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DOCTORAT THESIS SUMMARY

THE PROGNOSTIC VALUE OF LYMPHADENECTOMY IN GASTRIC CANCER

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Keywords: gastric cancer, lymphadenectomy, invaded lymph nodes, harvested lymph nodes, lymph node ratio, survival

ABSTRACT OF THE THESIS

INTRODUCTION

Gastric neoplasm is one of the cancers that raises public health problems worldwide due to its high frequency, high aggressiveness 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 death worldwide. Recent developments in diagnostic technology, clinical experience and statistical evidence have highlighted the importance of early detection and improved short- and long-term outcomes of gastric cancer.

The treatment of gastric cancer is based on guidelines developed by international studies, which include surgical treatment, chemotherapy and radiation therapy. Surgical treatment remains the mainstay of therapy, being represented by partial or total gastrectomy, to which is added the removal of ganglion groups from lymphatic drainage stations.

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 society and the Asian side.

Considered until recently the prerogative of Japanese surgery and the Asian world, lymphadenectomy is now a globally accepted standard in the treatment of gastric cancer. Focal point in conducting adjuvant therapy and in establishing the patient's prognosis.

For these reasons, we chose for the study the prognostic value of lymphadenectomy in gastric cancer, trying to analyze after the analysis of resection pieces the effectiveness of different types of lymphadenectomy in increasing survival in gastric neoplasm.

The prognosis of gastric cancer is closely correlated with the stage of the tumor at the time of diagnosis, and surgical treatment, especially adequate, extensive, accurate

lymphadenectomy performed by oncology teams trained in specialized centers, is the only one able to bring a substantial improvement in survival.

In the last decade there has been an increase in survival rates, due to the development of surgical techniques, as a result of an earlier diagnosis, a more complex adjuvant treatment and a closer supervision of the population at risk.

GENERAL PART

The general part included notions about the epidemiology, etiopathogenesis and morphopathology of gastric cancer, as well as about the diagnosis of gastric cancer, the latest staging systems and the main types of treatment in gastric cancer, focusing on lymphadenectomy and new prognostic factors in gastric cancer.

Gastric cancer ranks 5th in incidence among neoplasms, with 5.7% of new cases. More than 1 million new cases of gastric cancer are diagnosed worldwide each year. Gastric cancer is the third leading cause of cancer death in the world, after bronchopulmonary and colorectal cancer, 1 in 12 deaths from cancer is caused by gastric cancer.

In the appearance of gastric cancer, a series of factors are incriminated, both exogenous and endogenous, the diet remaining one of the most determining, gastric cancer being a malignancy of the digestive tract.

About 90-95% of gastric cancers are adenocarcinomas (diffuse, papillary, tubular, mucinous, intestinal type, etc.), the remaining 5% being leiomyosarcomas, lymphomas, carcinoid tumors, squamous cell carcinomas, undifferentiated, with cells "in the ring with seal").

The location of cancers in the stomach is distal in 40% of cases, proximal in 35% of cases and in the gastric body in 25% of cases.

The diagnosis of gastric cancer is based on clinical data, laboratory examinations, endoscopic examination (with biopsy or cytology), echoendoscopy, CT or MRI and laparoscopy or laparotomy. Imaging and surgical explorations contribute to the achievement of pre-therapeutic clinical staging.

Nodal invasion is one of the most important prognostic factors in the curative treatment of gastric cancer. Since 1997 the UICC / AJCC system has adopted category N describing 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.

The general direction of recent years is to adopt D2 lymphadenectomy as a standard procedure in gastric cancer, as a result of the survival benefit demonstrated by recent studies and as an expression of the increase in experience and surgical performance in this technique in specialized centers with high volume of patients with gastric cancer (“high-volume centers”).

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 proportion of lymph node ratio (LNR) which is defined as the ratio of metastatic lymph nodes to the total number of lymph nodes removed. 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.

The treatment of gastric cancer is complex, multimodal and multidisciplinary, combining depending on the stage of the disease, the associated pathology and the patient's age, surgical treatment, chemotherapy and radiotherapy.

Surgical treatment is the only therapeutic option that can ensure the patient's healing, aiming to remove the primary tumor in accordance with oncological principles and lymphadenectomy of lymphatic drainage stations.

The current terminology in gastric surgery includes:

- **Standard gastrectomy** is the main surgical procedure with curative intent. Involves resection of 2/3 of the stomach or the entire stomach associated with D2 lymphadenectomy (Japanese guide)
- **Modified surgery** in which the extent of gastric resection and / or lymphadenectomy (D1, D1 +) is reduced compared to standard gastrectomy
- **Extended surgery** consists of combined gastrectomy with resection of the invaded adjacent organs or gastrectomy with extended lymphadenectomy over D2

SPECIAL PART

OBJECTIVES

The doctoral thesis addresses a topic hotly debated in the literature: the extension of lymphadenectomy in gastric cancer and its role in the prognosis of gastric cancer patients.

The aim of the paper is to determine the fundamental role of lymphadenectomy in the staging of gastric cancer and its decisive impact on the long-term survival of patients with gastric neoplasm. Gastric resection R0 associated with lymphadenectomy D2 is considered today the standard surgical technique for gastric cancer

Metastasis in the lymph nodes is the most important prognostic factor in gastric cancer. The accuracy of the N setting is critical for subsequent surgeries.

Lymphadenectomy D2 standard collected a sufficient number of nodes to provide a staging exact illness, resulting in a significantly improved prognosis in gastric cancer

Personal contribution consisted of:

- the study and distribution of cases of gastric cancer in terms of degree of lymph invasion, number of nodes harvested and number of nodes invaded, N-ratio and pN;
- determination of correlations between the presence of lymphatic invasion and the degree of tumor differentiation, stage T and other parameters with prognostic factor;
- the study of lymphadenectomy performed, in terms of extension, morbidity and related mortality.

The main objective of the study is to highlight the role of lymphatic dissemination and lymphadenectomy in the prognosis of patients with gastric cancer.

MATERIAL AND METHODS

The study was performed prospectively on a number of 93 patients diagnosed with gastric neoplasm, who underwent radical gastrectomy with lymphadenectomy in the Surgery Clinic I of the Emergency County Clinical Hospital "Saint Andrew the Apostle" Constanta, for 5 years (January 1, 2012 - January 31, 2016).

Inclusion criteria:

- patients diagnosed with gastric adenocarcinoma by upper digestive endoscopy with biopsy
- T2-T4 operable stage cancers, M0
- cancers undergoing radical gastrectomy with D1 + lymphadenectomy or D2 / D3
- negative resection margins (R0)
- complete medical data

Exclusion criteria were:

- patients who had metastatic disease (hepatic, peritoneal, pulmonary secondary determinations preoperatively revealed by computed tomography or intraoperative examination),
- patients in whom surgical treatment was diagnostic / bioptic laparotomy, internal palliative derivations or stoma
- patients with gastric resections
- history of emergency gastric surgery
- patients who could not be followed

The cases were divided into two groups: group A containing cases in which D1 + lymphadenectomy was performed (23 cases) and group B comprising patients in which D2 / D3 lymphadenectomy (70 cases).

The study of each case was performed according to a standard file containing preoperative demographic data of the patient (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), vascular and perineural invasion, number of nodes harvested, number of nodes invaded, staging of TNM according to the 8th edition of AJCC, type of lymphadenectomy performed.

RESULTS

The mean age of the patients in the case studies studied was 74.04 ± 7.93 years for group A, respectively 65.88 ± 8.80 years, with limits between 43 and 85 years.

The number of male patients was double that of females, the ratio between the two sexes being in accordance with the data in the literature.

Distal localization of gastric cancer was the most common, followed by localization of the gastric body. Although the literature describes an ascent of gastric cancer sites to cardia, in the present study proximal locations were rare (5 cases).

In gastric cancer the main way of spreading gastric cancer is lymphatic and lymph node metastasis is an important factor in the prognosis of the disease.

The mean nodes harvested for group A were 14.47 ± 5.73 and 22.8 ± 7.60 for group B. The extreme values for the first group were 7 and 29 for the first group and 13 and 43 for the second group. The number of positive lymph range from minimum 0 and maximum 37, with a mean of 5.69 ± 5.66 for group A and 8.52 ± 7.98 respectively for group B.

The histopathology results of resection parts showed that only 17.2% of patients with gastric cancer study were without lymph node metastases (pN0), while 45.16% were in the pN3 stage.

The literature shows that certain morphopathological factors influence the lymphatic spread of gastric cancer. Thus, lymphatic invasion and lymph node metastasis are more common in young patients, in tumors located in the lower 1/3, in type IV tumors (Bormann macroscopic classification) and diffuse tumors (Lauren microscopic classification). G1 tumors are generally not associated with lymphatic metastases, but tumors in stages N2 and N3 are generally G3. T1 and T2 tumors are rarely associated with lymphatic metastases as opposed to T3 and T4 in which positive adenopathy is generally present. Lymphovascular and perineural invasion was present in over 80% of the cases studied, constituting negative prognostic factors in survival.

Patients in the study who had lymphatic invasion were significantly younger compared to those without lymphatic invasion.

For a correct staging of lymph node status in gastric cancer, in the TNM system, it is mandatory to collect and histopathological analysis of at least 15 lymph nodes. The literature shows that in most cases the number of excised lymph nodes is lower, only in 20-30% of patients more than 15 lymph nodes are dissected.

For these reasons, the accuracy of stage N in the TNM classification, which is essential for the prognostic assessment for gastric cancer patients, is influenced by the number of lymph nodes collected and examined.

Specialist studies have shown that patients in whom a large number of lymph nodes were excised had a better survival. The presence of a large number of positive lymph nodes causes a marked decrease in survival.

Surgical treatment of advanced gastric cancer involves gastric resection with the intention of radicalization and lymphadenectomy.

Overall 5-year survival by type of lymphadenectomy was 23.7%, with 22 patients alive at 60 months postoperatively out of a total of 93. Statistical analysis of patients revealed that 5-year survival is significantly higher in D2 lymphadenectomy compared to D1 / D1 + lymphadenectomy, ie 23.8% compared to 8.7%, thus being in accordance with the data in the literature that states D2 lymphadenectomy as a current standard through the benefits brought to patients' survival.

Superextended D3 lymphadenectomy was performed in a number of 28 patients, consisting of additional collection of different ganglion groups depending on the location of the primary tumor (10, 13, 14v, 16). The 5-year survival of patients who underwent superextended lymphadenectomy was higher than that of patients with standard D2 lymphadenectomy, being 35.7%

Although superextensive lymphadenectomy is considered to be a non-standard surgery, it is observed that it can bring a real benefit in the survival of patients with advanced gastric cancer in selected cases, with improved 5-year survival rates, as seen in this study.

The results of the study showed that in potentially curable gastric cancer, lymphatic dissemination negatively affects the prognosis. Although not always statistically significant, survival was better in patients without lymph invasion and intraoperative lymphadenopathy,

those with small numbers of positive lymph nodes and a low rate of lymph node metastasis and as early as pN and TNM. .

Excision of as many lymph nodes as possible and a D2 lymphadenectomy improve the prognosis of patients with gastric cancer who have undergone R0 surgical treatment.

CONCLUSIONS

Despite advances in early diagnosis, the development of surgical techniques and adjuvant chemotherapy protocols, radical gastrectomy remains the only curative treatment for gastric cancer.

It is currently generally accepted that radical gastrectomy with D2 lymphadenectomy significantly improves the prognosis of patients with gastric cancer, being considered a standard of treatment in gastric surgery.

Lymphadenectomy in gastric cancer has 3 objectives: to stage the disease, control local recurrences and superior long-term outcome for the patient.

The N parameter in TNM staging is one of the most important prognostic factors in the survival of gastric cancer patients. For accurate postoperative staging of stage N of the TNM classification, a minimum of 15 lymph nodes must be collected during lymph dissection. However, patients with positive lymph nodes are extremely heterogeneous in terms of prognosis and survival and should be stratified according to other parameters such as lymph node ratio LNR or LODDS.

NRLs and LODDS are considered independent prognostic factors and may be superior to N staging in that they quantify the total number of nodes harvested, not just the number of nodes invaded, to which stage N refers. The

Outcome of lymphadenectomy on long-term survival is correlated with the experience of surgical teams in digestive and oncological surgery.

The development in time of the lymphdysection technique, the rigorous training of surgeons in specialized centers and the acquisition of experience led to the emergence and completion of a superior technique of lymphadenectomy D2 with the preservation of the spleen and pancreas. This resulted in a lower morbidity and mortality rate than the previous ones and a safe and feasible lymph node dissection.

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

Gastric surgery tends to turn into a well-defined oncological subspecialty that must be performed in specialized centers with a large volume of gastric cancer patients and adequate facilities and which is urgently needed to be performed by teams trained with a high degree of expertise in oncological surgery. , respecting all its principles and standardized protocols.

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