SIGNIFICANT PROGNOSTIC FACTORS IN 283 PATIENTS AFTER SURGERY FOR ADENOCARCINOMA OF THE STOMACH

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Abstract

Even though the incidence of the adenocarcinoma of the stomach has decreased over the past decade, the prognosis of this disease remains generally poor. The aim of this study was to determine the influence of several clinicopathological factors on the outcome in a series of 283 patients after surgery for adenocarcinoma of the stomach in the years 1990–1997. MATERIALS Survival rates were calculated by the Kaplan-Meier estimation method and differences in survival curves between the corresponding variables were determined by the log-rank test on univariate analysis. Mean patient age at the time of operation was 64.7 years, 64.3 % were males. Total gastrectomy was performed in 54.1 % of patients, distal subtotal resection in 23.3 %, proximal subtotal resection in 4.9 %, palliative intestinal bypass in 11.0 %, exploratory laparotomy in 6.7 % of the cases. RESULTS: The 5-year overall survival rate was 18.4 %. In the univariate analysis, the survival-related factors were age (p=0.034), weight loss (p=0.014), palpable abdominal mass (p=0.010), low preoperative levels of haemoglobin (p=0.042) and albumin (p=0.018), tumour location (p<0.001) and its size (p<0.001), macroscopic appearance of tumour according to Borrmann (p=0.028), histological type according to Laurén (p=0.044), histopathological grading (p=0.001), stage according to the TNM classification (p<0.00001), degree of gastric wall invasion (p<0.00001), degree of lymph node invasion (p<0.00001), the presence of distant metastases (p<0.00001), the extent of performed surgery (p<0.003) and its intention, e.g. curative, palliative or exploration only (p<0.0001). CONCLUSION: Using univariate analysis, it was found that in patients after surgery for adenocarcinoma of the stomach, the main prognostic survival-related factors were stage of disease, degree of wall and lymph node invasion, presence of distant metastases, the intention of performed surgery, tumour location and its size. These findings will be used to develop a prognostic system based on the principle of artificial neural networks, which will integrate various prognostic factors to enable complex estimation of the prognosis.

INTRODUCTION

Adenocarcinoma of the stomach is one of the most common malignant diseases (*1*). It remains one of the major causes of cancer-related death worldwide,

even though its incidence has decreased over the past decade in most industrialized countries (*40, 44*). The prognosis of this disease is generally poor. In Western countries the overall survival rate at 5 years oscillates between 8 and 26 %, in the Czech Republic it is about 12 % (*2*). During the last 20 years, the resectability rate has increased (currently, 60–80 %), and the postoperative mortality has dropped from 14 to 6 % (*3-7*). The poor survival is related to delayed diagnosis and frequent local and regional recurrence (*41,46*). In an attempt to identify prognostic indicators in patients with gastric cancer, several variables representing pathological, clinical and therapeutic characteristics have already been studied in numerous retrospective reports (*8-14*).

The aim of this paper was to determine and analyse the influence of several clinicopathological variables on survival in a series of 283 patients after surgery for adenocarcinoma of the stomach.

MATERIALS AND METHODS

Between January 1990 and December 1997, 352 patients with adenocarcinoma of the stomach underwent surgery in the Department of Gastrointestinal Tumours of N. N. Petrov Research Institute of Oncology (St. Petersburg, Russian Federation). Patients with cancer of the gastric cardia or with incomplete or invalid database records were excluded from the study. Excluding 29 operative deaths (8.2 %), defined as those occurring within 30 days of operation [43], and patients who died from causes other than gastric cancer, the remaining 283 patients were discharged from the hospital and are the subject of the study. The mean follow-up was 6.1 years (range 1-11 years).

For statistical analysis we have used data from the prospectively organized archive database of the institution, established in 1987. This database includes comprehensive information about clinical course and hospitalization, diagnostics (with complete histopathological documentation), treatment, and about regular medical check-ups.

CLINICOPATHOLOGICAL FACTORS

The analysis of potential prognostic indicators included three types of factors – patient-related, tumour-related, and treatment-related.

Patient-related factors: sex, age (divided into three categories: ≤40 years, 41 to 64 years, ≥65 years), duration of symptoms, e.g. time interval between the appearance of the first symptoms and surgery (≤2 months, 3 to 5 months, ≥6 months), presence of potentially relevant clinical symptoms (weight loss, epigastric pain, melena [48], palpable abdominal mass), and some laboratory markers (preoperative haemoglobin and albumin levels).

Tumour-related factors: macroscopic appearance of tumour according to Borrmann, histological type according to Laurén (intestinal, diffuse or mixed type), histopathological grading, tumour localization (proximal third, mid-stomach, lower third or diffuse infiltration) and maximum diameter of the tumour (≤3 cm, 3 to 5 cm, ≥5 cm), stage of disease, and T, N, M parameters according to the 4th edition of the TNM classification of UICC (*16*).

Treatment-related factors: extent of performed surgery (total gastrectomy, distal or proximal subtotal gastric resection, palliative intestinal bypass or exploratory

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laparotomy), primary intention of the surgery (curative, palliative or non-curative exploratory laparotomy), whether splenectomy or combined resection of the pancreas was performed.

Standard resection included resection of the stomach and greater omentum. Although the standard extent of lymphadenectomy was D1 (groups 1-6), there was an intention to at least partially perform advanced D2 lymphadenectomy in some cases, e.g. where it was technically possible or when unfavourable prognostic factors were present (for example, in diffuse and infiltrative carcinomas). The surgery was considered as curative (or at least potentially curative), if it resulted in complete tumour removal with histologically negative resection margins. In all other cases the surgery was considered as palliative. Exploratory laparotomies were considered as non-curative surgeries.

STATISTICAL ANALYSIS

The survival data are expressed as 5-year survival rates. The survival rates in the different groups were calculated with the Kaplan-Meier estimation method, and survival curves were compared with the log-rank test on univariate analysis. A p value of < 0.05 was assigned statistical significance. All statistical analysis was performed with the statistical software package Statistica for Windows 6.0 (*15*).

RESULTS

There were 182 males (64.3 %) and 101 females (35.7 %). There was a male predominance of 1.80:1, which was observed in all age categories. The mean age was 64.7 years, ranging from 28 to 87 years.

Almost half of the patients (47.0 %) had durations of symptoms between 2 and 6 months. Weight loss was recorded in 57.2 % of the patients. Melena was recorded in 20.8 % of the patients. Epigastric pain was observed in 47.7 % of the patients. There was 6.7 % of palpable tumours. Preoperative anaemia (haemoglobin level under 120 g/l) was observed in 63.3 % of the patients; in 58.3 % of the cases preoperative albumin level was under 35 g/l.

Most tumours (82.7 %) were located in the distal two thirds of the stomach. In 10.2 % of the cases tumour was in the upper third, and it diffusely infiltrated the stomach in 7.1 % of the patients. In only 19.1 % of the patients tumour size was less than 3 cm (the biggest diameter was measured). In 38.2 % tumour size was 3 to 5 cm, in 42.8 % of the cases the tumour was bigger than 5 cm.

According to macroscopic classification, Borrmann type II was the most common (38.9 %), followed by type III (26.1 %), type I (14.5 %), and type IV (8.1 %) in advanced gastric cancers. Early gastric cancer (EGC), e.g. type 0 was found in only 12.4 % of the patients. The intestinal type of Laurén's classification accounted for 53.0 % of the cases, the diffuse type was detected in 30.7 % of the

patients, and in 16.3 % of the cases the type was described as mixed. The distribution of histopathological differentiation (denoted as G1–G4) was G1 – 14.8 %, G2 – 27.2 %, G3 – 44.2 %, G4 – 13.8 %.

According to TNM classification, 3.2 % of the patients had stage 0 disease (carcinoma in situ), 11.0 % – stage I, 17.0 % – stage II, 37.1 % – stage III, 31.8 % – stage IV. Lymph node metastases were found in 82.0 % of the patients. Distant metastases at the time of operation were found in 16.3 % of the patients.

The 5-year overall survival rate was 18.4 %. The 5-year survival rates according to the TNM stage were 77.8 % for stage 0, 51.6 % for stage I, 27.1 % for stage II, 11.4 % for stage III, and 4.4 % for stage IV (*Fig. 1*). The 5-year survival rate was 60.0 % for EGC, and 12.5 % for advanced gastric cancer.

The patients without lymph node metastases (N0) had a 5-year survival rate of 41.2 %. The presence of metastases in the lymph nodes markedly worsened the prognosis – the 5-year survival rate of the N1 patients was 19.8 %, and that of the N2 patients only 8.8 % (*Fig. 2*).

Total gastrectomy was performed in 54.1 % of the patients, distal subtotal resection in 23.3 %, proximal subtotal resection in 4.9 %, palliative intestinal bypass in 11.0 %, exploratory laparotomy in 6.7 % of the patients. More than a half of the surgeries (55.1 %) were considered as curative, palliative surgeries were performed in 38.2 % of the patients, exploratory laparotomies in 6.7 % of the cases. *Fig. 3* shows 5-year survival rates according to the extent of surgery.

Splenectomy was performed in 14.1 %, resection of the stomach combined with partial resection of the pancreas in 3.2 % of the cases.

ANALYSIS OF RESULTS

The results of the univariate analysis are summarized in *Tables 1, 2* and *3*. The results were grouped by the relationship of the factors. Age, weight loss, palpable abdominal tumour, decreased levels of haemoglobin and albumin, tumour site and size, macroscopic appearance according to Borrmann, histological type according to Laurén, histopathological grading, TNM stage, depth of gastric wall invasion (T), presence of lymph node metastasis (N) or distant metastasis (M), extent of performed surgery and its intention had prognostic significance in univariate analysis.

DISCUSSION

The aim of the present study was to identify several clinicopathological variables that influence the prognosis of patients with gastric adenocarcinoma after the surgery. Prognostic factors in gastric cancer are a source of controversy in many series (*3, 5, 7, 9, 11, 14*). In some papers, younger patients have paradoxically worse prognosis. It is possible that younger patients present with more advanced disease because the index of suspicion for malignant disease is low and thus symptoms are allowed to progress for a longer period before investigation is considered. Also,
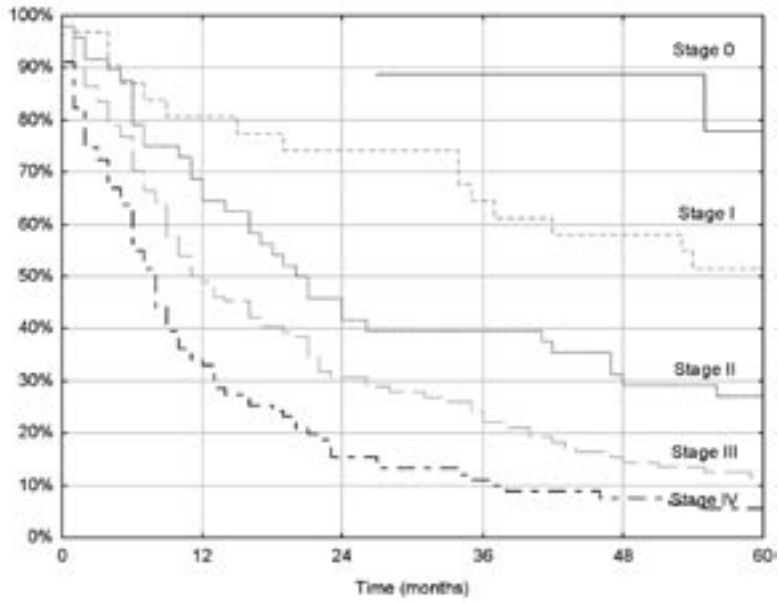
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Fig. 1
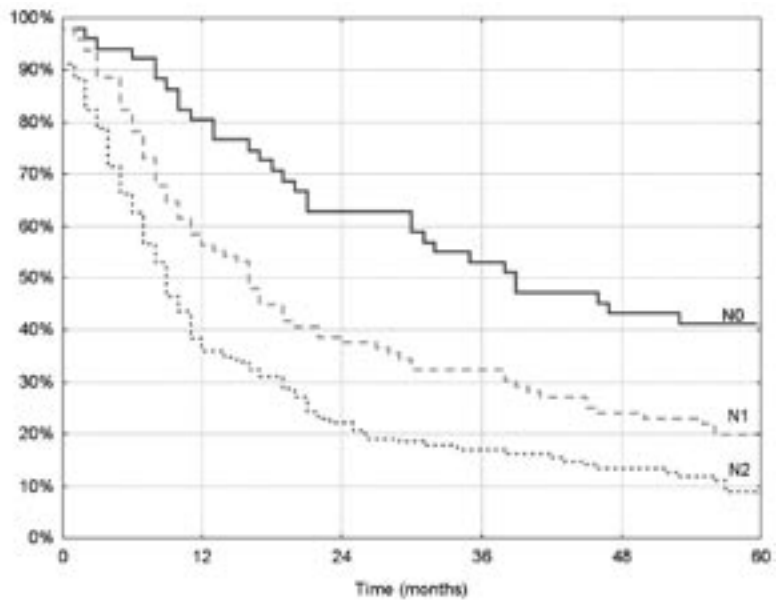Cumulative survival rates according to the TNM stage

Fig. 2
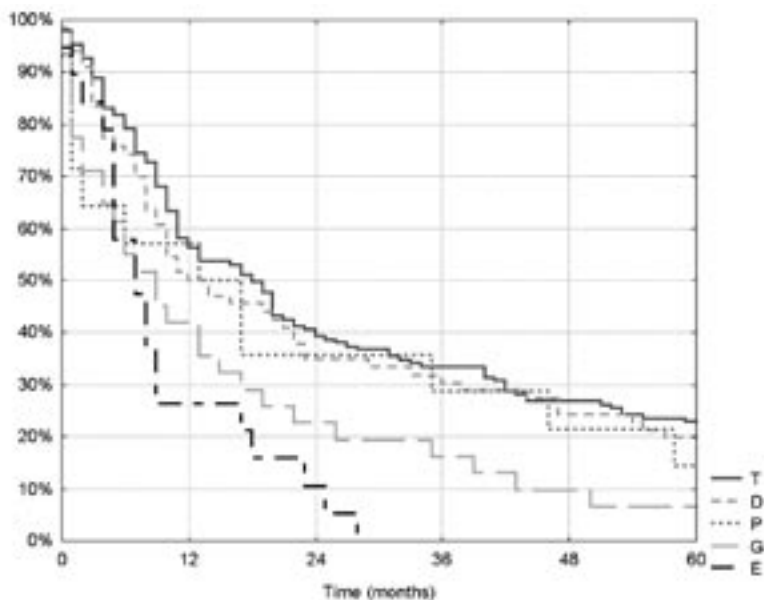Cumulative survival rates according to the lymph node state (N)

Fig. 3
Cumulative survival rates according to the extent of performed surgery (T – total gastrectomy, D – distal subtotal resection, P – proximal subtotal resection, G – palliative intestinal bypass, E – exploratory laparotomy)

there may be a greater biological activity of the tumour, which is more likely to be of the Laurén diffuse type. Other studies with large numbers of patients (*17, 18*) showed that younger patients have better survival. Finally, there are studies that showed no relation between age, sex and survival. In our paper, sex did not influence the survival and younger patients had significantly better prognosis. We explain this finding by the fact that younger patients have a better nutritional status (*47*) and a higher general resistance of the organism.

If, in certain studies (*20*), the time between appearance of the first symptoms and treatment is analysed, a poorer prognosis is seen in patients with a short duration (usually less than 6 months). However, other authors (*21*) have reported that prognosis is worse in patients with a long evolution. The study of *Harrison et al.* (*22*) showed no relation between duration of the symptoms and prognosis when considered alone, but in combination with tumour diameter duration of the symptoms had a prognostic significance. The reason for this relation is thought to be that patients with long-standing symptoms have slow-growing tumours, or gastric "ulcer cancers". Other studies (*10, 23*) have failed to show any relationship between symptom duration and prognosis. The present study revealed no differences in survival with regard to the preoperative duration of the symptoms. However, patients with weight loss, dysphagia or palpable abdominal mass had a worse prognosis.

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Table 1
Results of univariate analysis – patient-related factors

Variable	Number of patients (%)	5-YSR (%)	*p* value
Total	283 (100 %)	18.4	
Sex			
Male	182 (64.3)	20.3	n.s.
Female	101 (35.7)	14.9	
Age			
Under 40 years	9 (3.2)	33.3	
40 to 65 years	103 (36.4)	21.4	0.034
Over 65 years	171 (60.4)	15.8	
Symptom duration			
Under 2 months	91 (32.2)	20.9	
2 to 6 months	133 (47)	18.0	n.s.
Over 6 months	59 (20.8)	15.3	
Weight loss			
Yes	162 (57.2)	15.4	0.014
No	121 (42.8)	22.3	
Epigastric pain			
Yes	135 (47.7)	17.8	n.s.
No	148 (52.3)	18.9	
Melena			
Yes	59 (20.8)	15.3	n.s.
No	224 (79.2)	19.2	
Palpable abdominal mass			
Yes	19 (6.7)	0	0.010
No	264 (93.3)	19.7	
Preoperative haemoglobin			
Under 120 g/l	179 (63.3)	16.2	0.042
Over 120 g/l	104 (36.7)	22.1	
Preoperative albumin			
Under 35 g/l	165 (58.3)	15.8	0.018
Over 35 g/l	118 (41.7)	22.0	

Table 2
Results of univariate analysis – tumour-related factors

Variable	Number of patients (%)	5-YSR (%)	*p* value
Total	283 (100%)	18.4	
Tumour site			
Upper third	29 (10.2)	13.8	
Middle third	90 (31.8)	16.7	<0.001
Lower third	144 (50.9)	22.9	
Diffuse infiltration	20 (7.1)	0	
Tumour size			
Less than 3 cm	54 (19.1)	35.2	
3 to 5 cm	108 (38.2)	19.4	<0.001
Bigger than 5 cm	121 (42.8)	9.9	
Borrmann type (advanced cancer)			
I	41 (16.5)	17.1	
II	110 (44.4)	13.6	
III	74 (29.8)	10.8	0.028
IV	23 (9.3)	4.3	
Laurén classification			
Intestinal	150 (53)	22.0	
Diffuse	87 (30.7)	12.6	0.044
Mixed	46 (16.3)	17.4	
Histopathological grading			
G1	42 (14.8)	28.6	
G2	77 (27.2)	22.1	
G3	125 (44.2)	16.0	0.001
G4	39 (13.8)	7.7	
Disease stage			
0	9 (3.2)	77.8	
I	31 (11.0)	51.6	
II	48 (17.0)	27.1	<0.00001
III	105 (37.1)	11.4	
IV	90 (31.8)	4.4	
T category according to TNM			
T0	9 (3.2)	77.8	
T1	26 (9.2)	53.8	
T2	60 (21.2)	26.7	<0.00001
T3	104 (36.7)	10.6	
T4	84 (29.7)	4.8	
N category according to TNM			
N0	51 (18.0)	41.2	
N1	96 (33.9)	19.8	<0.00001
N2	136 (48.1)	8.8	
M category according to TNM			
M0	237 (83.7)	21.9	
M1	46 (16.3)	0	<0.00001

Variable	Number of patients (%)	5-YSR (%)	p value
Total	283 (100 %)	18.4	
Extent of surgery			
Total gastrectomy	153 (54.1)	22.9	
Distal subtotal resection	66 (23.3)	19.7	
Proximal subtotal resection	14 (4.9)	14.3	0.003
Intestinal bypass	31 (11.0)	6.5	
Exploratory laparotomy	19 (6.7)	0	
Intention of surgery			
Curative	156 (55.1)	28.2	
Palliative	108 (38.2)	7.4	<0.0001
Exploratory laparotomy	19 (6.7)	0	
Splenectomy			
Yes	40 (14.1)	12.5	
No	243 (85.9)	19.3	n.s.
Resection of the pancreas			
Yes	9 (3.2)	0	
No	274 (96.8)	19.0	n.s.

There is no doubt that the general condition of the patient is important for the prognosis of gastric cancer. However, its objective quantification is rather difficult. In our study, from the large number of available laboratory parameters, we have chosen two of them, which are usually decreased in oncological patients. These are preoperative serum levels of haemoglobin and albumin. Their decreased levels are related to the poorer survival. Similar results were obtained by *Kim et al. (38).*

Several authors (*4, 6, 8, 9, 14, 21, 23*) have suggested that the more proximal is the tumour, the worse is the survival rate, and in the recent time the incidence of proximal tumours seems to be increasing. The detection of proximal tumours is difficult, they grow faster and develop metastases more often (particularly to lymph nodes) (*24, 25, 26*). In our study (though we have excluded patients with infiltration of the cardia) we obtained similar results – the patients with tumour localized to the distal two thirds of the stomach had an overall 5-year survival rate of 20.5 %, whereas patients with tumours of the proximal third of the stomach had a 5-year survival rate of only 13.8 %. The worst prognosis was in patients with diffuse infiltration of the stomach (linitis plastica).

Some reports (*23*) have suggested that patients with smaller tumours have a superior prognosis. In our study, there was a statistically significant relationship between tumour size and survival – the best prognosis was found in patients with tumours with a diameter less than 3 cm.

Analysis of the relation of macroscopic appearance of tumour according to Borrmann and survival has showed that patients with type I (polypoid tumours) have the best prognosis, while patients with infiltrating tumours (types III and IV) have a significantly worse prognosis. It is possible that these differences are given by the fact that polypoid tumours are better diagnosed; the worse prognosis of infiltrating tumours is also caused by their higher biological aggressiveness.

With respect to the degree of cellular differentiation, the best prognosis has been found in well differentiated tumours (*6, 8, 29, 42*). Our study confirms those results – patients with low-grade tumours had a greater survival rate than those with high grade tumours, the difference being statistically significant.

In this and other studies it was found that the most important prognostic factors correlated to survival are depth of invasion of the gastric wall (*9, 10, 13, 14, 20, 28*), presence of regional lymph node metastases (*10, 20, 30-34*), and disease stage according to TNM classification. Depth of gastric wall invasion can be considered as a paramount factor, being the basis for most of the other prognostic indicators. For instance, the predictably good T1-T2 lesions are less associated with metastatic nodes, while the generally bad T3-T4 tumours readily encroach on nodes. Seemingly, nodal invasion (in many studies identified as an independent prognostic factor) is rather a reflection of the depth of penetration and advance of disease. In our study, patients with no lymph node involvement had a 5-year survival rate of 41.2 %, while prognosis of patients with infiltrated lymph nodes was much worse, with a 5-year survival rate of only 13.4 %.

In the last decades, a steady increase in tumour resectability rate has frequently been reported. *Gall and Hermanek* (*35*) reported an increase from 60.8 % to 75.9 % over two consecutive 5-year periods. This was due mainly to an increase in the number of palliative resections. There is no doubt that if a tumour is resectable, the prognosis is considerably better than when the lesion is irresectable. It is clear that prognosis far more depends on the stage of disease, so we cannot consider the operation factor as an independent prognostic indicator. The worst prognosis is seen in patients after palliative intestinal bypasses and inoperable patients (*45*). In our study, differences in the 5-year survival rate after total gastrectomy and distal subtotal resection of the stomach were not statistically significant (22.9 % vs. 19.7 %). In a randomized multicentric French study of *Gouzi et al. (36)*, gastrectomies and subtotal resections for treating cancer of the gastric antrum were compared. This study demonstrated no differences in the 5-year survival rate (48 %) and postoperative mortality. The Italian Stomach Cancer Group has investigated 271 patients in a non-randomized retrospective study (*37*). The authors have come to the conclusion that a subtotal resection of the stomach in patients with cancers of the stomach antrum and the middle third yields better results than gastrectomy. From the available literature we can conclude that a sufficient safety margin is more important than the decision about the type of surgery to be performed (e.g. total gastrectomy or distal subtotal gastrectomy). If a given safety margin permits subtotal resection, then this

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operation can be performed with sufficient safety. However, in most gastric cancers a safe resection margin can only be achieved with total gastrectomy, and subtotal resection with a substantial safety margin seems to be feasible in antral tumours only. In our study, total gastrectomy was the radical surgery of choice (54.1 % of the surgeries). Distal subtotal resections were performed in patients with less advanced cancers, without evident lymph node metastases, and in patients with exophytic or relatively small infiltrative tumours of the lower third of the stomach. Proximal subtotal resections were performed in early tumours of the upper third of the stomach, when the tumour did not spread over the cardiac sphincter or the abdominal part of the oesophagus. In cases where subtotal resection did not seem to be radical enough, total gastrectomy was indicated and performed (if technically feasible). Total gastrectomy was used for both curative and palliative treatment. Palliative gastrectomies were performed in cases where they were technically feasible, but curativity could not be accomplished, for example, due to the lymph node syndrome.

Although it has been stated that the association of splenectomy and combined resection of the pancreas diminishes the survival rate (*7, 9*), this was not confirmed in the present study.

In order to use the aforementioned findings in clinical practice, prognostic factors of the individual patient should not be analysed separately – their integration is essential. This can be achieved by several means. The traditionally used method is the development of the prognostic score system. As an example we can cite the score system developed by *Marubini et al. (39),* which divides patients into three categories with significantly different survival rates, based on the analysis of age, sex, tumour site, disease stage, surgical therapy, and histological type of tumour.

Using modern prediction methods, for example, artificial neural networks (ANN), seems to be promising. ANN is a mathematical model that simulates the behaviour of groups of models of biological neurons. ANNs are able, in quite an easy but reasonable way, to model such aspects of the biological neuron as its ability to combine information and recognize patterns. The artificial neural network can analyse and generalize the given data, and offer prognostic conclusions based on this analysis. The conception of ANN is particularly advantageous because it is adapted to perform analysis of a great amount if input factors. Artificial neural networks have already been used for a long time in various fields of medicine, for instance, in the treatment of prostate cancer, breast cancer, etc. *Botacci et al. (49)* used ANN to predict survival in patients with colorectal cancer after surgical therapy with relatively good results. There is a lack of similar studies in gastric cancer, therefore conducting such a study will be our next goal.

CONCLUSION

An analysis of a series of 283 patients after surgery for adenocarcinoma of the stomach has showed that the most important factors related to survival are disease

stage according to TNM classification, depth of gastric wall invasion, lymph node involvement, presence of distant metastases, the intention of performed surgery, tumour site and its size. Other, although less significant factors, are age, weight loss, palpable abdominal mass, low preoperative levels of haemoglobin and albumin, macroscopic appearance of tumour according to Borrmann, histological type according to Laurén, histopathological grading, and the extent of performed surgery. These findings will be used to develop a prognostic system based on the principle of artificial neural networks, which will integrate various prognostic factors to enable complex estimation of the prognosis.

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VÝZNAMNÉ PROGNOSTICKÉ FAKTORY V SOUBORU 283 NEMOCNÝCH PO OPERACI PRO ADENOKARCINOM ŽALUDKU

S o u h r n

I když v posledních letech došlo ke snížení incidence adenokarcinomu žaludku, zůstává prognóza tohoto onemocnění nepříznivá. Cílem předložené studie bylo zhodnotit vliv některých klinicko-patologických faktorů na přežití souboru 283 nemocných operovaných pro adenokarcinom žaludku v období let 1990–1997.

Pravděpodobnosti přežití různých skupin nemocných byly stanoveny pomocí Kaplan-Meierovy metody. Výsledky byly analyzovány retrospektivně a hodnoceny jednorozměrnou analýzou (log-rank test). Průměrný věk nemocných v době operace byl 64,7 let, 64,3 % souboru tvořili muži. Totální gastrektomie byla provedena u 54.1 % nemocných, distální subtotální resekce u 23,3 %, proximální subtotální resekce u 4,9 %, paliativní spojková operace u 11,0 %, explorativní laparotomie u 6,7 % nemocných.

Celkové pětileté přežití činilo 18,4 %. Statistická analýza prokázala, že prognosticky významnými faktory jsou věk (p=0,034), úbytek váhy (p=0,014), nález palpačně hmatného tumoru na břiše (p=0,010), snížené předoperační hodnoty hemoglobinu (p=0,042) a albuminu (p=0,018), lokalizace tumoru (p<0,001) a jeho velikost (p<0,001), makroskopický vzhled tumoru dle Borrmannovy klasifikace (p=0,028), histologický typ dle Laurénovy klasifikace (p=0,044), histopatologický grading (p=0,001), stadium onemocnění dle TNM klasifikace (p<0,00001), hloubka prorůstání do stěny žaludku (p<0,00001), stav lymfatických uzlin (p<0,00001), nález vzdálených metastáz (p<0,00001), typ provedené operace (p<0,003) a její cíl, tj. kurativní, paliativní nebo neléčebný (p<0,0001).

Stadium onemocnění, hloubka prorůstání do stěny žaludku, metastatické postižení uzlin, nález vzdálených metastáz a radikalita operace jsou hlavními prognostickými faktory souvisejícími s přežitím nemocných po operaci pro adenokarcinom žaludku. Uvedené výsledky budou následně použity k vytvoření prognostického systému založeného na principu umělých neurálních sítí, umožňujícího komplexní posouzení analyzovaných faktorů.

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