

RESEARCH ARTICLE

Individual Prognostic Factors in Gastric Cancer

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Objectives: The objective of this research was to study the prognostic factors in gastric cancer. **Methods:** We conducted a retrospective study on 5-year survival in 112 patients with gastric adenocarcinoma operated between 2004-2009. We used the Surgery Clinic I and Health Insurance House databases for study of the following parameters: age, sex, depth of invasion, histological type, surgery, number of lymph nodes excised and reported overrun / removed lymphnodes. **Results:** There was no significant survival difference related to gender aspects. We found significant differences in the survival rate in relation to the tumours confined to the mucosa and muscularis mucosae (100% and 60% respectively), compared to the cases with deeper invasion ($p < 0.05$). Intestinal type presented a superior however insignificant prognosis compared to diffuse type (22% versus 5.66%). Five years survival was slightly lower after D1 lymphadenectomy D1 compared to D2 lymphadenectomy (25.92% versus 29.16%). We found large differences among the number of perigastric lymph nodes (between 3 and 42 in groups of 1 to 6) nodules. Survival rates were significantly higher ($p < 0.05$) in patients with overrun lymphnodes between 0 and $< 20\%$, compared to those with overrun ones over 20% of all excised nodes (23.07%, 55.55% vs. 3.89%). **Conclusions:** Merely the number of removed lymph nodes may be a source of error in staging if not taken into account the groups they belong to; the most constant individual prognostic factors are the depth of invasion and overrun/removed lymph nodes report; D2 lymphadenectomy has superior results in terms of 5 years survival compared to D1 lymphadenectomy, but, at least in our study, the difference was insignificant.

Keywords: gastric cancer, lymphadenectomy, 5-year survival

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Introduction

Argues about gastric cancer surgery became “traditional” and have captured the surgical world’s attention in last decades. Whereas there is already a consensus established regarding the safe limits of surgical excision of the tumour and removal of perigastric lymph nodes, debates still exist regarding the opportunity of a D2 lymph nodes resection, highly supported by the Japanese school [1,2]. While for Japanese surgeons D2 lymphadenectomy has become a standard procedure, supported by major statistical studies [3], Western Europeans and Americans are more circumspect, embracing the idea that the benefits are annihilated by the increased percentage of postoperative complications [4].

Surgical technique

In radical gastric resection recommended limits are: proximal edge of 3 cm for T1-T2 tumours and 5 cm or more for T3-T4 tumours, except those invading the oesophagus where the limit of 5 cm is not mandatory. The distal limit must be pushed as far as possible, 10-15 cm from the apparent tumour boundary. At the lower end of the upper pole resection limits are 5 cm from the pylorus to the lesser curvature and 15 cm from the pylorus to the greater curvature. The lower gastric pole resection comprises the first 2-3 cm of duodenal bulb. Resection margins must be separately pathologically assessed.

D1 resection involves distal subtotal or total gastrectomy combined with resection of both cauls, including perigastric lymphatic stations (1, 3, 5 stations located along the lesser curvature and 2, 4, 6 stations located along the greater curvature) [5]. D2 resection involves removal besides D1 resection nodes located along the left gastric artery (station 7), common hepatic artery (station 8), celiac trunk (station 9) and of splenic artery (stations 10, 11). D4 comprises groups 14, 15, 16 lymph nodes resection and D3 has an intermediate position between D2 and D4. Of course, gastric tumour location indicates node-groups to be removed [6]. UICC (Union for International Cancer Control) / AJCC (American Joint Committee on Cancer) TNM classifies (1997) the removed lymph nodes as follows: N0: no metastasis N1: 1-6 positive lymph nodes (LN+), N2: 7-15 LN +, N3 over 15 LN +, while JRSC (Japanese Research Society for Cancer) (1981) recommends the following classification: n 0=none LN+, n1=LN+ in N1group, n2=LN+ in N2 group, n3=LN+ in N3 group. Lymphadenectomy for gastric cancer serves the following purposes: staging of disease, prevention of loco-regional recurrence, and, hence improvement in overall survival. Concerning the staging of the disease it is obvious that additional lymph nodes examined generally provide additional information on the extent of disease. The AJCC Cancer Staging Manual recommends a minimum of 16 lymph nodes to be examined [7]. Speaking of recurrence the anastomosis is the most common location of it, followed by remnant lymph nodes. Survival; patients that undergo D2 lymphadenectomy have better overall survi-

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val rate compared to patients undergoing less extensive lymphadenectomies. More extended lymphadenectomies may discover additional positive nodes, and thus a patient may be assigned a more advanced stage after undergoing D2 lymphadenectomy, which may be beneficial for adjuvant therapies. Differences concerning overall surviving rates between western and eastern statistics were explained through the differences regarding the biologic profile between eastern and western patient; western patients are older, have a higher body weight, and present a lower incidence of *Helicobacter pylori* infection, with more frequent proximal location of the tumors, presenting usually in later stages and receiving different adjuvant therapies [8,9].

Materials and methods

In a retrospective study we evaluated all data from patients operated for gastric cancer in the Surgical Clinic No 1 from the County Clinical Hospital during 2004-2009.

Data were obtained from the clinic database study. Survival was obtained by analysis of data obtained from Health Insurance Database.

We studied survival rate by age, depth of tumour invasion in the gastric wall, type of surgery, histological type, number and rate of tumour invaded lymph nodes from the total number of excised lymph nodes.

The study included all patients with gastric adenocarcinoma, regardless of location and pathological type. We excluded from the study those with gastric lymphoma and gastric stromal tumours.

We divided the operated patients according to the degree of operability in 3 groups:

1. patients who underwent a radical D1 resection without known residual neoplastic tissue (R0)
2. patients who underwent a radical D2 resection
3. patients receiving a palliative resection with assumed residual neoplastic tissue

Staging of gastric cancer was made in accordance with the definitions AJCC / UICC and represents accurate assessment of tumour infiltration depth of gastric wall (T), the situation nodes (N) and the presence of remote metastasis (M).

Pathologic type results were classified according to Lauren classification.

Statistical processing was performed using Microsoft Excel and Fischer exact test to calculate p taking its significance threshold <0.05.

Results

Of the 112 patients with a diagnosis of gastric malignancy, 82 (73, 21%) were males and 30 (26, 78%) women.

The mean age was 68 ± 10 , 95 years (34-92 years).

Tumour location was in the upper gastric pole in 11 cases (9,82%); mediogastric 20 cases (17,85%); lower pole and pylorus 39 cases (34,82%); plastic linitis 5 cases (4.46%); gastric stump cancer (after gastric resection history for benign) 4 cases (3.57%); tumour recurrence 7 cases

in which the location was hard to specify (6.25%). Besides these there were 26 cases of tumours invading the stomach entirely, making it impossible to specify the point of origin (23.21%).

Based on the type of surgery patients were divided as follows:

1. patients with a radical D1 resection - 27 (24, 1%)
2. patients with a radical D2 resection - 24 (21, 42%)
3. patients with a palliative resection - 51 (45, 53%)

Of the 24 D2 lymph nodes removal, in 14 cases splenectomy and 6 cases caudal splenopancreatectomy was performed for tumour invasion, and in 3 cases for safety removal of groups 10-11 of lymph nodes in obese patients. We did not perform any D3 or D4 resection.

The overall survival rate at 5 years was 12, 5%.

Staging of the 112 cases is presented in Table I.

Table I. Staging of the 112 cases of gastric cancer

Stage	No. of cases	5 years survival
0	1	1
IA	1	1
IB	5	4
IIA	8	4
IIB	26	3
IIIA	25	1
IIIB	28	0
IV	18	0

Intestinal and diffuse types according to Lauren classification were found in approximately equal rates in our study (53 and 50 cases) but we had also 9 cases of mixed type (Table II). Intestinal type according to Lauren classification has a significant better prognosis than the diffuse type. There were no 5 years survivors of the 9 patients with mixed type.

Related to surgery there was an obvious difference (statistically significant) between survival rates at 5 years after D2 versus D1 lymph nodes removal. We did not have any 5 year survivors from the patients with palliative resections.

The overall average number of lymph nodes excised was 12.60, with a range between 3 and 42. In the D1 lymph nodes removal average number of nodes excised was $9 \pm 2,82$, with a range between 3 and 38, and the average number in D2 lymph nodes removal was $19,5 \pm 7,09$, with a range between 15 and 42. We found large differences between the numbers of lymph nodes, especially in stations 1-6; on the lesser curvature we found between 2 and 38 and on the greater curvature between 3 and 13 lymph nodes.

Only 3 of the 24 cases (12%) of patients who underwent splenectomy or splenopancreatectomy developed postoperative complications: a duodenal stump fistula and two anastomotic fistulas, while the overall postoperative morbidity was 13.52%.

Five years survivors belonged only to N0 and N1 groups' patients, while there was no surviving patients with N2

and N3. The results regarding the rate of invaded lymph nodes on the total removed nodes are presented in Table II.

Table II. Data on the clinical and pathological aspects of 112 patients; 5 years survival

		No. of cases	5 years survival (%)	P
Depth of the tumor	Submucosa	2	2(100%)	0.02
	Mucosal Musc.	5	3(60%)	
	Musc. Layer	8	2(25%)	
	Subserosa	49	4(8,16%)	
	Serosa	48	3(6,25%)	
Lauren Type	Diffuse	53	3(5,66%)	0.03
	Intestinal	50	11(22%)	
	Mixed	9	0	
Surgery	D1	27	7(25,92%)	0.54
	D2	24	7(29,16%)	
	Palliative	51	0	
PN	N0	26	7(26,92%)	0.011
	N1	39	7(17,94%)	
AJCC/TNM	N2	30	0	
	N3	17	0	
	NR0	26	6(23,07%)	
NR	NR1(<20%)	9	5(55,55%)	0.001
	NR2(>20%)	77	3(3,89%)	

Discussion

Our study confirms data already proven in other studies, namely the prognostic importance of tumour depth of gastric wall invasion, the type of surgery performed and the degree of invasion of lymph nodes excised, both numerically and in percentage. Regarding the degree of gastric wall tumour invasion, the highest rates of survival were found, as expected, in early cases limited to the mucosa and muscle lining. Unfortunately we had only five cases of early cancer one of them in 0 and four in IA stage. Once beyond this layer there were no statistically significant differences in survival rate, even if the tumour extension reached the serous layer.

If the degree of tumour invasion in the gastric wall cannot be influenced, as it is related mainly to the patient's addressability, many other factors may be influenced by medical intervention.

In addition to extended lymph nodes removal another controversial topic in the literature is the attitude concerning the spleen and / or tail of the pancreas. [10].

According to Japanese authors, splenectomy is mandatory for lymph nodes removal, while most western authors recommend the preservation of the spleen and pancreatic tail, but without compromising the quality of lymph nodes removal in order to avoid postoperative complications associated with splenectomy and / or splenopancreatectomy [11, 12].

Likewise other papers [13] we also found large differences between the numbers of lymph nodes, especially perigastric; we found on the lesser curvature between 2 and 38 and on the greater curvature between 3 and 13 lymph nodes. These differences may influence nega-

tively mathematical assessment and staging according to UICC / AJCC, which takes into account the absolute number of lymph nodes excised, in contrast to JSCA classification which considers the location of excised nodes being one of the causes of stage migration [14,15].

Significant values of survival rates were found, especially taking into account the percentage of invaded lymph nodes (NR) of all excised. The relatively good prognosis enjoys those with less than 20% positive nodes (NR1).

Conclusions

In our statistics only 40% of patients have a chance to a radical surgery at the time of diagnosis, and only one of 10 a chance of 5 years survival; this fact entails measures to improve early diagnosis in our country-specific conditions i.e. screening in risk population (dyspepsia over 45 years old, dyspepsia and alarm symptoms, history of gastric surgery, etc).

Staging according to UICC/TNM classification taking into account the number of resected lymph nodes in absolute value, without taking into account their location, can be prone to errors due to large anatomical variations in the number of nodes in different stations.

Individual prognostic factors in our study were the degree of tumor invasion of the gastric wall and the rate of invaded lymph nodes of all excised nodes.

N ratio is a simple, effective and rational prognosis indicator of gastric cancer with lymph node metastases. In addition, identification of high risk patients with a poor prognosis based on determining the proportion of N may help establish an appropriate adjuvant therapy.

Despite controversies, D2 lymphadenectomy offers superior results in terms of long time survival, even if it entails splenectomy and / or caudal pancreatectomy.

References

1. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer, 2011, 14:113-123
2. Jansen, EP, Boot H., Verheij M., Van de Velde CJ - Optimal locoregional treatment in gastric cancer. J Clin Oncol, 2005;23:4509.
3. Sano, T., Sasako, M., Yamamoto, S. et al. - Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy. Japan Clinical Oncology Group study 9501. J Clin Oncol, 2004;22:2767.
4. 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.
5. Schmidt B, Yoon SS - D1 versus D2 lymphadenectomy for gastric cancer. J Surg Oncol, 2013; 07:259-264.
6. Andronesu P, Angelescu M, Miron A et al - Palliative total gastrectomy. Chirurgia (Bucuresti), 1996;45:97.
7. American Joint Committee on Cancer - AJCC Cancer Staging Manual 7. New York, NY: Springer; 2010.
8. Verdecchia A, Mariotto A, Gatta G, et al - Comparison of stomach cancer incidence and survival in four continents. Eur J Cancer, 2003; 39:1603-1609.
9. Degiuli M, Sasako M, Ponti A, et al - Italian Gastric Cancer Study Group - Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer. Br J Surg, 2014;101:23-31.
10. Li P, Huang CM, Zheng CH, et al - Laparoscopic spleen-preserving splenic hilar lymphadenectomy in 108 consecutive patients with upper gastric cancer World J Gastroenterol, 2014;20:11376-11383.

11. Griffith JP, Sue-Ling HM, Martin I, et al - Preservation of the spleen improves survival after radical surgery for gastric cancer. *Gut*, 1995;36:684.
12. Mendes de Almeida JC, Bettencourt A, Santos Costa C, Mendes de Almeida JM - Impact of distal pancreatectomy and splenectomy in D2 dissection for gastric cancer. First International Gastric Cancer Congress, 1995;2:1165.
13. Wagner PK - Lymph node counts in the upper abdomen: anatomical basis for lymphadenectomy in gastric cancer. *Br J Surg*, 1991;78:825-827.
14. Bando E, Yonemura Y, et al - Outcome of ratio of lymph node metastasis in gastric carcinoma. *Annals of Surgical Oncology*, 2002;9:775-784.
15. Kiss L., Kiss R., Kovacs Cs., Fleţan C. Metastazele din nodulii limfatici în cancerul gastric și rația metastatică din nodulii limfatici. *AMT*, 2013;2:77-81.