D2 LYMPHADENECTOMY AS AN INDEPENDENT PROGNOSTIC FACTOR IN GASTRIC CANCER

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ABSTRACT

Background: The last decades have been marked by debates based on the importance of lymphadenectomy in gastric cancer, lymphadenectomy being a topic of controversy between the Western Surgical Societies and the Asian side. Lymphadenectomy is currently a globally accepted standard in the treatment of gastric cancer.

Methods: The present study was performed prospectively on a number of 93 patients diagnosed with gastric cancer, who underwent radical gastrectomy with lymphadenectomy in the Surgery Department of the Emergency County Clinical Hospital, Constanta, between January 2012 - December 2016. In 70 cases, an extended D2 or standard D2 lymphadenectomy was performed, and for 23 patients: D1 + lymphadenectomy. The data were statistically analyzed in order to determine the prognostic value of lymphadenectomy in gastric cancer.

Results: The average age was 65.88 ± 8.80 years. The mean number of lymph nodes harvested in D2 lymphadenectomy was 22.8 ± 7.60 , with limits between 15 and 43, and the number of positive lymph nodes ranged from a minimum of 0 to a maximum of 37. Histopathological exam of specimens showed that only 17.2% of patients with gastric cancers were without lymph node metastases (pN0), while 45.16% were in the pN3 stage. Analysis of survival curves revealed that 5-year survival was significantly higher in D2 lymphadenectomy compared to D1 + lymphadenectomy (23.8% vs. 8.7%).

Conclusions: The current study validates D2 lymphadenectomy as a standard technique and the superiority of the prognosis in gastric cancer patients through results obtained in terms of 5-year survival.

Keywords: Gastric cancer, D2 lymphadenectomy, Lymph node ratio, Survival rate

Introduction

Gastric cancer is one of the cancers that raises major public health problems worldwide through late diagnosis, high aggressivity and low cure rate in the symptomatic phase. Gastric cancer is recognized as the 5th leading cause of cancer and the 3rd leading cause of mortality globally (1, 2).

Gastric cancer has a well-known lymph node tropism directly proportional to the degree of local invasion. Lymphadenectomy is currently the accepted standard surgical treatment worldwide.

Lymphadenectomy has been a hotly

debated topic in the surgical world for decades. In Asian countries, D2 lymphadenectomy has been considered a standard procedure since the 1960s, especially in Japan, where gastric cancer and its increased incidence have aroused great interest. This can be explained by the greater experience of Asian surgical centers specialized in this type of dissection and also by the younger age of Asian patients with fewer associated comorbidities, and also by their constitutional type with less abdominal fat which determines an increased feasibility of lymphodissection (3, 4, 5).

Compared to these elements, limited lymph dissections have been performed in Western

countries, D2 lymphadenectomy being seen as a more complicated technique which requires adequate training (3, 4). Also, Western countries have brought various criticisms to the results of Asian teams in terms of the fact that they were determined by retrospective evaluation and not by non-randomized studies (3, 6).

In addition, some Western studies conducted 30 years ago (RCTs and literature reviews) (3, 4, 6, 7) have highlighted the idea that D2 lymphadenectomy results in a higher rate of postoperative complications and higher perioperative mortality without a real benefit in survival. Recent data have demolished previous concepts and changed the view on D2 lymphadenectomy. The 15-year follow-up of the so controversial in the surgical world Dutch study finally concluded that D2 lymphadenectomy is superior to D1 lymphadenectomy in terms of survival (3, 8) and that the higher rate of mortality and postoperative complications following D2 lymphadenectomy was related to performing distal pancreatectomy and / or splenectomy, which were included in the standard D2 lymphadenectomy technique to provide adequate lymph node dissection (3,4). However, recent studies exclude patients with splenopancreatectomy and analyze separately only patients with lymphadenectomy D2 with preservation of the spleen and / or pancreas (3, 9, 10, 11, 12).

In addition to these results, Western countries have concluded that proper training in specialized centers facilitates safe D2 lymphodissection.

In conclusion, the general direction of recent years is to adopt D2 lymphadenectomy as a standard procedure in resectable gastric cancer as we finally reach a consensus between the European Society for Medical Oncology (ESMO) and the Japanese Gastric Cancer Association (JGCA) (13).

Material and Method

In this paper we analyze prospective 93 patients with gastric cancer who underwent radical gastrectomy with lymphadenectomy as curative treatment between January 2012 -

December 2016 in the Department of Surgery of Emergency Hospital Constanța. Patients with metastatic disease were not included. A standardized D2 lymphadenectomy with spleen / pancreas preservation was performed as a surgical procedure of choice in 70 cases. In the remaining 23 cases a modified lymphadenectomy (D1 +) was performed.

The extent of lymphadenectomy was determined by the type of gastrectomy according to the Japanese Gastric Cancer Association (JGCA) 2018 version (78). For total gastrectomy, D2 includes nodes in D1 stations plus 8a, 9, 11p, 11d and 12a. For distal gastrectomy lymph node dissection in D2 includes nodes in D1 stations plus 8a, 9, 11p and 12a.

The study of each case was performed according to a standard sheet containing the patient's preoperative demographic data (age, sex, comorbidities, nutritional status), pathological data - tumor location, type of gastrectomy, invasion of the stomach wall (T), lymph node invasion (N), microscopic appearance of the tumor (WHO classification 2010), degree of tumor differentiation (G), number of nodes harvested, number of nodes invaded, TNM staging according to the 8th edition of AJCC / UICC (American Joint Committee on Cancer / Union for International Cancer Control) of October 2017, the type of lymphadenectomy performed (3, 4).

The collected data were statistically analyzed with specific programs, the 5-year survival rates being calculated using the Kaplan-Meier survival analysis method. Log-rank tests were also performed to identify independent prognostic factors correlated with lymph node invasion. All statistical analyses were performed using the Statistical Package for the Social Science (SPSS) version 22.0 software.

Results

Out of a total of 93 patients, 63 were men (67.74%), the ratio of men:women being 2:1 consistent with the literature data, this ratio having a value of 2 worldwide and 2.9 in 2018 in Romania after GLOBOCAN 2018 (2). The mean age was 65.88 ± 8.80 , with limits between 43 and 85 years. Distal localization of gastric cancer

was the most common, followed by localization in the gastric body. Distal gastrectomy was the most common intervention, with a percentage of 56%, followed by total gastrectomy, performed in 41% of cases (figure 1).

Figure 1 Total gastrectomy specimen (personal archive)

The mean lymph nodes collected in D1 + lymphadenectomy were 14.47 ± 5.73 and 22.8 ± 7.60 in the D2 lymphadenectomy group. The extreme values for the first group were 7 and 29 and 13 and 43 for the second group. The amplitude of the positive lymph nodes variation starts from 0 invaded lymph nodes to 22 in the D1 lymphodissection group and from 0 to 37 in the D2 lymphadenectomy group.

Stage N3 was the most common - 50%, followed by N2 with 23%, N0 by 17% and N1 - 10% in patients who underwent D2 lymphadenectomy (figure 2).

Figure 2 N stage distribution

Analysis of Kaplan-Meier survival curves after stage N of lymph node invasion reveals that the best prognosis and the highest survival is stage N0 with a 5-year survival of 87.5%, 14 of 16 patients surviving 60 months. In the higher stages, survival decreases quite abruptly, being 27.3% for stage N1, only 3 out of 11 patients surviving up to 5 years (figure 3).

Figure 3 N stage survival

For stages N2 and N3, the 5-year survival rates were 16.7% and 2.4%, respectively. It should be noted that stage N3 has the darkest prognosis, only 1 patient out of the 42 included in this stage reaching the survival limit of 60 months.

The analysis of Kaplan-Meier survival curves according to the type of lymphadenectomy reveals that the 5-year survival is significantly higher in D2 lymphadenectomy compared to D1 + lymphadenectomy, ie 23.8% compared to 8.7%. In the group of D2 lymphadenectomy a number of 10 patients out of a total of 42 reached the survival limit of 60 months, while in the group of those with lymphadenectomy D1 + only 2 patients out of 23 survived to 5 years (figure 4). Regarding extended D2 lymphadenectomy, it showed the highest survival rate, namely 35.7%, with 10 patients reaching the 60-month limit out of 28, higher survival even compared to standard D2.

Figure 4 Survival rate dependent on the type of lymphadenectomy

Extended D2 lymphadenectomy was represented by: D2 + no 10 in 2 cases of proximal locations of gastric cancer and 4 cases of total gastrectomy; D2 + no 13 in 9 cases of antropiloric gastric cancer; D2 + no 14v in 8 cases of antral

neoplasms; D2 + PAN lymphadenectomy in 5 cases of locally advanced gastric cancer.

Although superextended lymphadenectomy is not considered standard, it is observed that it can bring a real benefit in the survival of patients with advanced gastric cancer in selected cases, with improved survival rates at 5 years, as seen in this paper.

Discussions

Lymph node invasion is one of the most important prognostic factors in gastric cancer, a determinant factor of local recurrences and long-term survival (12). Since 1997 the UICC / AJCC system has adopted N category as the number of metastatic lymph nodes in the TNM classification.

The latest edition of the UICC / AJCC system recommends examining at least 15 lymph nodes to establish N status in the TNM classification. Unfortunately, compliance with this recommendation is quite low, so that in the United States an average of 10 lymph nodes are harvested and evaluated and only in 29% of cases are more than 15 lymph nodes dissected (3, 14). For these reasons, the accuracy of stage N of the TNM classification, essential for the prognostic evaluation of gastric cancer patients, is influenced by the number of lymph nodes collected and examined (12, 14).

The basis of a thorough lymph dissection is the complete knowledge of the surgical and vascular anatomy of the upper abdominal region with the establishment of absolute landmarks in the operating field.

D2 or standard lymphadenectomy is indicated for T2-T4 tumors with curable potential and for T1N+ tumors (13). The spleen can be preserved in total gastrectomy for tumors that are not located at the level of the great gastric curvature. The role of splenectomy for tumors invading the large gastric curvature remains uncertain (3, 13) (figure 5).

Figure 5: Dissection of lymphnodes 7, 8a, 12a, 10

D2 + or super-extended lymphadenectomy is represented as a superior lymphadenectomy to D2 and classified as a non-standard gastrectomy (13). Some authors identify it with D3 lymphadenectomy or even with D3 lymphadenectomy + PAN (3).

Super-extended lymphadenectomy can be represented by: Dissection of the lymph node group 10 of the splenic hilum with / without splenectomy for cancers of the proximal portion of the stomach (13). This was included in the standard D2 lymphadenectomy in previous editions of the Japanese guidelines; Dissection of the 14v node group of the superior mesenteric vein for distal cancers with lymph node metastases in group 6 (D2 + 14v); Dissection of lymph node group 13 (retropancreatic lymph nodes) for cancers that invade the duodenum (D2 + 13). In the case of duodenal invasion, group 13 is considered the regional lymph node, in other cases it is M1 metastasis (13); Dissection of group 16 (para-aortic lymph nodes) after neoadjuvant chemotherapy in advanced gastric cancers with significant lymph node invasion (D2 + 16, D2 + PAN).

Superextended lymphadenectomy (D3) that includes systematic excision of the posterior groups (8p, 12p, 13, 16a2, 16b1) was associated in a recent observational study with a significant decrease in locoregional recurrences compared to standard D2 lymphadenectomy in advanced gastric cancers with histology diffuse / mixed (3, 14, 15). These results suggested the independent therapeutic role of dissection of the posterior

ganglion groups 8p, 12p and 13, outside the PAN groups (3). It has also been observed that gastric tumors with accentuated lymphotropism can be controlled therapeutically superior by superextended lymphadenectomy (D3) (3, 14, 15, 16).

Anatomo-pathological evaluation on the resection piece of the number of removed lymph nodes is essential. Hence the concept that the classification of a lymphadenectomy as D1 or D2 should not be done by the surgeon but by the pathologist (13). It is estimated that an average of 15 lymph nodes can be harvested from a D1 lymphadenectomy, 17-44 lymph nodes (average 27) from a D2 lymphadenectomy and 25-64 lymph nodes in a D3 lymphadenectomy (13).

In recent years a number of new parameters have been proposed and evaluated in order to obtain a higher accuracy than the N staging in the TNM classification.

One such parameter is the lymph nodes ratio (LNR) which is defined as the ratio of metastatic lymph nodes to the total number of lymph nodes removed (14, 15, 16). The role of LNR is to reduce the phenomenon of stage migration by analyzing both the number of nodes invaded and the total number of nodes harvested, compared to the classic TNM system which takes into account only the number of positive nodes (16, 17).

Another and more recently introduced prognostic indicator is represented by the logarithmic factor of positive lymph nodes called „Log odds of positive lymph nodes” (LODDS), which is defined as the logarithm of the ratio between the number of invaded lymph nodes and the number of negative lymph nodes (18, 19, 20).

Compared to the LNR system, the LODDS parameter is higher, having a higher sensitivity for evaluating the lymph nodes. This was also concluded by Sun and colleagues in a study of 2547 gastric cancer patients, demonstrating that the LODDS system has a higher prognostic value than the UICC / AJCC N classification and even than the LNR (15, 21).

In the current paper we calculated the LODDS parameter according to the formula

$\log \frac{(pnod+0.5)}{(tnod-pnod+0.5)}$ where pnod is the number of invaded nodes and tnod is the number of nodes harvested.

The grouping by value was done as follows:

LODDS1: LODDS ≤ -1.5
 LODDS2: $-1.5 < \text{LODDS} \leq -1.0$
 LODDS3: $-1.0 < \text{LODDS} \leq -0.5$
 LODDS4: $-0.5 < \text{LODDS} \leq 0$
 LODDS5: LODDS > 0

The LODDS system (Table 1) achieved a stage stratification superior to N parameter, but with some similarities in terms of dispersion and 5-year survival, LODDS 4 and 5 overlapping the pN3 stage with its substages.

Table 1: Patient division by the LODDS parameter

	Lot A	Lot B
LODDS1	4	14
LODDS2	0	0
LODDS3	4	13
LODDS4	9	24
LODDS5	6	19
Total	23	70

The prognosis of gastric cancer is closely correlated with the tumor stage at the time of diagnosis, and surgical treatment, especially an adequate, extensive, accurate lymphadenectomy, performed by oncologic teams trained in specialized centers, is the only one able to bring a substantial improvement in survival.

Conclusions

It is currently generally accepted that radical gastrectomy with D2 lymphadenectomy significantly improves the prognosis of patients with gastric cancer, being considered a standard treatment. The development over time of the lymphodissection technique, the rigorous training of surgeons in specialized centers and the acquisition of experience have led to the emergence and completion of a safe and feasible D2 lymphadenectomy.

LNR and LODDS are considered independent prognostic factors and may be superior to N staging because they quantify the total number of nodes harvested, not just the number of nodes invaded, to which N stage relates.

The result of lymphadenectomy on long-term survival is correlated with the experience of surgical teams in digestive and oncological

surgery.

Proper lymph dissection in order to achieve accurate staging and proper treatment is the key to controlling the disease and achieving superior survival.

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