DO PROXIMAL AND DISTAL GASTRIC TUMOURS BEHAVE DIFFERENTLY?

Tumores gástricos proximais e distais se comportam de forma diferente?

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HEADINGS - Stomach neoplasms. Prognosis. Survivorship. Mortality. Lymph Node Excision.

ABSTRACT - Background: Although the incidence of gastric (adenocarcinoma) cancer has been decreasing over time, it is still one of the most common malignancies worldwide, and proximal tumours tend to have a worse prognosis. Aim: To compare surgical outcomes and prognosis between proximal - excluding tumours of the cardia - and distal gastric cancer. Methods: Out of 293 cases reviewed - 209 with distal and 69 with proximal gastric cancer - were compared for clinical and pathological features, stage, surgical outcome, mortality and survival. Results: Statistically, there was no significant difference between patients in both groups regarding mortality (p=0.661), adjuvant chemotherapy (p=0.661), and radiation (p=1.000). However, there was significant difference in the degree of lymph node dissection employed (p=0.002) and the number of positive lymph nodes resected (p=0.038) between the two groups. The odds of death at five years for patients who had a D0 dissection was three times greater (odds ratio 2.78; 95%CI 1.33–5.82) than that for patients who had a D2 dissection, while for patients who had a D1 dissection the odds ratio was only 1.41 (95%CI 0.71–2.83) compared to D2-dissected patients. Conclusion: Although no significant differences were found between proximal and distal gastric cancer, the increased risk of death in D0- and D1-dissected patients clearly suggests an important role of radical D2 lymph node dissection in survival.

INTRODUCTION

Although the incidence of gastric cancer has decreased over the past decades, it still remains a relevant problem, being among the most common malignancies worldwide. According to the Globocan²⁰ 2014 project from the World Health Organization (WHO), there were approximately a million new gastric cancer cases worldwide (952,000 cases; 7% of all malignancies), ranking gastric cancer as the 5th most common tumor in absolute numbers. In Brazil, data from the National Cancer Institute for 2016 place gastric cancer as the 4th most common cancer in men (12,870 cases) and the 6th most common in women (7,520 cases). These figures place the stomach as the 6th most frequently organ affected by cancer in Brazil¹⁰.

In the past, tumors originating in the cardia and in the gastro-esophageal junction were usually addressed as proximal gastric tumors, indistinctly. The anatomical structure of the proximal third of the stomach, where the serosa is partially developed, increasing the likelihood that these tumors will be diagnosed at a more advanced stage, may also be associated with unfavorable prognosis on proximal tumors¹. Moreover, there is no clear agreement on the link between mortality and tumor location in the stomach. Earlier papers considered prognostic and survival differences and stated that cancers originating in the cardia and in the gastro-esophageal junction tended to have a worse prognosis than those affecting more distal portions of the organ¹¹,¹²,¹³.

However, some authors have shown that, when cases are analyzed at sub-stages, outcomes are similar¹⁴,¹⁵,¹⁶. Still, excluding the tumors located either in the gastro-esophageal junction with esophageal predominance or those affecting primarily the anatomical cardia (Siewert I and II types), no significant differences were observed on survival among primary tumors originated at the upper, middle, or lower stomach¹⁷,¹⁸.
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NOWADAYS, WHEN THERE IS A TENDENCY TO PROXIMAL MIGRATION OF THE PRIMARY TUMOUR IN THE STOMACH, THOSE PARAMETERS AND DIFFERENCES BETWEEN PROXIMAL AND DISTAL TUMOUR NEED TO BE REVISITED.

THESE STUDIES WERE DESIGNED TO ANALYZE BOTH SURGICAL AND ONCOLOGIC FINDINGS AND OUTCOMES OF GASTRIC CANCER, AND TO COMPARE DIFFERENCES BETWEEN PROXIMAL (EXCLUDING TUMOURS FROM ESOPHAGOGASTRIC ORIGIN) VS. DISTAL LESIONS.

METHODS

THIS WAS A RETROSPECTIVE COHORT STUDY OF 293 PATIENTS WITH ADENOCARCINOMA OF THE STOMACH WHO UNDERWENT TREATMENT AT A UNIVERSITY HOSPITAL (SÃO LUCAS HOSPITAL IN THE PONTIFÍCIA UNIVERSIDADE CATÓLICA), LOCATED IN THE CITY OF PORTO ALEGRE, RS, BRAZIL, FROM JANUARY 2002 TO JANUARY 2015. PATIENTS’ MEDICAL RECORDS FROM THE MEDICAL FILE SERVICE OF THE INSTITUTION WERE USED AS A RESEARCH SOURCE. CASES WITH MISSING OR INCOMPLETE DATA AS WELL AS THOSE WITH HISTOPATHOLOGICAL FINDINGS OTHER THAN ADENOCARCINOMA AND SIEWERT TUMOUR TYPES I AND II WERE EXCLUDED FROM THE ANALYSIS.

PREOPERATIVE ENDOSCOPY, PATHOLOGY AND SURGICAL REPORTS WERE REVIEWED, AND TUMOUR LOCATION WAS CLASSIFIED ACCORDING TO THE CRITERIA OF THE JAPANESE GASTRIC CANCER ASSOCIATION11. PROXIMAL GASTRIC CANCER (PGC) WAS CONSIDERED WHEN THE TUMOUR EXTENDED FROM ONE POINT TO MORE THAN 2 CM DISTAL TO THE GASTRO-ESOPHAGEAL JUNCTION (SIEWERT TYPE III) UP TO A CROSSING LINE BETWEEN THE LEFT GASTRIC ARTERY AND THE END OF THE LEFT GASTROEPIPLOIC TUMOUR. TUMOURS BELOW THIS CROSSING LINE WERE CONSIDERED DISTAL TUMOURS. DEMOGRAPHIC AND EPIDEMIOLOGICAL DATA, SUCH AS AGE, GENDER, TUMOUR SIZE, AND NUMBER OF DISSECTED AND INVOLVED LYMPH NODES WERE COLLECTED.

TUMOUR STAGING FOLLOWED THE GUIDELINES OF THE TNM (TUMOUR-NODE-METASTASIS) SYSTEM OF THE AMERICAN JOINT COMMITTEE ON CANCER (AJCC),7 TH EDITION.

POSTOPERATIVE SURGICAL Complications, EXCLUDING THOSE THAT OccURRED AFTER DISCHARGE, WERE CLASSIFIED ACCORDING TO THE SYSTEM PROPOSED BY CLAVIEN, IN 1992, AND MODIFIED BY DINDO, IN 20044.

STATISTICAL ANALYSIS

QUANTITATIVE DATA WERE EXpressed as MEAN AND STANDARD DEVIATION, OR MEDIAN AND MINIMUM-MAXIMUM RANGES, ACCORDING TO VARIABLE DISTRIBUTION. AS FOR QUALITATIVE DATA, ABSOLUTE FREQUENCIES AND PERCENTAGES WERE USED. DISTAL AND PROXIMAL CASES WERE ANALYZED USING THE WILCOXON-MANN-WHITNEY TEST AND THE CHI-SQUARE TEST, FOLLOWED BY ANALYSIS OF RESIDUES, IF NEEDED. COX REGRESSION WAS USED TO COMPARE SURVIVAL BETWEEN PATIENTS WITH PROXIMAL AND DISTAL TUMOURS, RESPECTIVELY. THE KAPLAN-MEIER METHOD WAS USED TO ESTIMATE SURVIVAL AS A FUNCTION OF TIME, AND THE LOG-RANK TEST WAS USED FOR COMPARISON OF SURVIVAL CURVES ACCORDING TO CLINIC-PATHOLOGICAL CHARACTERISTICS. STATISTICAL ANALYSIS WERE PERFORMED WITH THE HELP OF THE STATISTICAL PACKAGE FOR THE SOCIAL SCIENCES (SPSS), VERSION 18.013, AND THE LEVEL OF SIGNIFICANCE WAS SET AT p<0.05.

RESULTS

A TOTAL OF 293 PATIENTS DIAGNOSED WITH ADENOCARCINOMA OF THE STOMACH WERE INITIALLY INCLUDED IN THE STUDY. A HUNDRED AND EIGHTY-EIGHT (64%) WERE MEN AND 105 (36%) WOMEN. IN 15 CASES, INITIAL TUMOUR LOCATION COULD NOT BE DETERMINED ACCURATELY ENOUGH TO BE INCLUDED IN THE STUDY. FIVE OF THEM CLASSIFIED AS MULTIFOCAL, FOUR AS ANASTOMOTIC RECURRENCE, AND IN SIX CASES, AVAILABLE DATA WERE NOT RELIABLE. THEREFORE, 278 PATIENTS, 69 (25%) OF THEM WITH PGC AND 209 (75%) WITH DISTAL GASTRIC CANCER (DGC) WERE INCLUDED. TABLE 1 SHOWS THE CLINIC-PATHOLOGICAL FINDINGS OF THE PATIENTS.

TABLE 1 - Clinic-pathological findings of patients depending on the location of primary tumor in the stomach

| Local tumor | Proximal n (%) | Distal n (%) | p |
|-------------|----------------|--------------|---|
| Male/Female | 40 (58.29) | 139 (66.5) | 0.0246 |
| Age; years  | 64.6 | 65.3 | 0.635 |
| Admission; average (sd); days | 20.4 (18.3) | 18.6 (14.9) | 0.577 |
| Leision; median (variation) cm | 7.2 (0.4 – 18.0) | 4.6 (0.4 – 14.3) | <0.001 |
| Resected lymph nodes (median variation) | 20.5 (0 – 47) | 13.0 (0 – 84) | <0.001 |
| Positive lymph nodes (median variation) | 4.0 (0 – 46) | 2.0 (0 – 40) | 0.038 |
| Metastases; median (variation) months | 27.0 (18 – 62) | 13.0 (0 – 42) | 0.037 |
| AJCC Clinical stage | | | |
| 0 | 0 (0) | 0 (0) | 1.0 (0.5) |
| 1A | 9 (13.4) | 23 (37.3) | 27 (13.7) |
| 1B | 2 (3) | 23 (37.3) | 13 (6.6) |
| 2A | 7 (10.4) | 11 (16.4) | 27 (13.7) |
| 2B | 4 (6) | 23 (37.3) | 11 (5.6) |
| 3A | 25 (37.3) | 37 (18.8) | 37 (18.8) |
| 3B | 11 (16.4) | 44 (22.3) | |
| 4 | | | |
| Level of differentiation | | | |
| Well-differentiated (1) | 2 (3.6) | 7 (4.5) | 0.038 |
| Moderately differentiated (2) | 16 (25.8) | 74 (47.1) | |
| Poorly differentiated (3) | 38 (67.9) | 76 (48.4) | |
| Subtype (Lauren) | | | |
| Intestinal (1) | 15 (25.4) | 51 (29.8) | 0.025 |
| Diffuse (2) | 29 (49.2) | 67 (39.2) | |
| Mixed (3) | 7 (11.9) | 25 (14.6) | |
| Undetermined (4) | 8 (13.6) | 28 (16.4) | |
| Lymphadenectomy | | | |
| D0 | 12 (20) | 64 (37.4) | 0.002 |
| D1 | 21 (35) | 71 (41.5) | |
| D2 | 26 (43.3) | 36 (21.1) | |
| Dx | 1 (1.7) | 0 (0) | |
| Adjuvant chemotherapy | | | |
| No | 23 (74.2) | 74 (67.9) | 0.661 |
| Yes | 8 (25.8) | 35 (32.1) | |
| Adjuvant radiation | | | |
| No | 22 (73.3) | 80 (74.1) | 1.000 |
| Yes | 8 (26.7) | 28 (25.9) | |
| Death | | | |
| Yes | 14 (31.8) | 45 (34.6) | 0.661 |
| No | 30 (68.2) | 85 (65.4) | |

In the PGC group, the median range number of lymph nodes removed was 20 (0–47), significantly lower (p<0.001) than in the DGC group, which was 13 (0–84). Positive range lymph nodes were also lower in the PGC group as compared to the DGC group, 2 (0–40) and 4 (0–46), respectively (p=0.038). As for lymph node status, the probability of being alive in five years was 48% (11%) for N1 (n=34), 37% (11%) for N2 (n=41), and 23% (7%) for N3 (n=73), with no significant difference between these groups, statistically.

Patients who underwent D0 lymph node dissection had a median survival of 26 months, which was less than that of patients who underwent D1 dissection (54 months) or D2 dissection (63 months). Moreover, for patients with a D0 lymph node dissection, the cumulative probability of being alive in five years was 30% (8%), while for those who had a D1 or D2 dissection, these probabilities were 48% (7%) and 53% (9%), respectively. However, differences in survival between the levels of lymph node dissection were not statistically significant.

Figure 1 shows the overall survival curve according to
As expected, the majority of patients in both groups had advanced tumors. Proximal tumors were larger in size (p<0.001), presented with a higher number of positive lymph nodes (p=0.038), and were significantly less differentiated, as for histopathology, than distal lesions (p=0.038). Early lesions (T1) accounted for 19% of all tumors (16% of PGC and 20% of DGC). On the other hand, 20% of patients had disseminated tumor already (M1) at diagnosis, also 16% and 20%, respectively.

Overall, average (SD) tumor size was 5.8 (3.7 cm), ranging from 4 mm to 20 cm. Average (SD) size in the DGC and PGC groups were 7.4 (4.3 cm) and 5 (2.8 cm), respectively (p<0.001). Tumor size was directly related to mortality, where patients with tumors larger than 8 cm in diameter had a significantly shorter survival than those with lesions smaller than 5 cm (6 vs. 50 months; p<0.001). Furthermore, patients with tumors larger than 8 cm died earlier within 60 months (81% vs. 53%) as compared to those patients with lesions smaller than 5 cm. The probability of being alive in five years was 14% (4.7%) for patients with tumors larger than 8 cm, while for patients with tumors smaller than 5 cm, this probability was 42% (7%). Statistically, the effect of tumor size on survival did not differ between proximal and distal locations.

As for factors related to survival, T4 tumors were found to be strongly positively associated with N3 lymph node involvement (p=0.001), where more than half (58%) of T4 cases were N3. The majority of T2/T3 tumors were associated with a lower lymph node involvement (N1 and N2), and only a small percentage of them (8%) were N3.

Patients with T4 tumors (n=158) had the worst outcomes, and the probability of being alive in five years was 32% (5.4%). When cases with tumors confined into the muscle or up to the serosa (T2/T3) were analyzed together (n=47), the probability of being alive in five years was 47% (11.4%). T4 cases had a median survival of only 21 months, while T2/T3 cases had a median survival of 54 months, but this difference was not statistically significant. Patients with T4 tumors presented 2.17 times [0.94–5.02; 95% CI] more chances to die within five years than patients with lesions with less impairment of the organ wall.

There were postoperative complications in 25% of patients with PGC and 23% of patients with DGC. The most common complication in both groups was pneumonia, which affected 30 (14%) patients, followed by fistula in 17 (8%), sepsis in 8 (4%), and wound infection in 6 (2.8%). Intra hospital mortality rate was 5% (n=6).

Overall recurrence was 37%; 48 out of 128 cases were followed up till the end of the study, being peritoneal surface (n=29) and liver (n=11) the most common sites. There was no statistically significant difference between the two groups regarding the use of adjuvant therapy, where 11 (8%) patients receiving chemotherapy alone and 31 (23%) receiving also radiotherapy did relapse.

Survival rates were calculated based on the follow-up of 278 patients, and cumulative probability of being alive in five years was estimated in 35% (7.4%) for patients with PGC and 32% (4.5%) for patients with DGC. This difference was not statistically significant between both groups either.

Figure 2 shows the overall survival curve for patients in the two groups throughout study period. When adjusted for tumor size and degree of lymph node dissection performed, the higher the number of positive lymph nodes, the greater the mortality (p=0.007).

**DISCUSSION**

It is well known that aggressiveness of gastric cancer depends on a number of factors, including wall invasion pattern and lymph node status, which are the two most important findings to estimate prognosis and to guide decision making. Furthermore, the presence of regional lymph node metastases alone is the most important independent prognostic factor for survival in these patients. Although proximal lesions did show deeper invasion and higher lymph node involvement,
outcomes did not differ significantly between the two groups. Does tumor size matter? In patients with other types of cancer, such as breast or lung cancer, tumor size is still an important predictor. In gastric cancer, however, the prognostic value of tumor size remains controversial. Some authors showed that tumor size can be an important factor as for aggressiveness. This is consistent with the present study, where a direct relationship was found between lesion diameter and aggressiveness. The larger the tumor, the more aggressive, with deeper invasion in stomach wall and higher degree of lymph node involvement. Nevertheless, proximal lesions were significantly larger than distal ones.

Treatment of gastric cancer is multi-factorial, but surgery still plays a primary role in management, since it is the only approach that can lead to cure. The stage at which the disease is detected plays a crucial role in treatment choice. The use of chemotherapy or radiotherapy combined with surgery is well established, with clear benefits in survival and disease progression. This approach was strengthened especially after the classic study by Macdonald et al. in 2001, with the combination of preoperative chemotherapy and postoperative radiation, which showed an increase in overall survival from 27 to 36 months with surgery alone. Cunningham, in 2006, showed improvement in overall and progression-free survival with per-operative chemotherapy.

Nevertheless, prognosis of gastric cancer is still quite dismal – despite constant improvements in adjuvant therapy with the development of new drugs and association of target therapy that have, undoubtedly, improved survival –, especially for those cases with poor histology. In such cases, even after radical resection, about 20-40% of the patients die due to recurrence and present peritoneal dissemination, which is, in fact, the main cause of treatment failure, and where serosal involvement is a predisposing factor. In this study, no difference was found on peritoneal recurrence according to primary tumor location, and this was not affected by either preoperative or postoperative adjuvant treatment.

Overall survival in five years for patients operated on for advanced gastric cancer differs among countries and medical institutions, but it is generally below 30% in Western countries, such as those of Europe and in the United States. In Asian countries, such as Japan and South Korea, survival is significantly higher, reaching approximately 70%-80%. In the present study, survival was identical in both groups, with a rate of 37% for PGC and 36% for DGC, consistent with published results. Despite therapeutic advances over the past decades, especially regarding adjuvant therapy, mortality of gastric adenocarcinoma remains high. The results of the present study showed no significant differences in surgical outcome or prognosis between proximal and distal lesions. As expected, and similar to previous studies, the degree of lymph node involvement and tumor size were independent factors that affected survival.

CONCLUSION

Although significant differences between distal and proximal gastric tumors have not been observed, the increased risk of death in D0 and D1-dissected cases clearly suggests a main role of radical D2 lymphadenectomy in the treatment of this disease.

REFERENCES

1. Bruno L, Nesí G, Montiñaro F, Carassale G, Lassig R, Bocchi V, et al. Clinicopathologic findings and results of surgical treatment in cardiac adenocarcinoma. J Surg Oncol. 2000 May;74(1):33-35.
2. Carbone F1, Lepiane P, Santoro R, Lorusso R, Mancini P, Spedutti L, et al. Extended multimodality resection for gastric adenocarcinoma. J Surg Oncol. 2005 May 1;90(2):95-100.
3. Chae S, Lee A, Lee JH. The effectiveness of the new (7th) UICC classification in the prognostic evaluation of gastric cancer patients: a comparative study between the 5th/6th and 7th UICC N classification. Gastric Cancer. 2011 Jun;14(2):166-71.
4. Clavien P, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schaldach, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009 Aug;250(2):187-96.
5. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastric carcinoma. N Engl J Med. 2006 Jul 6;355(1):11-20.
6. Deng J, Liang H, Sun D, Wang D, Pan Y. Suitability of 7th UICC N stage for predicting the overall survival of gastric cancer patients after curative resection in China. Ann Surg Oncol. 2010 May;17(5):1259-66.
7. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC cancer staging manual. New York: Springer; 2010.
8. Feltj J, Scejnomataram I, Ennk M, Dikshit R, Eser S, Mathews C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No.11 [Internet]. Lyon, France: InternationalAgency for Research on Cancer; 2013 [cited 2015 Nov 09]. Available from: http://globocan.iarc.fr.
9. Giuliani A, Caporale A, Di Bari M, Demorco M, Gozzo P, Corona M, et al. Maximum gastric cancer diameter as a prognostic indicator: univariate and multivariate analysis. J Exp Clin Cancer Res. 2003 Dec 22(4):531-8.
10. Gomes da Silva JA. [National Institute of Cancer] 2014 estimates: incidence of cancer in Brazil [Internet]. Rio de Janeiro: INCA; 2014 [cited 2015 Nov 09]. Available from: http://www.inca.gov.br/bvscontrolcancer/publicacoes/ Estimativa_2014.pdf.
11. Howlader N, Ries LAA, Stinchcomb D, Edwards BK. The impact of the u ndeported Veterans Affairs data on national cancer statistics analysis using population-based SEER registries. J Natl Cancer Inst. 2009 Apr 1;101(7):533-6.
12. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer. 2011 Jun;14(2):101-12.
13. Kim DY, Joo KJ, Ryu SY, Park YK, Kim YJ, Kim SK. Clinicopathological characteristics and prognosis of carcinoma of the gastric cardia. Dig Surg. 2006;23(5-6):313-18.
14. Kunisaki C, Akiyama H, Nomura M, Matsuura G, Otsuka Y, Ono H, et al. Surgical outcomes for early gastric cancer in the upper third of the stomach. J Am Coll Surg. 2005 Jan;200(1):15-9.
15. Kunisaki C, Akiyama H, Nomura M, Matsuura G, Otsuka Y, Ono HA, et al. Surgical outcomes in patients with T4 gastric carcinoma. J Am Coll Surg. 2006 Feb;202(2):223-30.
16. Kunisaki C, Makino H, Takakawa R, Oshima T, Nagano Y, Kosaka T, et al. Tumor diameter as a prognostic factor in patients with gastric cancer. Ann Surg Oncol. 2008 Jul;15(7):1959-67.
17. Lee IS, Park YS, Ryu MH, Song MJ, Yook JH, Oh ST, et al. Impact of extranodal extension on prognosis in lymph node-positive gastric cancer. Br J Surg. 2014 Nov;101(12):1576-84.
18. Macdonald JS, Smallley SR, Benedetti, HundalhsA, EstesNC, Steinemann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001 Sep 6;345(10):79-87.
19. Mita K, Ito H, Fukumoto M, Murabayashi K, Koizumi K, Hayashi T, et al. Surgical outcomes and survival after extended multigorgan resection for T4 gastric cancer. Am J Surg. 2012 Jan;203(1):107-11.
20. Mochizuki S, Maehara Y, Konoe N, Dokiya S, Nose Y, Risk factor which predict pattern of recurrence after curative surgery for patients with advanced gastric cancer. Surg Oncol. 1992 Oct;1(5):341-6.
21. Park YJ, von Karsa L, Herrero R. Prevention strategies for gastric cancer: a global perspective. Clin Endosc. 2014 Nov;47(4):478-89.
22. PSW Statistics for Windows Version. Ergebnisse des internationalen Klassifikation- und Prognose-Score: Workshop: The Clavien-Dindo classification of surgical complications: five-year experience. J Surg Oncol. 2005 May 1;90(2):95-100.
23. Sanchez-Bueno F, Garcia-Marcilla JA, Perez-Flores D, Perez-Abad JM, Vicente R, Aranda F, et al. Prognostic factors in a series of 297 patients with gastric adenocarcinoma undergoing surgical resection. Br J Surg. 1998 Feb;85(2):255-60.
24. Soreide JA, van Heerden JA, Burgart LJ, Donohue JH, Sarr MG, Ilstrup DM. Surgical aspects of patients with adenocarcinoma of the stomach operated on for cure. Arch Surg. 1996 May;131(5):481-6; discussion 486-8.
25. Zidovitch MS, Kim SP, Yao KA, Wee JS, Feinglass J, Bennett CL, et al. Surgical outcomes of patients with gastric cancer: the importance of primary tumor location and microvesSEL invasion. Surgery. 2003 Oct;134(4):720-7; discussion 727-9.
26. Verdecchia A, Francesc I, Brenner H, Gatta G, Micheli A, Mangone L, et al. Recent advances in survival in Europe: 2000-2002 period: analysis of EUROCARE-4 data. Lancet Oncol. 2007 Sep 8;8(9):784-96.
27. Zilelberst, Brown et al. Results of gastrectomy D2 for the cancer gastic: dissecação da cadeia linfática ou ressecção linfonodal múltipla? ABCD, arq bras cir. dig. Set 2012, vol 25, no:3, p.161-164. ISSN 0102-6720.