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Tumor-Related Bleeding, Perforation, and Stenosis as Prognostic Factors of Gastric Cancer

Rola dodatkowych czynników prognostycznych nowotworu złośliwego żołądka: krwawienia, perforacji i obstrukcji

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Abstract

Background. Prognostic factors in cancer patients help to predict long-term survival. In addition to established prognostic factors such as the TNM classification, there are tumor characteristics of uncertain value regarding long-term survival, such as tumor-related bleeding, tumor perforation, and stenosis of the gastric cancer.
Objectives. The aim of the present study was to evaluate these aspects regarding their prognostic value.
Material and Methods. Five hundred ninety-four patients with gastric cancer were treated from November 1993 to June 2002 at the Department of Surgery, University Hospital Carl Gustav Carus, Dresden, Germany. Data were collected retrospectively to August 2000 and prospectively thereafter. Four hundred eighteen patients were operated on by a resection procedure (70.3%). The remaining 29.7% received palliative surgical and/or non-surgical treatment. Tumor-related complications such as bleeding, perforation, and stenosis were noted in 177 patients of the resection group. The data were examined by ANOVA and survival analysis was done using the Kaplan-Meier method. Multivariate analysis was performed using the Cox regression test.
Results and Conclusions. The conventional predictors pT, pN, M, UICC stage, R-status, and grading were significant predictors of long-term outcome in the multivariate analysis. Bleeding and stenosis were predictors of survival in univariate analysis, but significance could not be reached for these factors in the multivariate testing (**Adv Clin Exp Med 2006, 15, 6, 1015–1022**).

Key words: gastric cancer; prognostic factors; tumour complications: bleeding, perforation, stenosis; long term survival.

Streszczenie

Wprowadzenie. Czynniki prognostyczne umożliwiają oszacowanie przebiegu choroby pacjentów z nowotworem złośliwym. Oprócz pełnych czynników prognostycznych, jak cecha „TNM", występują dodatkowe czynniki, np. krwawienie, obstrukcja lub perforacja wywołana przez raka żołądka, które mają wpływ na przeżywalność.
Cel pracy. Ocena wpływu dodatkowych czynników nowotworowych na przeżywalność w badanej grupie pacjentów.
Materiał i metody. W okresie od listopada 1993 r. do czerwca 2002 r. 594 pacjentów chorych na raka żołądka było leczonych w Klinice i Poliklinice Chirurgii Narządowej, Klatki Piersiowej i Naczyniowej Uniwersytetu Carla Gustava Carusa w Dreźnie. Do sierpnia 2000 r. zbierano retrospektywnie dane o pacjentach, od września 2000 r. – prospektywnie. U 418 pacjentów przeprowadzono zabiegi resekcyjne (70,3%) żołądka. Pozostałych 29,7% pacjentów leczono paliatywnie chirurgicznie lub niechirurgicznie. Zabiegi resekcyjne przeprowadzono u 177 pacjentów z krwawieniem, obstrukcją lub perforacją spowodowanymi przez raka żołądka. Do gromadzenia danych używano programu komputerowego Visual FoxPro (w. 11). Analizy statystyczne przeprowadzono za pomocą programu SPSS® (w. 11.5). Obliczenia dokonano w systemie ANOVA, analizę przeżywalności przeprowadzono według metody Kaplana-Meiera. Analizę wieloczynnikową dokonano według regresyjnego testu Coxa. Grupa pacjentów z perforacją nowotworową nie została uwzględniona w wyliczeniach statystycznych ze względu na niewielką liczbę pacjentów.
Wyniki. Cechy pT, pN, M, klasyfikacja UICC-1997 oraz „R" i cecha zróżnicowania (*grading*) nowotworu miały statystycznie znaczący wpływ na przeżywalność pacjentów. Krwawienie i obstrukcja spowodowane przez raka żołądka miały ujemny wpływ na przeżywalność według analizy metodą Kaplana-Meiera. Poddane jednak analizie za pomocą testu regresji Coxa nie miały statystycznego wpływu na przeżywalność (**Adv Clin Exp Med 2006, 15, 6, 1015–1022**).

Słowa kluczowe: rak żołądka, czynniki prognostyczne; powikłania nowotworowe, krwawienie, perforacja, stenoza, przeżywalność pacjentów.

In the western world, the prognosis of gastric cancer is poor since it is generally diagnosed at an advanced stage, contrary to the situation in Japan. As a result of aggressive screening there, more early cancer stages are detected with only a few symptoms [15, 16]. Patients with advanced cancer often present with symptoms such as pain or gastric dysfunction. Tumor bleeding, perforation, or stenosis are rarely the first signs of the disease. To date there have been only a few studies exploring the long-term prognostic relevance of these symptoms [17, 19].

The TNM-classification is an established basis for the prediction of long-term outcome in gastric cancer patients. Bleeding, stenosis, or perforation as the first symptoms of tumor disease are less reliable prognostic factors [1, 2, 5, 8, 10]. The aim of the present study was to explore the value of these tumor-related complications as predictors of survival in patients treated for gastric cancer.

Material and Methods

Five hundred ninety-four patients (254 women, 340 men) were treated for gastric cancer between November 1993 and June 2002 at the Department of Surgery, University of Dresden. The data were collected retrospectively until August 2000 and then prospectively for the rest of the patients until June 2002. Follow-up data were obtained from the departments tumor dispensary (462 patients) or from a questionnaire sent to the attending oncologists (132 patients).

The median age was 66 years (range: 26–91 years). An operative procedure with curative intention was performed in 418 cases (70.3%, Fig. 1). The baseline characteristics of the patients who underwent a resection procedure are presented in Table 1. The remaining patients (176, 29.7%) underwent palliative treatment. Fifty-one gastrotomies were performed to stop the bleeding or to suture the perforation, but resection was not accomplished due to metastatic disease. Twenty-one patients received a jejunal tube for maintaining enteral nutrition. Palliation could not be achieved in 104 cases because of advanced cancer stage.

Statistics

VisualFoxPro (Version 11) software was used for data collection. Statistical analysis was performed by SPSS (version 11.5). The data were examined by ANOVA. Survival analysis was performed using the Kaplan-Meier method. Statistical significance ($p = 0.05$) was tested using the log-rank test. Multivariate analysis was performed applying the Cox regression model. The variables were age, gender, tumor location (distal, middle, proximal, total carcinoma), pT, pN, M, R-status, grading, Laurén classification, hemorrhage, and stenosis. No statistical analysis was possible for tumor perforation due to the low number of patients (seven) in this group.

Results

Tumor-related complications such as bleeding, stenosis, or perforation as the first symptoms were present in 288 of the 594 patients (48.5%). One hundred fifty patients showed both bleeding and stenosis. An operative procedure was performed in 65% of these cases. Only stenosis as a tumor-related complication was present in 100 patients, 58 of whom were operated on. Bleeding as a solitary symptom was noted in 31 patients, of whom 48% underwent surgery. All 7 patients presenting with perforation underwent an operation (Tab. 2). Forty percent of resected patients with tumor-related complications were older than 60 years, 22% older than 70 years, and 4% older than 80 years (Fig. 2).

Bleeding

Gastrointestinal bleeding was a complication during the course of the tumor disease in 181 patients (30.5% of all patients with gastric cancer). It was the first symptom in patients with gastric cancer in 94 cases. A resection procedure was performed in 48% with hemorrhage as a solitary symptom and in 65% with simultaneous bleeding and stenosis (Tab. 2). Tumor bleeding was more often present in older patients (Fig. 3). Most of these 112 patients were older than 60 years (89%). The five-year survival rate for patients with resection and bleeding was 46% and for those without bleeding and resection 49%. There was no significant difference ($p = 0.86$) (Fig. 4). Univariate and multivariate analysis revealed no significant relation to long-term outcome (Tab. 4).

Perforation

Seven cases were found with gastric cancer-related perforation (1.2% of all gastric cancer patients treated) presenting with diffuse peritonitis in four patients at the point of laparotomy. An early stage of perforation was found in the remaining three patients. Because of the small group, statistical analysis was not possible.

Two of the patients were treated by immediate gastrectomies. There was one gastrectomy per-

Table 1. Baseline characteristics of the patients with gastric cancer and a resection procedure

Tabela 1. Charakterystyka pacjentów po resekcji raka żołądka

Characteristics (Cechy)	Operated patients (Operowani pacjenci)	Without tumor-related complications* (Bez powikłań*)	With tumor-related complications* (Z powikłaniami*)
	418	241	177
Median age in years (Średni wiek w latach)	66	66	67
Sex (M/F) (Płeć m/k)	203/215	109/132	94/89
Location of tumor (Umiejscowienie nowotworu)			
upper third (górny żołądek)	185	123	62
middle third (środkowy żołądek)	113	79	34
distal third (dolny żołądek)	117	39	78
total carcinoma of the stomach (cały żołądek)	3		3
Pathological stage of disease (Cecha „T")			
T1	89	83	6
T2	155	116	39
T3	94	32	62
T4	80	10	70
pN-Stages (Cecha „pN")			
pN0	156	96	60
pN1	136	92	44
pN2	126	53	73
M-Stages (Cecha „M")			
M0	337	231	106
M1	81	10	71
R Stages (Cecha „R")			
R0	397	230	167
R1	21	11	10
G-Stages (Cecha „G")			
G1	15	11	4
G2	129	86	43
G3	240	133	107
G4	34	11	23
Laurén classification: (Typ według Lauréna:			
intestinal (jelitowy)	185	112	73
diffuse (rozlany)	210	123	87
mixed (mieszany)	23	6	17
Bleeding (Krwawienie)	112		112
Stenosis (Stenoza)	155		155

* Tumor-related complications: tumor bleeding, tumor stenosis, tumor perforation.
* Powikłania nowotworowe: krwawienie, obstrukcja, perforacja.

Table 2. Patients with tumor-related complications

Tabela 2. Pacjenci z powikłaniami jako pierwszym objawem nowotworu

Complications (Powikłania)	All patients (Wszyscy pacjenci)	Operated patients (Operowani pacjenci)	%
Bleeding (Krwawienie)	31	15	48
Stenosis (Stenoza)	100	58	58
Bleeding and stenosis (Krwawienie i stenoza)	150	97	65
Perforation (Perforacja)	7	7	100
Total (Razem)	288	177	

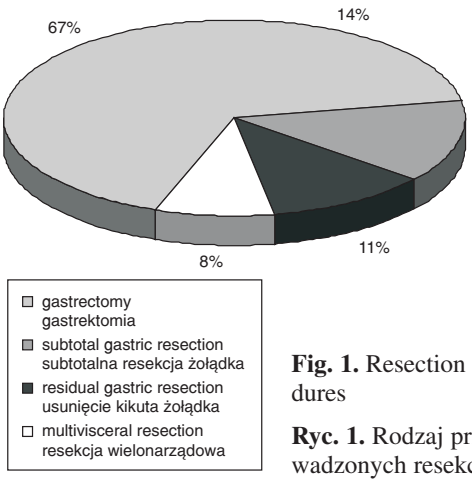

Fig. 1. Resection procedures

Ryc. 1. Rodzaj przeprowadzonych resekcji

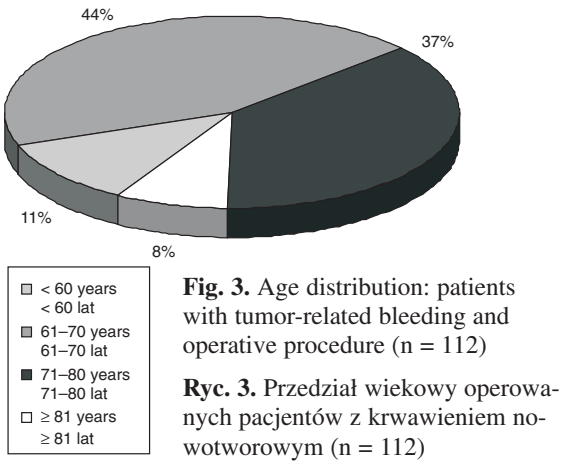

Fig. 3. Age distribution: patients with tumor-related bleeding and operative procedure (n = 112)

Ryc. 3. Przedział wiekowy operowanych pacjentów z krwawieniem nowotworowym (n = 112)

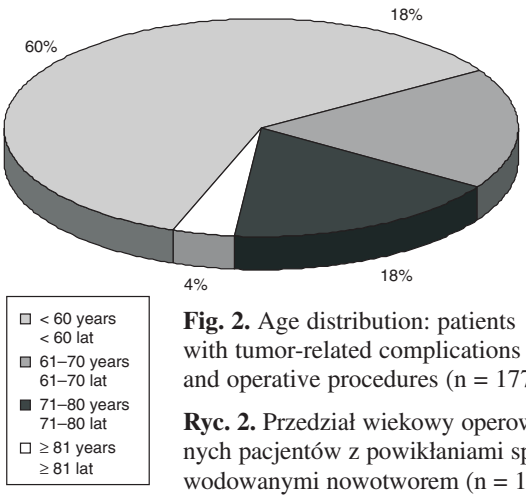

Fig. 2. Age distribution: patients with tumor-related complications and operative procedures (n = 177)

Ryc. 2. Przedział wiekowy operowanych pacjentów z powikłaniami spowodowanymi nowotworem (n = 177)

formed after a Billroth-II resection because of a perforation which had occurred three months earlier in a different hospital. After receiving the histological results, a total gastrectomy was performed at the present institution. In the other case, a subtotal gastrectomy was carried out because of an antral tumor perforation. The patients died six and seven months postoperatively.

Another two patients were treated by laparotomy, lavage, and defect closing only because of their bad general health status. Both patients died during the postoperative course (third and ninth postoperative days). Since these were the only deaths in the immediate postoperative course, the in-hospital mortality was two out of seven patients.

The remaining three patients were operated on presuming a diagnosis of a perforated benign gastric ulceration. Excision of the ulcer and defect closing were performed. After receiving the final histopathological diagnosis, a gastrectomy was performed on each patient. One patient died three months postoperatively because of a cardiac event. The others survived 13 and 14 months. The causes of death were local recurrence and metastatic disease (Tab. 3).

Stenosis

Stenoses were detected endoscopically in a high percentage of these patients (250/594 patients, or 42%). The stenoses were clinically significant in 63 of the 250 patients (25.2%). Most of the carcinomas in symptomatic patients were

Table 3. Perforation as the first symptom: clinical data

Tabela 3. Charakterystyka pacjentów z perforacją jako pierwszym objawem nowotworu

Patient (Pacjent)	Gender (male/ /female) (Płeć m/k)	Age in years (Wiek w latach)	ASA-classification (Klasyfikacja ASA*)	Tumor location (Umiejscowienie nowotworu żołądka)	Laurén classification (Klasyfikacja Lauréna)	Grading (*Grading*)	UICC	Survival in months (Przeżywalność w miesiącach)
B.CH	f	70	4	distal (dolna)	diffuse (rozlany)	G4	III	7
S.H	m	68	4	distal (dolna)	diffuse (rozlany)	G4	IV	0.1
B.K	f	65	4	distal (dolna)	diffuse (rozlany)	G4	IV	3
W.G	m	60	4	middle (środkowa)	diffuse (rozlany)	G4	IV	6
B.J	m	45	3	distal (dolna)	diffuse (rozlany)	G4	IIIA	14
K.P	m	41	3	total (całkowita)	diffuse (rozlany)	G4	IV	0.3
F.S	m	39	2	distal (dolna)	intestinal (jelitowy)	G3	IIIA	13

*ASA – American Society of Anesthesiologists.
ASA – Amerykańskie Stowarzyszenie Anestezjologiczne.

located in the lower part of the stomach (70%). In the group of patients receiving a resection procedure, 155 patients (37%) with signs of stenosis were present (Tab. 2)

The five-year survival rate for patients undergoing resection and stenosis was 38% and for those without stenosis and resection 54%. The log-rank test revealed a significant difference ($p = 0.02$) (Fig. 5), but multivariate testing could not confirm "stenosis" as an independent prognostic factor (Tab. 4).

In univariate analysis there was significant correlation for all of the examined variables except the Lauren classification. Multivariate testing revealed only the established factors pT, pN, M, UICC stage, R-status, and grading as significant prognostic variables for long-term outcome (Tab. 4).

Discussion

There are only a few published reports on the value of tumor complications such as bleeding, perforation, and stenosis as prognostic markers for long-term outcome. Generally, these symptoms are classified as less reliable prognostic factors [2, 4, 7, 8, 10, 17].

Bleeding

The management of cancer-related gastric bleeding does not differ essentially from the treatment of hemorrhage due to a benign ulcer. Blackshaw reported an impaired prognosis for those patients with an emergency operation due to gastric cancer. Indications for these laparotomies were several tumor-related complications, except stenosis or perforation [5]. Generally it is recommended to try to achieve hemostasis first endoscopically [10]. Facing life-threatening hemorrhage as a first symptom without successful endoscopic treatment, an operative procedure under emergency conditions is required. The bleeding source should be identified by gastrotomy, followed by operative hemostasis [12].

Gastrectomy under emergency conditions due to tumor bleeding has a high perioperative mortality, as presented by Cheung in 1991. He observed 52 patients with symptoms of tumor hemorrhage. Gastrectomy in cases of emergency was performed in 22 patients. Forty-two percent died during the perioperative course. In contrast, the 30 remaining patients undergoing elective surgical procedures showed a mortality of only 13% [8]. Gertsch reports a survival of 2 to 92 months in his follow-up after emergency gastrectomies due to bleeding or perforation [11].

The group of seven patients in the present study with acute tumor bleeding (Forrest Ia bleeding) was first treated endoscopically, achieving hemostasis in five of the seven patients. The patients later underwent resection under elective conditions. The remaining two patients without successful endoscopic treatment were not resecta-

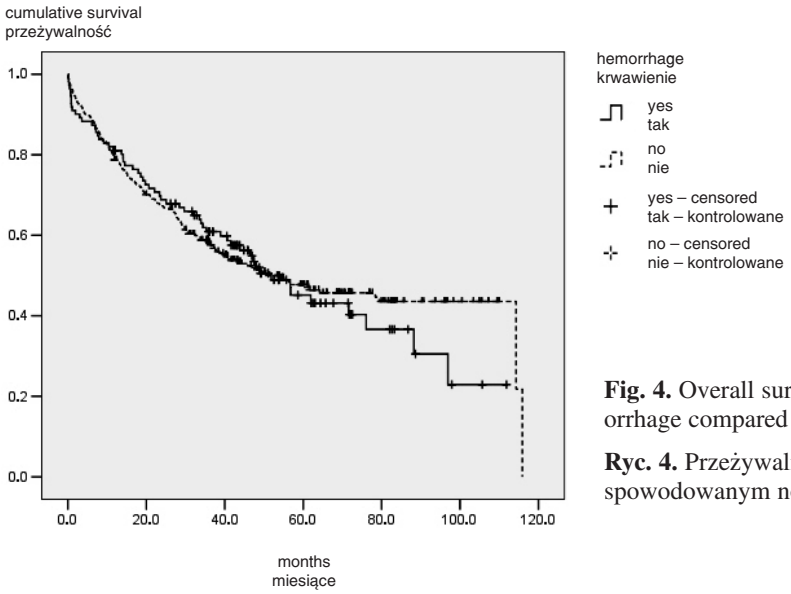

Fig. 4. Overall survival: patients with tumor-related hemorrhage compared with patients without bleeding

Ryc. 4. Przeżywalność pacjentów bez i z krwawieniem spowodowanym nowotworem

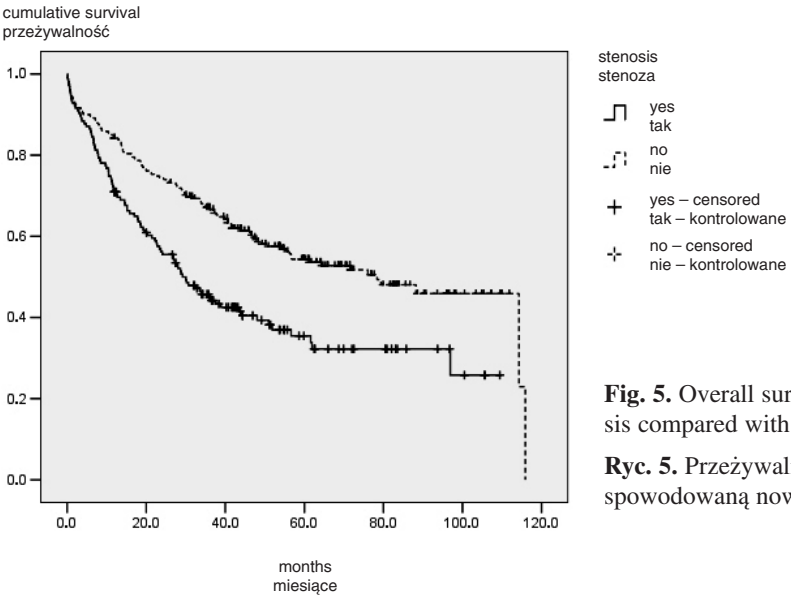

Fig. 5. Overall survival: patients with tumor-related stenosis compared with patients without stenosis

Ryc. 5. Przeżywalność pacjentów bez i z obstrukcją spowodowaną nowotworem

ble due to their bad general status. Bleeding control was achieved by transcatheter arterial embolization via the left gastric artery. Both patients died during their stay in hospital (1 day and 12 days post intervention).

Selective arterial embolization in the event of tumor bleeding is an established palliative procedure in selected cases [6]. Overall, tumor-related hemorrhage shows a vast perioperative mortality if the patients are resected in emergency conditions. The in-hospital mortality for this group is about 20–42%, compared with 13% for the group resected under elective conditions [8, 11]. As to the long-term outcome, the data of the present study indicate that tumor bleeding does not have a negative impact on prognosis.

Perforation

"On the evening of May the 5th, 1821, Napoleon I died at the age of 52 years on St. Helena. Because of his testimony an autopsy was performed. The cause of death was a gastric cancer perforation" [3].

A perforation usually occurs at an advanced tumor stage and it mostly affects males. Tumors of the lower part of the stomach perforate more frequently. An acute abdomen due to tumor perforation is rare. Statistically, a surgeon will see this situation once in his life [1]. Several authors report an incidence of 0.9 to 4% of gastric cancer patients [11, 13, 14]. The underlying cause of perforation will often be not recognized before obtaining the histopathological result. The patients generally present in a poor physical state. The postoperative course is influenced by cachexia, tumor-related

Table 4. Results of the univariate and multivariate analysis

Tabela 4. Wyniki analizy pojedynczych i wielu cech

Parameter (Cechy)	Univariate analysis (Analiza funkcji jednej zmiennej) p	Multivariate analysis (Analiza funkcji wielu zmiennych) p
Age (Wiek)	< 0.001	0.80
Gender (Płeć)	< 0.002	0.90
Tumor location (Umiejscowienie nowotworu)	< 0.001	0.10
pT	< 0.001	< 0.001
pN	< 0.001	< 0.001
M	< 0.001	< 0.001
UICC	< 0.001	< 0.001
R-status (Cecha R)	< 0.002	< 0.001
Grading (*Grading*)	< 0.008	< 0.001
Laurén classification (Klasyfikacja Lauréna)	0.20	0.10
Hemorrhage (Krwawienie)	0.09	0.80
Stenosis (Stenoza)	< 0.02	0.60

immunoincompetence, and hypoproteinemia. Besides these carcinoma-related problems, mortality is influenced by age and other disorders [11, 18].

Four of the patients of the present study had an ASA IV classification expressing multiple co-morbidities besides the perforating cancer disease. This may explain the high perioperative mortality (28.5%) of the patient group. Other groups report in-hospital mortality of 4.2% to 31% [11, 16, 18]. The median survival was six months in this group. The poor long-term survival can be explained by the large number of advanced cancer stages.

Stenosis

Clinically it is very often impossible to differentiate between a stenosis of benign or malignant cause. Evidence for a malignant origin may be found in the patients' history. Patients with a benign stenosis have their discomforts for years: 80% of all carcinoma patients complained of their symptoms for less than one year [9, 15]. Symptoms of stenosis as the first event of gastric cancer are recognized in up to 20% of patients [19]. In the patients of the present study, this situation was found in 19%. Generally, stenosis is an expression of an advanced cancer stage.

In the present study, peritoneal carcinosis was detected in 36.5% of the patients with tumor stenosis compared with 26% without stenosis. This explains the impaired prognosis of patients with tumor-related stenosis in this cohort (38% vs. 51.6% five-year survival rate), as similarly reported by Watanabe et al. However, multivariate analysis did not show an independent effect on long-term outcome of patients presenting with tumor stenosis [19].

The authors conclude that tumor bleeding, tumor perforation, and tumor stenosis in gastric cancer are tumor-related complications which had a significant impact on the prognosis of the patient, as shown in univariate analysis. However, in multivariate analysis this effect was not evident, indicating that the impairment of the prognosis might be mainly due to more advanced tumor stages and co-morbidities in patients presenting with theses complications.

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