended and is in the most of cases not necessary (13, 16, 37-39). Even in scenarios of higher risk for splenic hilum node involvement, i.e., with proximal and mid greater curvature primaries, spleen-preserving hilum lymphadenectomy can be performed with satis-

factory results (40). Splenectomy and pancreatectomy might be considered beneficial only in case the primary tumor or the LN metastasis involve these organs (16, 39).

The evaluation of the possible role of an extended lymphadenectomy in reducing the risk of a local recurrence has been reported in several studies (32, 34, 41-43).

Patients who underwent a D2 with para-aortic LN dissection (PAND) presented better outcome in terms of mortality and morbidity, compared to the only D2 have been reported (21). However, another study (34) reported that D2 with PAND has no improving in survival or recurrence rate in T2-subserosa, T3, T4 stages with similar perioperative mortality and an increase in morbidity for the D2 PAND group.

Wu et al. found in a RCT (41) evaluating D1 vs. D3 that morbidity rate was higher in D3 and overall survival was significantly higher and regional recurrence rate lower in D3 (35). De Manzoni reported a higher recurrence rate in D3 group in case of intestinal pattern then in mixed/diffuse pattern with a similar mortality thus emphasizing the necessity to tailor lymphadenectomy to the histology (32).

Cytoreductive surgery

In the event of local or diffuse peritoneal carcinosis (PC) the best approach combines systemic chemotherapy, radical surgery and intra-peritoneal chemotherapy (IPC). This multimodal treatment radically changed the outcomes (44-48).

Differently from ovarian cancer as well as for other diseases (49, 50) in GC with PC, cytoreductive surgery (CRS) alone is not accompanied by survival benefits. As showed by Yamamura et al. CRS alone cannot be effective in treating PC because of invisible cancer cells remain even after surgical procedure. As a counterpart, CRS plus peri-operative chemotherapy is feasible and safe with a significant increase in survival rate in GC with PC (51-54). Furthermore, a meta-analysis clearly showed a survival benefit in patients affected by advanced GC, with or without PC, treated with IPC (44). An independent favourable prognostic factor during CRS if associated to IPC is the completeness of cytoreduction (52, 55-57). A recent meta-

analysis reported an increase in 1, 2, 3, and 5-years survival rate in CC-0/CC-1 cytoreduction (58) and CC-0 showed better outcomes than CC-1 with an increased survival at 1 and 3 years. The Peritoneal Cancer Index (PCI) evaluation is mandatory in selecting patients for CRS+IPC treatment. Yonemura et al. showed that it was possible to obtain a complete cytoreduction in 91% of cases in presence of a $PCI \leq 6$ but only in 42% with a $PCI \geq 7$. Moreover, the survival rate in PCI score ≤ 6 was significantly better than in PCI score ≥ 7 (45). Survival rates at different time points change significantly above and below a PCI of 12 with a progressive decrease for higher PCI scores (57, 59-61).

Surgery for IV stage gastric cancer

Chemotherapy remains the main therapeutic approach for stage IV GC and surgery is usually confined to a palliative resection or by-pass operation to relieve symptoms. However, the median survival time of this cohort of patients remains to be around 13-16 months (62). Furthermore, the REGATTA trial demonstrated that the initial removal of the primary tumor in stage IV GC could be beneficial just in case of only one affected organ other than the site of primary tumor (63).

Stage IV GC patients are heterogeneous and could be divided into four categories (62) (64):

- Category 1: absence of macroscopic PC and potentially resectable metastases
- Category 2: absence of macroscopic PC and marginally resectable metastases
- Category 3: presence of macroscopic PC without other distant metastases
- Category 4: presence of macroscopic PC and other organ metastases.

According to recent studies, patients in category 1 could be eligible for neoadjuvant chemotherapy and subsequent gastrectomy plus metastasectomy. For the other categories, much attention is being paid to conversion therapy. It is defined as a surgical treatment aiming at an R0 resection after chemotherapy for tumors that were originally unresectable for technical or oncological reasons (64). In a study on 259 patients with IV stage GC, planned resection after neoadjuvant chemotherapy was performed in 7 patients and con-

version surgery in 77. Although only 51,2% of patients underwent R0 resection, median survival time was 41.3 months, that is much longer than that reported from the first-line chemotherapy trials (62). Metastectomy along with resection of the primary tumor might be feasible for this population, once the metastases have responded well to the chemotherapy. Some authors recommend the surgical treatment of hepatic metastases from gastric cancer to be taken into consideration after careful evaluation of each single case, as only a radical approach with curative intent is worthy (65).

Mini-invasive surgical approach

Although studies about mini-invasive surgical approach mixed AC and early gastric cancer patients exist, no dedicated studies to AC were conducted. Results however suggest the possibility to apply the mini-invasive approach to AC without PC.

Laparoscopic surgery

In early gastric cancer laparoscopic resections associated to D1 lymphadenectomy obtained better results than open technique in terms of postoperative pain, time to return to normal bowel function and resumption of oral feeding, time to recovery, length of hospital stay, cosmetic results and financial outcome (66-69). Morbidity and mortality rates in laparoscopy are not statistically different to open resections (29) (22, 70). The role of laparoscopy in D2 or higher for lymphadenectomy is still matter of debate. According to some authors, laparoscopy reduces the accuracy in dissecting lymph nodes, especially from high risk nodal stations. Wang et al. in a meta-analysis including 17 trials (2313 patients) comparing laparoscopic and open total gastrectomy (71) demonstrated a longer operative time, earlier hospital discharge, earlier passage of flatus, quicker resumption of oral intake, fewer analgesic uses, and reduced postoperative morbidity in laparoscopic approach. No difference was found in terms of hospital mortality, resected lymph nodes, proximal resection margin and 5-year overall and disease-free survival. Another meta-analysis of 15 non-randomized trails substantially confirmed the outcomes (72).

Robotic surgery

No sufficient data exist about feasibility, safety and eventual advantages of robotic gastrectomy compared to open or laparoscopic gastrectomy in early gastric cancer neither in AC. No reports exist about the use of robotic gastrectomy in patients with AC and PC.

Liao et al. published a meta-analysis of 4 studies (5780 patients) comparing robotic and open gastrectomy. Longer operation time, lower blood loss and shorter hospital stay were associated to robotic gastrectomy. Overall morbidity and number of resected lymph nodes were not different (73).

Conclusions

Therapeutic approach of AC is based on radical surgery with adequate lymphadenectomy, associated to appropriate systemic and intra-abdominal chemotherapy. In presence of PC reaching a complete removal of visible disease is even more important. In stage IV GC conversion therapy could be considered in selected patients with good response to chemotherapy. No definitive evidences exist regarding the oncological and surgical superiority of the mini-invasive approach over the classical open technique.

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