ORIGINAL ARTICLE

Gastric cancer: histological response of tumor and metastatic lymph nodes for perioperative chemotherapy

Cáncer gástrico: respuesta histológica del tumor y los ganglios linfáticos metastásicos para la quimioterapia perioperatoria

Telma Fonseca[1,2], Mariana Coimbra[2], Elisabete Barbosa[1,2], and José Barbosa[1,2]*

[1]Department of General Surgery, Centro Hospitalar Universitário São João; [2]Faculty of Medicine of Porto University, Porto, Portugal

Abstract

Background: *Gastric cancer is the fourth cancer most common in the world and the second cause of cancer-related deaths. Perioperative chemotherapy may reduce tumor burden and decrease lymph node invasion, improving R0 resections rates. On the other hand, administered before surgery, chemotherapy may cause fibrosis and tissue edema, with potential increase of surgical difficulty and in the number of post-operative complications. Therefore, we aim to investigate the effect of perioperative chemotherapy for tumor burden and metastatic lymph nodes of gastric cancer.* **Methods:** *Retrospective analysis of all patients submitted to perioperative chemotherapy and surgery, between January 2010 and June 2020, which showed lymph node regression and tumor regression (Becker's classification).* **Results:** *A total of 112 patients with an average age of 61.9 years were analyzed. About 90.2% completed three cycles of perioperative chemotherapy. Good tumor response to chemotherapy (<10% residual tumor) was achieved in 21.3% of patients. Only three patients obtained a complete pathological response. A median lymph node response of 33.3% was achieved in our series.* **Conclusion:** *Despite no evident outstanding regression rate was observed, perioperative chemotherapy seems to be useful in obtaining a R0 resection in gastric cancer, even in advanced gastric cancer.*

Keywords: *Gastric cancer. Histological response. Perioperative chemotherapy.*

Resumen

Introducción: *El cáncer de estómago es el cuarto tipo de cáncer más común y la segunda causa de muerte relacionada con el cáncer. La quimioterapia perioperatoria puede reducir la carga tumoral y disminuir la invasión de los ganglios linfáticos. Por otro lado, administrada antes de la cirugía, la quimioterapia puede causar fibrosis y edema tisular, aumentando potencialmente la dificultad quirúrgica y el número de complicaciones posoperatorias. Nuestro objetivo es investigar el efecto de la quimioterapia perioperatoria sobre la carga tumoral y los ganglios metastásicos en el cáncer gástrico.* **Métodos:** *Análisis retrospectivo de todos los pacientes sometidos a quimioterapia y cirugía, entre enero de 2010 y junio de 2020.* **Resultados:** *Se analizaron 112 pacientes con una edad media de 61.9 años. El 90.2% completó 3 ciclos de quimioterapia perioperatoria. Se logró una buena respuesta tumoral a la quimioterapia (< 10% de tumor residual) en el 21.3% de los pacientes. Tres pacientes lograron una respuesta patológica completa. En nuestra serie se logró una mediana de respuesta de los ganglios linfáticos del 33.3%.* **Conclusión:** *Aunque no se observó una tasa de regresión manifiesta, la quimioterapia perioperatoria parece ser útil para lograr una resección R0 en el cáncer gástrico, incluso en el cáncer gástrico avanzado.*

Palabras clave: *Cáncer gástrico. Respuesta histológica. Quimioterapia perioperatoria.*

***Correspondence:**
Telma Fonseca
E-mail: tnvfonseca@gmail.com

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Introduction

Gastric cancer is the fourth most prevalent cancer worldwide[1], right after lung, breast and colorectal cancers; and the second leading cause of cancer-related deaths[2]. Despite a major decline observed in incidence and mortality over the past several decades[2], mortality remains considerably high even after surgery, which is the only curative therapy for gastric cancer[3]. In 2006 Cunningham et al. demonstrated that perioperative chemotherapy improves overall and progression-free survival when compared to surgery alone[4-6]. Historically, most gastric cancers are diagnosed at locally advanced stages; therefore. standard treatment was no longer unimodal (surgery-based), but the use of perioperative chemotherapy regimens was implemented[7-9]. This combined therapy has shown benefits on curative resection rates, disease-free survival, and overall survival[7,10]. Different studies examined the use of perioperative chemotherapy. The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial[11] showed that the 5-year survival for patients randomized to perioperative epirubicin, cisplatin, and fluorouracil (ECF), was significantly improved compared to those undergoing surgery alone[12]. Even though perioperative chemotherapy may reduce tumor burden, eradicate possible lymph node metastasis[10,13] and improve R0 resection rates[4,13], case series demonstrated that it may cause fibrosis and tissue edema, leading to more complicated surgical procedures and higher post-surgical morbidity[4]. In contrast, a meta-analysis[14] found no significant difference in perioperative or postoperative complication rates between a group of patients submitted to preoperative chemotherapy and surgery versus to surgery alone. Schuhmacher et al.[15] challenges the contribution of perioperative chemotherapy in a patient with a more extensive lymphadenectomy[16].

In the literature, it is widely accepted that gastric adenocarcinoma with signet ring cells is less responsive to chemotherapy when compared to intestinal gastric cancer type[17,18]. However, Rougier et al.[19] and Lemoine et al.[17] found no differences in survival in signet ring cell adenocarcinoma, despite a lower response rate to chemotherapy. This difference may be explained by a higher peritoneal involvement, with requirement of higher concentrations of chemotherapy[17]. Therefore, signet cells gastric adenocarcinoma patients seem to benefit less from perioperative chemotherapy, raising the need to consider and evaluate drugs with better response in intraperitoneal disease or drugs with higher peritoneal cavity penetration. Zurlo et al. suggest that the intestinal histotype might have a better response to a perioperative regime when compared to diffuse type to whom an adjuvant chemotherapy approach might ensure better survival[20].

In this study, we aimed to investigate the rate of histological tumor regression and metastatic lymph nodes response to perioperative chemotherapy in gastric cancer patients and factors associated with this response.

Material and methods

Retrospective, transversal, and observational study of consecutive patients diagnosed with gastric cancer who underwent perioperative chemotherapy followed by gastrectomy, between January of 2010 and June of 2020. Exclusion criteria included: age under 18 years and insufficient clinical data. A total of 112 patients were included. Socio-demographical characteristics (age, gender, and BMI), pre-operative clinical information, treatment, and outcomes were obtained from the hospital database.

Chemotherapy regimen was chosen by the Oncologist, after discussion of every case on MDT meeting, and included mainly regimes such as EOX (IV administration of 50 mg/m^2 epirubicin and 130 mg/m^2 oxaliplatin on day 1, and 625 mg/m^2 capecitabine *per os* twice a day on days 1-14, this regimen was repeated every 21 days), Folfox (IV administration of 85 mg/m^2 oxaliplatin, 200 mg/m^2 leucovorin and IV push administration of 400 mg/m^2 fluorouracil, and 2400 mg/m^2 fluorouracil IV continuous infusion for 46 h, this regimen was repeated every 14 days), FLOT (docetaxel 50 mg/m^2, oxaliplatin 85 mg/m^2, leucovorin 100 mg/m^2, and 5-fluorouracil 2600 mg/m^2 as a 24 h infusion, all given on day 1 and administered every 2 weeks) and mDCF (docetaxel 40 mg/m^2, cisplatin 40 mg/m^2, and IV push administration of 400 mg/m^2 fluorouracil, and 2000 mg/m^2 fluorouracil IV continuous infusion for 46 h, administered every 21 days). Options for surgical resection included subtotal and total gastrectomy.

Histopathological tumor regression was evaluated in the 112 surgical resection specimens, based on estimation of residual tumor tissue percentage at the primary tumor site in comparison to the identifiable former tumor bed, according to the Becker's criteria[21]. Tumor bed was identified by flattening/ulceration of

the mucosa, fibrosis, necrosis, and presence of macrophages. Regression was graded into the following categories: G1a (no residual tumor cells); G1b (< 10% residual tumor cells); G2 (10-50% residual tumor cells); and G3 (> 50% residual tumor cells). Lymph nodes without any signs of metastatic involvement were regarded to be tumor free. Fibrosis and xanthomatous macrophages were considered regression changes in lymph nodes.

Statistical analysis was performed using SPSS 26.0®. All continuous variables were assessed for normality and described accordingly. For comparative analysis, parametric and non-parametric tests were used when needed. $p < 0.05$ was considered statistically significant.

Results

A total of 112 patients, 58% males, with a mean age (SD) of 61.9 (10.1) y.o., were included in our study. Clinico-pathological features are described on table 1. Accounting for 56.5% of cases, antrum was the most common anatomic location of the tumor.

The majority (90.2%) completed at least three cycles, with a 56,5-day median duration. While intestinal type neoplasm was the most observed histological type, with 43.6% of cases.

Good tumor response to chemotherapy (< 10% residual tumor) was achieved in 21.3% of patients, but in 50.9% only regression of < 50% could be obtained – table 2 (n = 108, four cases omitted due to lack of information in the histological report). Age, gender, and patient's BMI presented no statistical association with the tumor response. Furthermore, neither tumor location nor chemotherapy regime or duration showed significant difference in tumor response to chemotherapy.

Regarding lymph node response, 11 patients achieved complete regression, while 28 patients presented no lymph node response at all – table 2 (n = 85, due to lack of information in the clinical process). Median lymph node response was 33.3%. As with the age, gender, BMI, and chemotherapy regime and duration did not present any statistical association with lymph node response to chemotherapy.

A total of 3222 lymph nodes were removed (median of 26.5 lymph nodes per patient, min = 6, max = 72). In G1a staging patients, (n = 3), 88 nodes were removed, none of which with metastatic involvement, 10 lymph nodes with complete response to chemotherapy (LNR 100%). In G1b patients (n = 20), 459 nodes were removed, 56 of which with metastatic involvement, 57 presented a good response to chemotherapy. In G2 staging patients (n = 30), 808 nodes were removed, 186 with metastatic involvement, and only 121 responded to chemotherapy. In G3 staging patients (n = 55), 1743 nodes were resected, 445 with metastatic involvement, and only 131 responded to chemotherapy.

Lymph node regression was higher among patients with better tumoral response to chemotherapy with G1b patients presenting 63.57% median lymph node regression while G2 and G3 presented significantly lower response rates, 33.92% and 30.78%, respectively ($p = 0.009$) (Table 3). A significant negative correlation

Table 1. Sample descriptive statistics (n = 112)

Demographic and tumor data	n
Age, mean (SD)	61.9 (10.1)
BMI, mean (SD)	25 (4.99)
Gender, n (%)	
Male	65 (58)
Female	47 (42)
Chemotherapy duration (median days, P5-P95)	56.5 (24.7-127.5)
Chemotherapy regime, n (%)	
EOX (Epirubicin, oxaliplatin, capecitabine) EOX (Epirubicin, oxaliplatin, capecitabine)	47 (42.3)
FOLFOX (Folinic acid, 5-FU, oxaliplatin)	8 (7.1)
mDCF (Docetaxel, levofolinate, 5-FU, cisplatin)	20 (17.9)
FLOT (5-FU, folinic acid, oxaliplatin, and docetaxel)	29 (25.9)
Other	8 (7.1)
Anatomic location (%)	
Antrum	56.5
Body	35.2
Fundus	8.3
Lauren classification (%)	
Intestinal type	43.6
Diffuse type	15.4
Unclassified	41
Operative procedure, n (%)	
Distal gastrectomy	47 (42)
Total gastrectomy	65 (58)
Pre-therapeutic staging	
cStage II	52 (46.4)
cStage III	50 (44.6)
cStage IV	10 (9)
Post-therapeutic staging	
ypStage 0 (complete response)	3 (2.7)
ypStage I	19 (17)
ypStage II	33 (29.5)
ypStage III	39 (34.8)
ypaStage IV	18 (16)

SD: standard deviation, BMI: body mass index

Table 2. Tumoral and lymph node regression

Tumor and lymphatic regression	n (%)
Becker - Tumoral regression*	
G1a	3 (2.7)
G1b	20 (18.6)
G2	30 (27.8)
G3	55 (50.9)
Lymph node regression**	
Complete regression	11 (12.9)
Parcial regression	46 (54.1)
Stable disease	28 (32.9)

*n = 108, **n = 85

Table 3. Comparation between tumoral regression and lymph node regression

Becker (tumoral regression)	Lymph node regression (%)	p
G1a	100	0.009
G1b	63.57	
G2	33.92	
G3	30.78	

was found between lymph node regression and post-chemotherapy histological stage ($p < 0.001$).

As for signet ring cell tumors (n = 37), 363 (33.2%) lymph nodes presented metastatic involvement of a total of 1093 lymph nodes resected, but only 156 (14.3%) of them shows signals of regression. Regarding intestinal type, there were 81 (6.5%) metastatic lymph nodes of 1239 resected, having 87 (7.0%) of these regressed. Curiously, signet ring cell tumors seem to have significantly higher lymph node regression ($p = 0.041$). Still, no significant differences were found between different chemotherapy schemes and the rate of tumoral and lymph node regression.

Although the follow-up time of 19 patients is < 1 year, we can say that there is a positive correlation between lymph node regression and survival length ($p = 0.018$).

Discussion

There is no consensus on most appropriate approach to the management of localized gastric adenocarcinoma. Gastrectomy with D2 lymphadenectomy has been generally regarded as the standard treatment for achieving cure[22]. An D2 lymphadenectomy is recommended in all patients with a resectable gastric tumor, as we know this procedure is associated with lower locoregional recurrence[13]. Recently, perioperative chemotherapy has gained an increasingly important role in the treatment of advanced gastric cancer, by contributing to reduce tumor burden and decrease lymph node invasion. However, there are not enough studies about the effects in metastatic lymph nodes or if it is possible to limit lymph node resection in patients submitted to chemotherapy preoperatively.

In spite of only three cases resulting in complete histological tumoral regression and eleven in total regression in metastatic lymph nodes, we noticed a correlation between chemotherapy response in lymph nodes invaded and primary tumor. Spiegel et al.[12] suggested that neoadjuvant chemotherapy, besides disease downstaging before attempted surgical resection, also allows selection of patients for surgery based on disease biology. This means that those who did not present disease progression during perioperative period will be better candidates for surgery, whereas those who do develop overt metastasis can be spared the morbidity of surgery. Thus, perioperative chemotherapy should be considered as a selection method for surgery, enabling better outcomes of both R0 resection rate and disease-free survival time. As opposed to our results, Kinoshita et al. showed that even metastatic lymph nodes clinically exhibiting favorable response to chemotherapy also presented an unsatisfactory histological response[13]. As of these incongruous results, a D2 lymphadenectomy should be performed even in patients with a good objective response of the primary tumor and metastatic lymph nodes[6].

As signet ring cells tumors show worse prognosis and response to chemotherapy, it is emphasized the importance of early diagnosis and treatment and more effective agent and chemotherapy administration routes should also be further considered and evaluated. Interestingly and contrary what was reported by Lemoine et al.[17], we have concluded that patients with gastric cancer with signet ring cells seemed to have a slight better lymph node regression with chemotherapy when compared with intestinal type, perhaps due to the use of more aggressive and more prolonged schemes. Perioperative chemotherapy was found to be an independent predictor of poor survival and it was suggested that neoadjuvant treatment toxicity was correlated with worse outcome[23,24]. On the other hand, whereas signet ring cells gastric adenocarcinoma is thought to be less chemosensitive than intestinal type, recent reports suggest it could have a

specific sensitivity profile and be more sensitive to taxane-based chemotherapy or antiangiogenics[24]. However, this has yet to be confirmed in a specific prospective trial.

In our sample, survival is correlated with metastatic regression of the lymph nodes in response to perioperative chemotherapy. Lymph node dissection is an important part of the surgical treatment of advanced gastric cancer due to the high incidence of lymph node metastasis. The appropriate lymphadenectomy associated with ganglion regression, may be the reason why perioperative chemotherapy in gastric cancer plays a role in increasing the survival of patients with advanced gastric cancer, allowing the reduction of lymph nodes metastases, more important than the reduction of tumor mass.

Notably, this was a retrospective study, based on a limited number of patients, not all patients completed the perioperative treatment and we included cases with advanced disease.

Conclusion

While this study did not present an outstanding lymph node regression rate, an important decrease in tumor burden (we observed a pathological complete response in three cases) and number of invaded lymph nodes was observed. In addition, we found a correlation between lymph node regression and tumor regression. Nonetheless, for now we must not neglect that an adequate tumor resection and D2 lymphadenectomy must always be performed to obtain R0 resections. Further prospective studies should be carried out to evaluate the effect of perioperative chemotherapy on survival and to compare the combined effect with lymphadenectomy in both early and advanced stages of gastric cancer. Maybe in the future, we can consider the hypothesis of a conservative approach in cases with the evidence of clinic complete regression after adequate chemotherapy regimens.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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