Mini-Review

Neoadjuvant treatment for gastric cancer in the West: a critical review

Wilson L. da Costa Jr, Felipe J.F. Coimbra, Rafael Horácio de Brito, Héber S.C. Ribeiro, Alessandro L. Diniz, André Luís de Godoy, Igor Correia de Farias

Department of Abdominal Surgery, A. C. Camargo Cancer Center, São Paulo, Brazil

Correspondence to: Wilson L. da Costa Jr. Department of Abdominal Surgery, Hospital A. C. Camargo, Rua Antonio Prudente, 211 Liberdade, CEP 01501-900, São Paulo, Brazil. Email: dr.wilsoncosta@gmail.com; coimbra.felipe@uol.com.br.

Abstract: Improvements in surgical treatment have approximated the survival results in Western countries to those observed in Asia. However, even with optimal surgery, at least 30% of patients treated with curative intent will have recurrence. This review is focused on the neoadjuvant chemotherapy phase III trials performed in the West, highlighting their limitations and favorable results. Also, a rationale describing the reasons why this multimodality set of treatment is favored in Western countries is developed. Also, some controversies regarding perioperative chemotherapy are presented, such as the addition of radiotherapy, the association with hyperthermic intraperitoneal chemotherapy (HIPEC) and the criteria used for patient selection, in order to identify those who could have better response rates to chemotherapy.

Keywords: Gastric cancer; multimodality treatment

Submitted Nov 12, 2014. Accepted for publication Dec 03, 2014.
doi: 10.3978/j.issn.2224-4778.2014.12.01
View this article at: http://dx.doi.org/10.3978/j.issn.2224-4778.2014.12.01

Surgical treatment and survival

Several studies have attributed 5-year survival ranging between 20% and 30% for gastric cancer patients treated with curative intent in Western countries (1). This number is significantly lower than that observed in large Eastern randomized studies, in which patients whose tumors were stage II and III and were treated with surgery alone, attained overall survival between 60% and 70% at 5 years (2,3). Several explanations can justify this difference, such as the higher incidence of early tumors in Eastern countries and more proximal and advanced lesions in the West (4,5). However, when analyzing the survival results by staging in Western reference centers, we observe numbers that significantly approach those of Eastern services (6,7).

This similarity is mainly due to the standardization of D2 lymphadenectomy as part of curative surgical treatment in the West. Based on the controversial results of two randomized trials in the late 1990s, which showed no benefit of D2 lymph node dissection compared to D1 (8,9), in several Western centers resections were commonly associated with a more limited lymphadenectomy. This scenario produced results as those observed in an American series, in which, among 3,814 individuals operated on, 70% had fewer than 15 lymph nodes in the surgical specimen (10). This scenario has changed with the increasing adoption of the Japanese Gastric Cancer Association (JGCA) guidelines (11) by more groups and the performance of D2 lymphadenectomy in their patients; also, the 15-year update of the "Dutch trial", which demonstrated that D2 dissection was associated with a decrease in cancer-related deaths and also locoregional recurrence, provided the needed evidence (12).

Standard surgical treatment is associated with better survival results in the literature. Nevertheless, recurrence still occurs in approximately 30% of patients (13). A concept to consider is the role of lymphadenectomy in the pattern of recurrence. In a Korean series among individuals treated with D2-lymphadenectomy who had relapsed, the primary site was peritoneal (33.9%) and exclusive locoregional recurrence only occurred in 19.3% of cases. This pattern was not repeated, for example, in a study with 1,172 patients from a large American cancer center, which contained a higher incidence of proximal tumors, as 59.4% of tumors had tumors in the upper third of the

stomach or the gastroesophageal junction. The other 41% were located in the middle third (19.3%), antrum (17.7%) or the whole stomach (3.5%). Also, some patients were treated with a more limited lymphadenectomy, D1 or D1+ (19%), while the other 81% had a D2 dissection. In this series, overall recurrence rate was higher (42%) and it was exclusively locoregional in 25.9% of cases, distant in 28.1% and peritoneal in 13.6%. Multiple sites of recurrence were identified in the other 32.5% of individuals. Overall, in this study with some patients receiving more limited lymph node dissection, 54.3% had locorregional recurrence (14).

These relapse rates, in spite of optimal surgical treatment in large centers, has led to research into various forms of multidisciplinary therapy, which today make up the routine in gastric cancer treatment.

Multidisciplinary treatment and survival

The addition of adjuvant chemotherapy in patients treated with D2 lymphadenectomy was associated with significant improvement in overall and disease-free survival in two Eastern studies (2,3). A large meta-analysis with a majority of Western series and 3,838 patients identified a 6% gain in overall survival (15). From this data, it can be concluded that the combination of chemotherapy and surgery seems to be the best strategy of multimodal treatment with curative intent in patients with advanced gastric cancer.

The question that remains regards the best timing for the institution of chemotherapy, prior or after surgery. As part of the perioperative chemotherapy trials, the use of neoadjuvant treatment was investigated. It must be reminded that neoadjuvant chemotherapy is to be characterized as the one performed before surgery in individuals with resectable and non-metastatic tumors.

Randomized studies of neoadjuvant chemotherapy in the West

MAGIC trial

The first randomized study that investigated this treatment modality was the MAGIC trial, in which 503 patients with resectable adenocarcinoma of the stomach, gastroesophageal junction or distal esophagus were randomized between perioperative chemotherapy (neoadjuvant and adjuvant chemotherapy) and surgery *vs.* surgery alone. The chemotherapy regimen included epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2) on day 1 and continuous intravenous infusion of 5-fluorouracil (200 mg/m^2) for 21 days. Drugs were administered in three preoperative and three postoperative cycles.

Significant limitations of this study included inadequate staging, as the use of endoscopic ultrasound (EUS) or laparoscopy were infrequent. In some cases, not even a computed tomography (CT) scan was performed. The other main criticism refers to the quality of surgical treatment, since only 41% of patients received a D2 lymphadenectomy, which explains the poor survival numbers observed in the surgical group (23% at 5 years).

A significant improvement in overall survival was identified in the group undergoing perioperative chemotherapy, on the order of 13% [36% *vs.* 23% at 5 years; hazard ratio (HR)=0.75; P=0.009], with a similar gain in disease-free survival (HR=0.66; P<0.001) (16).

ACCORD-07 trial

Quite similar to the MAGIC trial was the French trial ACCORD-07, published in 2011, which included 224 patients with resectable gastric adenocarcinoma or gastroesophageal junction who were randomized between perioperative chemotherapy and surgery *vs.* surgery alone. Only two chemotherapy drugs were used and the regimen consisted of 2-3 preoperative cycles with cisplatin (100 mg/m^2) on day 1 and continuous intravenous infusion of 5-fluorouracil (800 mg/m^2/day) for 5 consecutive days, repeated every 28 days. After surgery, 3-4 cycles were programmed.

Similar limitations were also observed, as very low survival in the surgical arm (24% at 5 years), inadequate staging, this time without EUS or laparoscopy, and limited lymph node dissection, with a median number of dissected lymph nodes of 19. Another important detail in interpreting this trial results regards the large number of gastroesophageal junction tumors (75%), with only 41% of the individuals in the study undergoing a gastrectomy. The explanation for this finding relates to the fact that this was originally a study designed for esophageal cancer patients, which only included gastric cancer ones at a later period.

The gain in overall survival was 14% (38% *vs.* 24%; HR=0.69; P<0.02) and in disease-free survival it was 15% (34% *vs.* 19%; HR=0.65; P<0.003) (17).

EORTC trial

This randomized German study presents some contrasts

Table 1 Pathology and perioperative outcomes in the three randomized Western trials of neoadjuvant chemotherapy

Study	No. of patients	R0 resection (%)		T0-2 tumors (%)		N0-1 tumors (%)		Postoperative morbidity (%)		Postoperative mortality (%)		Disease progression during chemotherapy, n (%)
		S	CTS	S	CTS	S	CTS	S	CTS	S	CTS	
MAGIC trial	503	70.3	79.3*	36.8	51.7*	70.5	84.4*	45.3	45.7	5.9	5.6	25/237# (10.5)
ACCORD-07 trial	224	74.0	87.0*	32.0	42.0	20.0	33.0	19.1	25.7	4.5	4.6	3/113# (2.7)
EORTC trial	144	66.7	81.9*	50.0	65.6	51.6	80.0	16.2	27.1	1.4	4.3	4/72# (5.6)

*, Result is statistically significant; #, the number of patients in the chemotherapy arm who started treatment and whose data was available. S, Surgery; CTS, perioperative chemotherapy + surgery.

compared to the previous ones. The number of patients [144] was lower, as the study was discontinued due to difficulties in recruitment. The chemotherapy regimen was also different, with the multidisciplinary treatment arm receiving only two cycles of neoadjuvant chemotherapy, in which the drugs were cisplatin 50 mg/m^2 on days 1, 15 and 29 and 5-fluorouracil 2,000 mg/m^2 continuous infusion over 24 hours on days 1, 8, 15, 22, 29 and 36.

The staging used was complete and included CT scans, EUS and laparoscopy for all individuals. Surgical treatment adopted also had striking features, with 94% of patients undergoing a D2 lymphadenectomy and a median of 31 lymph nodes dissected. The survival of the surgical arm, 69.9% at 2 years and estimated median of 52 months was one of the factors that help explain why the study failed to show an improvement in overall survival [HR 0.84; 95% confidence interval (CI): 0.52-1.35; P=0.466]. Other factors include a greater number of patients with nonmetastatic stage IV tumors according to the 5th edition of Tumor Node Metastasis (TNM) (18) and a lower tolerance to neoadjuvant treatment, with only 65% of patients completing the proposed two cycles (19).

Benefits of neoadjuvant treatment

The benefit of multimodality treatment with the addition of chemotherapy to surgery is unquestionable, either adjuvant (2,3) or neoadjuvant (16,17,19). However, some factors make its use very attractive before surgical treatment.

Neoadjuvant chemotherapy in all three studies was associated with a higher rate of complete resection (R0) and a larger number of tumors T1-2 or N0-1, which characterizes downstaging. The literature has shown that post-surgical pathological staging in patients treated with neoadjuvant chemotherapy persists as a prognostic factor for survival (20), as well as the percentage of viable tumor cells after treatment (21). Moreover, two of the major criticisms of this modality were not significant in these studies: there was not a significant increase in postoperative morbidity and mortality and the risk of disease progression during treatment was only slightly significant (*Table 1*).

Nevertheless, the biggest benefit of neoadjuvant treatment is the increased ability of patients to tolerate it. Even in the two large Eastern studies of adjuvant chemotherapy, the percentage of individuals who completed treatment was relatively low, at 65.8% in the Japanese S-1 trial (3) and 67% in the CLASSIC trial (2). This is probably due to nutritional difficulties the patients undergo in the postoperative period of gastrectomies, when median weight loss may reach 15% (22). In the two major Western studies, this contrast is striking. In the MAGIC trial, among the 237 patients who started chemotherapy, 215 completed the three preoperative cycles (91%); meanwhile, only 104 of 209 patients (50%) completed the postoperative (16) scheme. Similarly, in the French study, although 87% of patients received all neoadjuvant chemotherapy, only 50% were able to start the adjuvant scheme (17).

Controversies in multidisciplinary treatment of gastric cancer

Addition of radiotherapy

The first large study that investigated the multidisciplinary treatment of gastric cancer in the West was that of MacDonald and colleagues, published in 2001, which demonstrated a significant increase in overall survival in surgical patients who received adjuvant chemoradiotherapy. The extremely limited surgical treatment observed in the study, where only 10% of patients underwent D2 lymphadenectomy, enables the conclusion that this scheme of adjuvant therapy is beneficial to precisely those subjects

whose surgery was incomplete. Another important finding in this same study is the significant toxicity associated with treatment, both hematologic (54%) and gastrointestinal (33%). The technical advances of radiotherapy have allowed a progressive reduction in its toxicity; however, some treatment-related negative factors should not be overlooked, such as irradiation of poorly oxygenated tissues, making this therapy less effective, and the fact that the radiation field encompasses tissue that is used in the alimentary tract reconstruction, such as the proximal jejunum (23).

Neoadjuvant chemoradiotherapy in patients with gastric cancer has been investigated in phase II studies (24). This set of multimodality treatment could be indicated in cases of tumors of the gastroesophageal junction whose planned surgical treatment consists of an esophagectomy with proximal partial gastrectomy, following data from the recently published CROSS trial. In this Dutch study that included 336 patients with esophageal or gastroesophageal junction tumors staged as T1N1 or T2-3N0-1M0, with 75% of adenocarcinomas, neoadjuvant treatment consisted of radiotherapy at a dose of 41.4 Gy associated with five cycles of carboplatin and paclitaxel. A significant improvement in overall survival in patients undergoing multimodality treatment was observed. As shown in other studies, the addition of radiotherapy was associated with higher complete pathological response rates, which were reported in 23% of patients diagnosed with adenocarcinoma. R0 resections and lymph node downstaging were also common (25).

Further evidence should be provided by two ongoing randomized Western studies. One is the CRITICS trial, which compares perioperative chemotherapy and surgery with another arm of neoadjuvant chemotherapy followed by surgery and adjuvant chemoradiotherapy (26). The other one, the TOPGEAR study, is a multi-institutional Australian randomized study investigating the role of neoadjuvant chemoradiotherapy in patients with gastric cancer (27).

Addition of hyperthermic intraperitoneal chemotherapy (HIPEC)

In patients who underwent D2 lymphadenectomy and later recurred, the peritoneum was the first and main site of recurrence in about 40% of the cases. The factors most often associated with this pattern of relapse were serosa invasion, lymph node metastasis and diffuse-type tumors (13,14).

The use of adjuvant HIPEC was associated with better overall survival and a reduction in peritoneal recurrence in non-metastatic patients in a randomized Japanese study (28). This gain in survival was confirmed in a subsequent meta-analysis that included a large majority of Eastern studies (29). In the West, small series have investigated the association of systemic perioperative chemotherapy and HIPEC, with promising results and acceptable toxicity (30,31).

In order to further investigate this association between systemic perioperative chemotherapy and HIPEC, a randomized trial in Europe is ongoing, comparing two groups of perioperative chemotherapy and surgery with or without HIPEC, with a proposed recruitment of 306 patients (32).

Selection of responders

The best scenario in cancer treatment is one that allows better selection of treatment modality according to clinical and tumor characteristics of each patient at diagnosis.

In a multicenter study of gastric cancer cell lines, molecular profiles that characterized groups of patients with significantly different prognosis were identified. One of these groups, with the intestinal genomic subtype, had significantly better survival and also a better chance of responding to chemotherapy treatment (33). This line of research will probably determine tailored multimodality treatments for each group of patients. However, nowadays, the goal is still to identify good and bad responders through clinical and pathological variables.

Three recent large series investigated the role that Lauren histological type plays in the response to neoadjuvant treatment. In a Korean study with 143 patients, those with diffuse-type tumors who underwent neoadjuvant treatment had worse survival (34). A different result was observed in a German series of 850 patients treated with neoadjuvant chemotherapy, in which factors related to prognosis were postoperative staging, resection status (R0 better than R1/R2) and the occurrence of postoperative complications (35). The same group also investigated only patients with diffuse-type lesions and found that, although the response rate to chemotherapy is lower among individuals with these tumors, those that responded had better long-term outcomes (36).

Prognostic scores are perhaps the most useful tools in the identification of responders currently. In a German series with 410 patients, a scoring system was developed and its variables were tumor site, histological type and degree of differentiation. High-risk patients were identified and had poorer survival in addition to a lower rate of clinical and pathologic response to neoadjuvant treatment. These

patients had poorly-differentiated diffuse-type tumors located in the lower third of the stomach (37).

Conclusions

Patients with gastric cancer in stage II and III are candidates for multidisciplinary treatment with chemotherapy. While conclusive evidence in the identification of patients who have low response rates to systemic treatment is still lacking, the indication of perioperative chemotherapy is preferred in most Western countries. This option can be justified not only by data showing an increase in R0 resections and downstaging, with postoperative staging remaining as a prognostic factor, but mainly by the patient being in better conditions to tolerate treatment before surgery.

Acknowledgements

The authors would like to acknowledge the help of Mr. Todd Price, an English-native speaker and medical translator who helped with the translation of the manuscript.
Disclosure: The authors declare no conflict of interest.

References

1. Dicken BJ, Bigam DL, Cass C, et al. Gastric adenocarcinoma: review and considerations for future directions. Ann Surg 2005;241:27-39.
2. Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012;379:315-21.
3. Sasako M, Sakuramoto S, Katai H, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol 2011;29:4387-93.
4. Van Cutsem E, Dicato M, Geva R, et al. The diagnosis and management of gastric cancer: expert discussion and recommendations from the 12th ESMO/World Congress on Gastrointestinal Cancer, Barcelona, 2010. Ann Oncol 2011;22 Suppl 5:v1-9.
5. Noguchi Y, Yoshikawa T, Tsuburaya A, et al. Is gastric carcinoma different between Japan and the United States? Cancer 2000;89:2237-46.
6. Karpeh MS, Leon L, Klimstra D, et al. Lymph node staging in gastric cancer: is location more important than Number? An analysis of 1,038 patients. Ann Surg 2000;232:362-71.
7. Coimbra FJ, Costa WL Jr, Montagnini AL, et al. The interaction between N-category and N-ratio as a new tool to improve lymph node metastasis staging in gastric cancer: results of a single cancer center in Brazil. Eur J Surg Oncol 2011;37:47-54.
8. Cuschieri A, Weeden S, Fielding J, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Cancer 1999;79:1522-30.
9. Bonenkamp JJ, Hermans J, Sasako M, et al. Extended lymph-node dissection for gastric cancer. N Engl J Med 1999;340:908-14.
10. Smith DD, Schwarz RR, Schwarz RE. Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. J Clin Oncol 2005;23:7114-24.
11. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer 2011;14:113-23.
12. Songun I, Putter H, Kranenbarg EM, et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010;11:439-49.
13. Yoo CH, Noh SH, Shin DW, et al. Recurrence following curative resection for gastric carcinoma. Br J Surg 2000;87:236-42.
14. D'Angelica M, Gonen M, Brennan MF, et al. Patterns of initial recurrence in completely resected gastric adenocarcinoma. Ann Surg 2004;240:808-16.
15. GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group, Paoletti X, Oba K, et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. JAMA 2010;303:1729-37.
16. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.
17. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715-21.
18. Sobin LH, Wittekind C. eds. The AJCC Tumor-node-metastasis 5th ed. New York: Wiley-Liss, 1997.
19. Schuhmacher C, Gretschel S, Lordick F, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European

Organisation for Research and Treatment of Cancer randomized trial 40954. J Clin Oncol 2010;28:5210-8.
20. Mansour JC, Tang L, Shah M, et al. Does graded histologic response after neoadjuvant chemotherapy predict survival for completely resected gastric cancer? Ann Surg Oncol 2007;14:3412-8.
21. Becker K, Langer R, Reim D, et al. Significance of histopathological tumor regression after neoadjuvant chemotherapy in gastric adenocarcinomas: a summary of 480 cases. Ann Surg 2011;253:934-9.
22. Bae JM, Park JW, Yang HK, et al. Nutritional status of gastric cancer patients after total gastrectomy. World J Surg 1998;22:254-60; discussion 260-1.
23. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725-30.
24. Patel PR, Mansfield PF, Crane CH, et al. Clinical stage after preoperative chemoradiation is a better predictor of patient outcome than the baseline stage for localized gastric cancer. Cancer 2007;110:989-95.
25. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-84.
26. Dikken JL, van Sandick JW, Maurits Swellengrebel HA, et al. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). BMC Cancer 2011;11:329.
27. Trial of preoperative therapy for gastric and esophagogastric junction adenocarcinoma (TOPGEAR). Available online: https://clinicaltrials.gov/ct2/show/NCT01924819?term=Trial+of+preoperative+therapy+for+gastric+and+esophagogastric+junction+adenocarcinoma&rank=1
28. Fujimoto S, Takahashi M, Mutou T, et al. Successful intraperitoneal hyperthermic chemoperfusion for the prevention of postoperative peritoneal recurrence in patients with advanced gastric carcinoma. Cancer 1999;85:529-34.
29. Yan TD, Black D, Sugarbaker PH, et al. A systematic review and meta-analysis of the randomized controlled trials on adjuvant intraperitoneal chemotherapy for resectable gastric cancer. Ann Surg Oncol 2007;14:2702-13.
30. Costa WL Jr, Coimbra FJ, Ribeiro HS, et al. Safety and preliminary results of perioperative chemotherapy and hyperthermic intraperitoneal chemotherapy (HIPEC) for high-risk gastric cancer patients. World J Surg Oncol 2012;10:195.
31. Saladino E, Fleres F, Mazzeo C, et al. The role of prophylactic hyperthermic intraperitoneal chemotherapy in the management of serosal involved gastric cancer. Anticancer Res 2014;34:2019-22.
32. Glehen O, Passot G, Villeneuve L, et al. GASTRICHIP: D2 resection and hyperthermic intraperitoneal chemotherapy in locally advanced gastric carcinoma: a randomized and multicenter phase III study. BMC Cancer 2014;14:183.
33. Tan IB, Ivanova T, Lim KH, et al. Intrinsic subtypes of gastric cancer, based on gene expression pattern, predict survival and respond differently to chemotherapy. Gastroenterology 2011;141:476-85, 485.e1-11.
34. Koh YW, Park YS, Ryu MH, et al. Postoperative nodal status and diffuse-type histology are independent prognostic factors in resectable advanced gastric carcinomas after preoperative chemotherapy. Am J Surg Pathol 2013;37:1022-9.
35. Schmidt T, Sicic L, Blank S, et al. Prognostic value of histopathological regression in 850 neoadjuvantly treated oesophagogastric adenocarcinomas. Br J Cancer 2014;110:1712-20.
36. Heger U, Blank S, Wiecha C, et al. Is preoperative chemotherapy followed by surgery the appropriate treatment for signet ring cell containing adenocarcinomas of the esophagogastric junction and stomach? Ann Surg Oncol 2014;21:1739-48.
37. Lorenzen S, Blank S, Lordick F, et al. Prediction of response and prognosis by a score including only pretherapeutic parameters in 410 neoadjuvant treated gastric cancer patients. Ann Surg Oncol 2012;19:2119-27.

Cite this article as: da Costa WL Jr, Coimbra FJ, de Brito RH, Ribeiro HS, Diniz AL, de Godoy AL, de Farias IC. Neoadjuvant treatment for gastric cancer in the West: a critical review. Transl Gastrointest Cancer 2015;4(2):148-153. doi: 10.3978/j.issn.2224-4778.2014.12.01

