

# GASTRIC CANCER: PROGNOSTIC FACTORS OF RECURRENCE AFTER GASTRECTOMY FOR GASTRIC CARCINOMA

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**Keywords:** gastric carcinoma, lymph node metasyasis, stage of disease

**Abstract:** In the absence of residual disease  $R_0$  after resection, the stage of the disease will determine the patient's ultimate prognosis. Of the estimated 24.000 new case seen annually in the United States, most patients present the stages III or IV of the disease. The effort to improve survival includes the neoadjuvant therapy. Although the incidence of gastric cancer is declining in Europe, the prognostic remains unfavourable, and little improvement in survival over time has been reported. The estimated mean European 5-year relative survival rate for 1994 was of 23%. And for 2009, in Italy it was of 42%, and in Poland of 24%. **Objectives:** The current study analyzed the patients who died of recurrent gastric carcinoma and identified the histopathological indicators associated with early and late recurrence. **Methods:** The study included 68 patients who died of recurrent gastric carcinoma after gastrectomy that was performed in the I<sup>st</sup> surgical clinic, between 01.01. 1980-01.10.2006. 52 patients died within 2 years after gastrectomy (early recurrence group), and 17 patients died >2 years after gastrectomy (late recurrence group). In order to determine the independent factors correlated with the timing of recurrence, multivariate analysis was performed. **Results:** Comparing the early recurrence category with the late recurrence group, the following was observed: presence of lymphatic invasion in 63% as against 39%, stages III and IV of the disease in 88% as against 61%, the early recurrence was characterized by a tumour size >5 cm. (91% in the early recurrence group and 74% in the late recurrence category). The mean survival time was influenced by the lymphatic invasion ( $p < 0,01$ ), vascular invasion ( $p < 0,05$ ), level of lymph node positivity ( $p < 0,01$ ), stage of disease ( $p < 0,01$ ), and lymph node dissection extension ( $p < 0,01$ ). The survival was determinate by the vascular invasion ( $p < 0,05$ ), lymphatic metastasis ( $p < 0,01$ ), and node dissection ( $p < 0,01$ ). On multivariate analysis, survival was independently associated with the stage of disease (stage I,II vs III,IV), or the level of node invasion ( $N_0, N_1$  vs  $N_2, N_3$ ). **Conclusions:** Patients with advanced disease (III,IV) and with extended lymph node metastasis died within 2 years after gastrectomy with early recurrence of the disease.

**Cuvinte cheie:** cancer gastric, metastaze ganglionare, stadiul bolii

**Rezumat:** În absența bolii reziduale ( $R_0$ ) după rezecție, stadiul bolii va determina prognosticul principal al pacientului. Se estimează că majoritatea celor 24.000 de cazuri noi anuale din USA se prezintă în stadii III, IV de boală. Efortul de îmbunătățire a supraviețuirii include terapia neoadjuvantă. Deși incidența de cancer gastric este în scădere în Europa, prognosticul rămâne nefavorabil, fiind raportate creșteri mici ale supraviețuirii în ultimii ani. Supraviețuirea la 5 ani estimată în Europa în 1994 a fost de 23%. Scopul studiului: Studiul actual analizează pacienții care au decedat prin recidiva cancerului gastric și identifică indicatorii histologici asociați recidivei precoce și tardive. Metodă: Studiul nostru include 68 de pacienți care au decedat prin recidiva cancerului gastric după gastrectomie efectuată în Clinica Chirurgie I din Sibiu în intervalul 1980 – 2007. 52 de pacienți au decedat sub 2 ani după gastrectomie (grupa de recidivă precoce) și 17 pacienți au decedat după 2 ani de la gastrectomie (grupa cu recidivă tardivă). Au fost realizate analize multivariate pentru a determina factorii independenți legați de momentul recidivei. Rezultate: Comparând categoria de recidivă precoce cu cea tardivă s-a observat: prezența invaziei limfatice în 63% față de 39%, stadiul III și IV de boală 88% față de 61%, recidiva precoce s-a caracterizat prin tumori  $\geq 5$  cm, aspect decelat în 91% din recidiva precoce, față de 74% din grupa de recidivă tardivă. Durata de supraviețuire medie a fost influențată de invazia limfatică ( $p < 0,01$ ), invazia vasculară ( $p < 0,05$ ) și de gradul de disecție ganglionară ( $p < 0,01$ ). Analiza multivariată privind supraviețuirea a arătat că aceasta a fost asociată în mod independent cu stadiul bolii (stadiile I, II față de III, IV) sau cu extensia metastazelor ganglionare ( $N_0, N_1, N_2, N_3$ ). Concluzii: Pacienții cu stadii avansate a bolii (St. III, IV), precum și cei cu metastaze ganglionare extinse ( $N_2, N_3$ ) decedează frecvent prin recidivă precoce, sub 2 ani de la gastrectomie. Nivelul  $N_+$ , stadiul TNM al bolii, au fost decelați ca cei mai importanți factori prognostici de supraviețuire după gastrectomie din cancerul gastric

## INTRODUCTION

For early less invasive cancers and diffuse-type gastric

cancers, localization can be difficult at operation, and the surgeon should be well trained. There are no pathognomonic

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symptoms of gastric cancer, and the results of the treated gastric cancer in later stages are poor.(4) There is no universal agreement among the AJCC (American Joint Commission on Cancer), and the JRS GC (Japanese Research Society for Gastric Cancer) in using the TNM system.(27,28) The "R" classification is the single most important prognostic factor in determining survival rate. After a R<sub>0</sub> resection, the best determinants of prognosis are the depth of tumour invasion (T stage), and the extension of the lymph node metastasis (N stage).(29,30,31) The prognostic significance of the 1997 edition of the AJCC cancer staging manual with a new "N" stage definition bound on the number of positive lymph nodes, has been supported recently by the analysis of the data from the German Cancer Groups.(5) Many studies have classified the prognostic factors of gastric carcinoma as follows: tumour size, the depth of wall invasion, the lymph node metastasis and the stage of disease.(6,7,8) The prognostic factors are useful in distinguishing the recurrent patients from those surviving without recurrence. Radical resection is the most effective treatment modality for gastric cancer and R<sub>0</sub> resection is the most important indicator of long term survival in the patients with gastric cancer, (9) while long term survival of the patients with invasion to adjuvant organs, despite improvements in technique, has been reported to be poor.(10) The survival rate at 3 years after the resections with curative potential is less than 53% in the absence of resections extended at the neighbouring organs. For locally advanced gastric cancer, with adjuvant organ infiltration, extended resection is required to achieve R<sub>0</sub> resection with negative surgical margins. Aggressive surgical treatment and patient selection for locally advanced gastric cancer still remain controversial. In the current study, we analyzed 68 patients who died of cancer recurrence, after gastrectomy, and we tried to see the histological results indicators with early and late recurrence after gastrectomy. In our study, multivariate analysis was performed in order to see the correlation of the independent factors with the interval until the occurrence of the recurrence. In our study, the patients with stage IV of the disease were included in the statistics analysis because the presence of peritoneal and liver metastasis influence the survival period after resection.

### PURPOSE OF THE STUDY

The present study analyses the patients that have died from gastric cancer recurrence and identifies the histopathological indicators associated to early and late recurrence.

### MATERIAL AND METHOD

A total number of 250 patients with gastrectomy for carcinoma were analyzed in our study. They were admitted in the Department of Surgical Clinic, between 1980 and 2007. 52(20%) patients died within 2 years after surgery (early recurrence), 17(60%) died 2 years after the surgery (late recurrence). The histological type was classified into well differentiated carcinoma and poorly differentiated carcinoma. The well differentiated carcinoma included the tubular, mucinous well differentiated adenocarcinoma, while the poorly differentiated type, included the sigret-ring cell carcinoma, and the mucinous carcinoma.(11,12) The clinical-pathologic findings obtained from the patients' medical documents, came from surgical records, pathology results, patient age, size of tumour, location, histologic type of tumour, depth of wall infiltration, type of gastrectomy performed, lymph node dissection, stage (TNM) of the disease, level of N invasion. Multivariate analysis was performed by using the cox proportional hazards model, and statistically significant

differences were analyzed by the chi-square test and "t" test. The type of advanced carcinoma with parietal invasion extending into the muscularis propria or beyond, was classified according to the JRS GC.(14) The determination of the depth of the invasion and nodal involvement was usually based on histological findings of the resected specimen. Evidence of peritoneal dissemination, or hepatic metastasis, was macroscopically defined at laparotomy when the evident metastatic lesions were not completely resectable.

### RESULTS

Comparing the data of pathological findings on the primary tumour, the characteristics of the patients with an advanced carcinoma of the stomach, detected in two periods of time, it has been observed that: the incidence on the women over 70 years old was higher for the gastric cancers in the upper two thirds of the stomach, these tumours being of more than 10 cm in size: undifferentiated type adenocarcinoma being significantly increased in the group of patients recently studied as against the patients of an older period of time. There was a significant decrease in the incidence of tumors in the patients younger than 70 years, of male gender. We have also observed a decrease of the number of differentiated adenocarcinoma and with a diameter between 5 and 10 centimetres. Between the two categories of patients, there were no differences in the distribution of the depth of parietal invasion, metastasis to lymph none, peritoneal or hepatic dissemination. In table no.1, we present the distribution of tumour size based on the topographic localization of advanced gastric carcinoma.

**Table no. 1. Distribution of tumour size according to the main location of advanced stomach carcinoma**

Location	Frequency (%)		
	Æ< 5 cm	Æ=5-10 cm	Æ>10 cm
Cardia	17	43,9	39
Body	24	38	38
Antrum	20	63	17

Total gastrectomy was performed in 38,6 % of cases in the initial group (1990-2000), as opposed to 56 % in the recent group (p<0,001). This increase is attributed to an increase in the number of tumours detected in the 1/3 proximal stomach and to the large tumours originating in the middle one third of the stomach and involving the upper gastric pole. The operation was considered curative when all the evident carcinoma, including metastatic nodes, was excised. Curative operation was performed in 56% of the patients. Table 2 presents the clinical and pathologic findings in 69 patients who died of recurrence after gastrectomy.

**Table 2. Distribution of deaths secondary to recurrence after gastrectomy**

Clinical features	Nr	%
<b>Age</b>		
<60	20	29
≥60	49	71
<b>Location</b>		
Lower two-thirds	49	71
Upper one-third	20	29
<b>Size (cm)</b>		
< 5	9	13
>5	60	87
<b>Lymphatic invasion</b>		
Present	29	42
Absent	40	58
<b>Vascular invasion</b>		

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Present	8	11
Absent	61	89
<b>Level of N +</b>		
N <sub>0</sub> N <sub>1</sub>	27	37
>N <sub>1</sub>	62	63
<b>No. of N +</b>		
≤ 6 NL +	36	48
≥ 7 NL +	74	52
<b>Stage of disease</b>		
I, II	12	17
III, IV	57	83
<b>Macroscopic type</b>		
Infiltrative	48	69
Localized	20	31
<b>Depth of wall invasion</b>		
Beyond muscularis	62	90
Within muscularis	7	10
<b>Histology</b>		
Well differentiated	34	49
Poorly differentiated	35	51

The survival curves declined rapidly during the first years and remained constant for about 10 years. The survival rate at 5 years was of 23,7% and the overall survival rate was of 12,2% at 5 years..

**Table no. 3. Five-year survival rate for each significant variable (comparative analysis)**

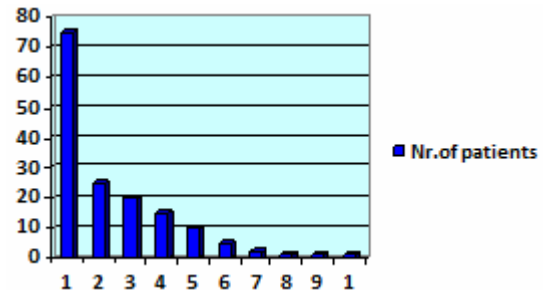
Variable	5 year survival rate (%)	P value
<b>Age</b>		
Younger and older than 50 years	37	N.s.
<b>Main location</b>		
Cardia	31	< 0,05
Others	26	
<b>Size of tumour</b>		
<5 cm	60	< 0,01
5–10 cm	32	
>10 cm	14	
<b>Histology</b>		
Differentiated	40	< 0,01
Undifferentiated	34	
<b>Type of intervention</b>		
Total gastrectomy	25	< 0,01
Distal gastrectomy	46	

There were no statistically significant differences in the survival rate with regard to age, sex; yet, there were statistically significant differences with regard to the tumour location, size and histological types of tumour and the type of operation. A good prognosis was noted when a carcinoma was located in the lower two-thirds of the stomach, in the case of tumours smaller than 5 cm, of a differentiated type adenocarcinoma and for those tumours which underwent a distal partial gastrectomy. Tumours linked to a poor prognosis were located in the 1/3 part of the stomach, larger than 10 cm and undifferentiated and which in most of the cases underwent total systemic gastrectomy. The significant decline of the location of the gastric carcinoma in the lower two-thirds of the stomach and with a diameter less than 10 cm, ulcerated and comprised of differentiated type adenocarcinoma may explain the lack of general survival at 5 years. In the patients with primitive gastric carcinoma, the incidence of the nodes' metastasis was of 59% cases and it was associated with the increase of the disease recurrence and increased mortality rate when compared with LN-negative patients. The extension of LN metastases was

inversely correlated with the survival rate. In 11% of the lymphatic nodes, absent metastasis was detected. In the cases where the neoplasm exceeded the submucosa, the survival rate did not differ significantly in relation to the depth of the invasion. Death from recurrent gastric carcinoma occurred most frequently during the first year after surgery and 75% of tumour related death occurred within 2 years (figure no. 1)

We defined the early recurrence groups for the patients who died within 2 years after surgery with a number of 52 cases and for the late recurrence groups with 17 patients who died > 2 years after surgery. The early recurrence group was characterized by a tumour size of 5cm. (90% in the early recurrence groups vs 73% in the late recurrence groups), positive lymph node metastasis 42% stage III or IV disease 83% extended lymph node metastasis > N<sub>1</sub> in 65%. The mean survival time was significantly influenced by the presence of the lymphatic invasion (p<0,05%), by the level of N+ (p<0,01), and the stage of the disease (p<0,01) (table no. 4).

**Figure no. 1. Number of patients who died of recurrent gastric carcinoma**



**Table no. 4. Early vs. late recurrence after resection in gastric carcinoma**

Clinical features	Early recurrence n = 52 n = %	Late recurrence n = 17 n = %	P value
<b>Location</b>			
Lower two-thirds	69	76	n.s.
Upper one-third	31	24	
<b>Size(cm)</b>			
mean	9,1	7,5	<0,01
<b>Range</b>			
< 5 cm	9	25	<0,01
≥ 5 cm	91	75	
<b>Macroscopic Type</b>			
Localized	31	23	n.s.
Infiltrative	69	77	
<b>Depth of wall invasion</b>			
Within muscularis	7	17	n.s.
Beyond muscularis	93	83	
<b>Histological Type</b>			
Well differentiated	50	46	n.s.
Poorly differentiated	51	54	
<b>Lymphatic Invasion</b>			
Present	65	37	<0,01
Absent	35	63	
<b>Vascular invasion</b>			
Absent	84	98	n.s.
Present	16	2	
<b>Level of LN</b>			

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<i>metastases</i>	27	64	<0,01
N <sub>0</sub> , N <sub>1</sub>	73	36	
N <sub>2or</sub> N <sub>3</sub>			
<i>Nr. of LN +</i>			
≤ 6	44	60	
≥ 7	56	40	
<i>Stage of disease</i>			
I, II	12	38	<0,01
III, IV	88	62	
<i>Type of gastrectomy</i>			
Distal gastrectomy	38	40	n.s.
Total gastrectomy	62	60	

However, the histological type, the tumour location, the depth of wall invasion and the type of gastrectomy performed did not seem to influence the survival time after gastrectomy.

### DISCUSSIONS

Long term survival of the patients with gastric cancer remains unfavorable because of the invasion of the tumour through the muscularis layer and early spread in the lymphatic system. Nearly 70-75% of the tumors in Europe were advanced tumours, invading the submucosa (T<sub>2</sub> to T<sub>4</sub>). The results of our series, confirmed that death from recurrent carcinoma occurred within 2 years after resection (75%) and 6% due to late recurrence (>5 years). In our study, the level of lymph node metastasis and the size of the tumour were correlated with the recurrence. In the late recurrence patients, the tumour was characterized by a small tumour size and negative or limited node invasion. Slim and col. (14) have shown that LN metastasis remains an important prognostic factor in the patients with potentially curable gastric cancer. This is similar with our study, which demonstrated that regional LN metastasis and recurrent nodal involvement have an adverse effect on survival (Table 4). Therefore, gastric resection, as well as the complete removal of metastatic LMs, is considered essential in curative gastrectomy. The depth of wall invasion and the level of lymph node involvement are the most important prognostic factors after the curative operation in gastric cancer.(7,15) The prognostic significance of lymph node dissection remains controversial.(16,17) In more that 60% of the patients from late recurrence group, the lymph node metastasis was absent or limited to the perigastric nodes with a tumour size < 8 cm. Involvement of the lymphatic channels in the primary tumour and the lymph nodes, helps to predict the timing of recurrence after resection, while the tumour size with the level of node invasion are important for the deaths due to recurrence. In a previous study made by Adachy, the depth of the wall invasion was not a predictor of the timing of recurrent death after curative resection of gastric carcinoma.(18) The current study demonstrated that the depth of the wall invasion was a predictor of recurrence, but not for the timing of death after resection. In the patients with recurrence, distant metastasis was encountered in 90%, of which the peritoneal dissemination was most frequently involved. Patients who received a total gastrectomy had a worse five-year survival rate than that of the patients who underwent subtotal gastrectomy, because the former addressed the more extended diseases. Previous studies of late gastric cancer deaths showed similar survival times as our study did.(19,20). A U.S. study (19) showed a larger proportion of diffuse adenocarcinoma forms as opposed to the intestinal cancers in late deaths, aspects that were also emphasized by us. They suggest that on very long term, diffuse gastric cancer has a worse prognosis than the intestinal cancer. Lymphatic invasion in the primary tumour was associated with early recurrence and

the presence of lymphatic invasion indicated a possible extended lymphatic invasion in the early deaths. Early recurrence cases were N<sub>2</sub>, N<sub>3</sub> tumours confirmed after gastrectomy with D<sub>1</sub> dissection, whereas the late recurrence was by tumours with N<sub>0</sub>, N<sub>1</sub> and with a more extended lymphadenectomy than D<sub>1</sub>.(23) Our multivariate study suggested that the extension of N-dissection is associated with the timing of recurrence. In our series, the mean survival time after D<sub>0</sub>, D<sub>1</sub> gastrectomy was of 6-8 months. In the patients with advanced stage (III, IV), limited lymph node dissection was frequently performed and the stage of disease was the most significant independent factor for the survival time together with the level of LN invasion.(21,22) In our experience, the quality of the N-dissection, extends the survival time after resection and the stage of the disease or the level of N+ are important prognostic factors. In the current study, our results showed that lymph node metastasis, lymphatic invasion, tumour size, stage of disease and the quality of D-dissection are parameters associated with the timing of recurrence after gastrectomy. Our experience showed that the patients with stage III, IV of disease and those with N<sub>3</sub>, N<sub>4</sub> died within 2 years after gastrectomy. The accuracy of the gastric tumour stage, through the size of the tumour, and the number of the involved nodes, is a strong prognostic indicator.(24,25,26)

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