

# Type IV Borrmann gastric adenocarcinoma: analysis of curative resection results

## *Adenocarcinoma gástrico Borrmann tipo IV: análise dos resultados da ressecção curativa*

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### A B S T R A C T

**Objective:** To evaluate the results obtained with curative resection of Borrmann IV gastric adenocarcinoma (B IV) through the analysis of clinical, surgical and pathological data, identifying which of these prognostic factors were associated with survival.

**Methods:** We retrospectively analyzed 123 patients with B IV gastric adenocarcinoma undergoing surgical treatment at the Department of the pelvic-abdominal surgeries of the National Cancer Institute (INCA) from January 1997 to December 2005. The group undergoing curative resection was examined for various prognostic factors regarding overall survival. **Results:** Of the 123 patients studied, 68 underwent gastrectomy, 52 (42.3%) with curative intent and 16 (13%) palliative resection, while 55 (44.7%) had disease not subject to resection. Three postoperative deaths followed the curative resection, constituting a mortality rate of 5.76%. In nine (17.3%) patients there were technical complications, and esophagojejunal fistula seven cases, the most frequent. All technical complications and deaths occurred after total gastrectomy, which was the most commonly performed curative resection type in this series. The most common pattern of recurrence was peritoneal carcinomatosis. The location of the tumor, lymph node metastasis, lymphatic invasion and pathological staging were considered significant prognostic factors. The median survival time was 29 months, with a rate of five-year survival of 33% in patients undergoing curative resection. **Conclusion:** The curative resection of B IV gastric adenocarcinoma had a positive impact on survival of patients with the disease in stages IB, II and III, with up to 15 lymph nodes (pN2) and localized type.

**Keywords:** Stomach. Prognosis. Adenocarcinoma. Stomach neoplasms / surgery. Outcome assessment (health care).

### INTRODUCTION

The classification of advanced gastric cancer, proposed by Borrmann in 1926<sup>1</sup> according to the macroscopic aspect, is still widely used by surgeons, pathologists and endoscopists around the world<sup>2</sup>. The Borrmann type IV gastric adenocarcinoma (B IV), defined as infiltrative, may commit the stomach diffusely or in a localized fashion, in accordance with the extent of gastric involvement<sup>3</sup>. In 1858, Brinton coined the term *linitis plastica*<sup>4</sup> to describe the infiltrative gastric carcinoma occupying the entire stomach (diffuse form), also called cirrhus carcinoma in English literature<sup>3</sup>.

Approximately 10 to 15% of all gastric adenocarcinomas are classified as type B IV, and some studies show its association with factors known to be of

poor prognosis<sup>5-7</sup>. Thus, despite advances in treatment of gastric cancer, the surgical results of the B IV remains poor, with lower rates of curative resection<sup>5-8</sup> and survival<sup>6,7,9</sup> in comparison with other types of gastric carcinomas.

Although questioned<sup>10</sup>, surgical therapy remains the only treatment modality capable of providing cure. The most appropriate operation to be performed remains a subject of discussion, although there is agreement that radical resection with D2 lymphadenectomy is associated with better outcomes, with increased survival time<sup>5,7,11</sup>.

In this study we retrospectively evaluated the results obtained with resection with curative intent of B IV gastric adenocarcinoma through the analysis of clinical, surgical and pathological data, identifying which of these prognostic factors were associated with survival.

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## METHODS

We conducted a retrospective cohort study, from January 1997 to December 2005, where the medical records of 123 patients with B IV gastric adenocarcinoma undergoing surgical treatment at the Department of abdominal surgery, pelvic INCA were evaluated. Of these, 68 underwent gastrectomy, 52 with curative intent and 16 as palliative resection, while 55 were not susceptible to disease resection (Figure 1). The study was approved by the Ethics Committee in Research of the Instituto Nacional do Câncer and registered under the number 02/09.

In 52 patients undergoing surgery with curative intent we analyzed variables such as symptoms of the disease, and demographic ones such as gender and age. The pathological factors macroscopically evaluated were tumor size and its location in the stomach, while the microscopically studied were the degree of differentiation, the predominant histologic pattern, the depth of invasion of the lesion, the number of lymph nodes resected and involved in the surgical specimen, lymphatic, neural and vascular invasion, as well as pathological staging (pTNM). The surgical variables analyzed were: type of surgery (subtotal versus total gastrectomy), type of lymphadenectomy (D1 vs. D2) and operative mortality. Disease staging was performed according to the rules of the 6th edition of the Classification of Malignant Tumors of the International Union Against Cancer (UICC)<sup>12</sup>.

According to the extent of involvement, the B IV gastric adenocarcinoma was classified into two types: 1 - diffuse (*linitis plastica*) when the lesion involved the whole organ, ranging from the fundus to the pylorus; 2 - localized, when involving up to 2/3 of the stomach<sup>3</sup>.

The decision to perform total (TG) or subtotal (STG) gastrectomy was made based on the distance from the proximal tumor in relation to the gastroesophageal junction (GEJ). Patients with tumor located in the proximal half of the stomach or *linitis plastica* underwent TG, while those who had the tumor in the distal third or lower half were subjected to STG.

Curative resection was defined as that which left no macroscopic residual disease, with free surgical margins at histology, both proximal and distal, and absence of distant metastasis, i.e., an R0 resection according to the rules of UICC<sup>12</sup>.

Both the limited lymphadenectomy (D1) and the extended one (D2) were performed according to the criteria described by the Japanese Gastric Cancer Association (JGCA)<sup>13</sup>. D1 lymphadenectomy was used only in patients with a poor state of health. Distant metastases were considered the following situations observed during surgery: liver metastasis, peritoneal dissemination, positive peritoneal cytology and positive lymph nodes beyond the station N2 (level 13, 14, 15 or 16). In these cases the resection was considered palliative even with an R0 operation.

The operative mortality was defined as occurred in the first 30 days after surgery, and recurrence of the disease when it was diagnosed within three months from the resection at first considered curative. The type of recurrence was classified based on imaging studies or intraoperative and biopsy findings in patients who underwent reoperation.

### Statistical Analysis

In the sample of 52 patients who underwent operation with curative intent we evaluated 13 variables/

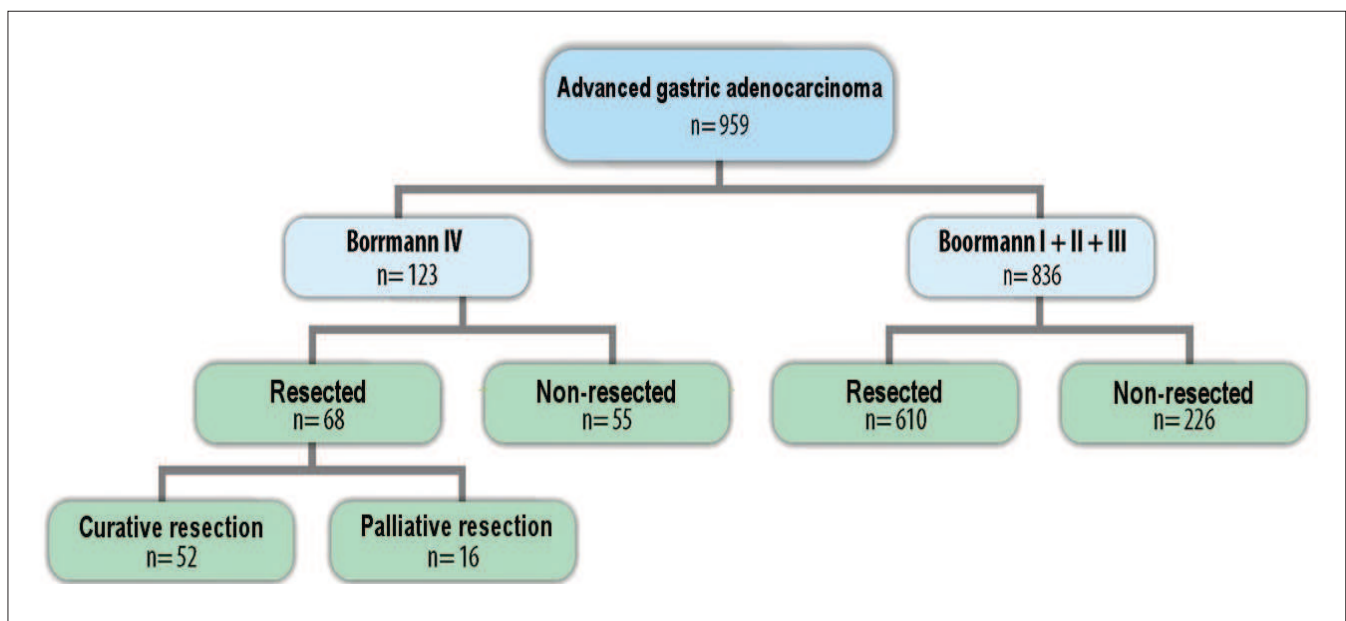


Figure 1 - Patients with advanced gastric carcinoma (>T2) operated at INCA.

prognostic factors for survival, univariate analysis being performed, with use of the Mann-Whitney and Kruskal-Wallis tests. We used multivariate analysis by logistic regression with application of the Wald test, considering the statistically significant variables found in univariate analysis, with the goal of finding significant independent prognostic factors.

The overall survival curves were estimated by the Kaplan-Meier and the difference between them was evaluated by log-rank test. All  $p$  values  $<0.05$  were considered statistically significant. Statistical analysis was done by Statistical Package for Social Science (SPSS) version 8.0.

## RESULTS

Of the 123 patients with B IV gastric adenocarcinoma, 68 underwent gastrectomy, generating a resectability rate of 55.3%. The operation with curative intent was performed in 42.3% (52/123) of patients, 44.7% (55/123) of tumors being unresectable and 13% (16/123) being operated palliatively.

In patients undergoing resection with curative intent, there were 30 men (57.7%) and 22 women (42.3%), with a median age of 62 years (ranging from 31 to 79 years). The most common symptoms were epigastric pain and weight loss, present in 75% (39/52) and 71% (37/52), respectively. The mean tumor size was 8.7 cm (4.5 to 24 cm).

The gastric segment resulting from curative resection showed several factors of poor prognosis associated with this tumor. The most common degree of differentiation was the poorly differentiated (G3), present in 80.7% (42/52), while the most frequent histological pattern was the signet ring cells, observed in 71% (37/52). As for the depth of invasion, three were T2, 48 were T3 and one T4, displaying serous invasion in 94.2% (49/52). There were no lymph node metastases (pN0) in seven patients, whereas in 45 (86.5%) they were present. Thus, by the time of the initial diagnosis, 84.6% (44/52) of B IV patients had disease in stages III or IV, or locally advanced.

The most common type of resection performed was the TG, in 67.3% (35/52) patients, while the STG was carried out in 32.7% (17/52). All *linitis plastica* cases were treated with TG, whilst the localized B IV tumors were treated with STG or TG. All these operations were accompanied by lymphadenectomy, D2 in 42 patients (80.7%) and D1 in 10 (19.3%).

The curative resections generated surgical specimens with a median of 36 lymph nodes (5-82), with eight metastatic (0-58). The median of removed and histologically examined lymph nodes was 37 (16-82) in the D2 lymphadenectomy and 20 (5-68) in D1, this difference being significant ( $p = 0.02$ ).

There were three postoperative deaths, resulting in a mortality rate of 5.76% (3 / 52), two related to esophagojejunal fistula and one due to massive pulmonary embolism. We recorded nine cases of technical complications (17.3%), esophagojejunal fistula being present in seven patients, the most frequent, followed by two duodenal stump fistulas. The deaths and complications occurred in TG. When operative mortality was related to the type of lymphadenectomy, we found that D2 dissection had lower rates of morbidity (16.6% x 30%) and mortality (4.76% x 10%), respectively, compared to D1.

Recurrence was detected in 31 (59.6%) patients and peritoneal metastasis were observed in 19 (61.3%), showing that this is the most common pattern of recurrence, followed by distant hematogenous metastasis in five cases. None of the patients who underwent curative resection received adjunctive treatment.

Univariate analysis of prognostic factors that could be associated with survival revealed that the tumor (localized versus diffuse), lymph node metastasis, lymphatic invasion and pathologic stage were significant (Table 1). When such factors were assessed by multivariate analysis, only lymphatic invasion and pathological staging were considered independent prognostic factors for survival.

The median survival time was 29 months in patients undergoing resection with curative intent, 10 months in those with palliative resection and only three months in those not operated. Overall survival in the 52 patients undergoing curative operation was 59% in two years and 33% in five years, with a median follow-up of 27 months. In the 71 patients who had non-curative operation, survival at two years was 4% and 0% in five, this difference being significant ( $p = 0.001$ ) (Figure 2). In patients with palliative resection, two year survival was 13% and 0% in five years, also significant ( $p = 0.004$ ) in favor of the curative resection. In non-resected patients it was not possible to calculate the survival rate, as there were no more survivors after two years.

Figure 3 shows the survival curves in five years with curative resection, which were 83% in patients in stage IB / II, 42% for stage III and 0% for stage IV ( $p = 0.001$ ). In analyzing the curves as a function of lymph node involvement, the five-year survival was 69% in N0 patients, 39%, 36% and 0% in groups N1, N2 and N3, respectively, this difference being also significant ( $p = 0.03$ ), as shown in figure 4.

The analysis of survival considering the location of the tumor in the stomach showed that the curative resection resulted in higher five year rates in patients with localized lesions when compared to the diffuse forms (42% vs 11%,  $p = 0.04$ ) (Figure 5). The patients submitted to STG had a five-year survival rate of 44%, while those with TG had 26% ( $p = 0.03$ ).

We recorded 34 deaths in the group of 52 patients who underwent curative resection, 31 due to disease recurrence and three arising from the operation. Ten patients

**Table 1** - Univariate analysis of patients undergoing curative resection.

Variable	Age	N	Average	SD	Median	Test	p
<60		22	26,86	20,93	25,50	U = -0.92	0,359
>60		30	34,87	29,84	28,00		
Sex							
Female		22	29,00	23,32	23,00	U = -0.55	0,578
Male		30	33,30	28,88	29,00		
Location							
Diffuse		18	23,11	30,32	18,50	U = -2.47	0,013
Located		34	35,91	23,53	30,50		
Type of operation							
TG		35	27,63	26,53	22,00	U = -1.73	0,084
STG		17	39,41	25,39	31,00		
Histologic pattern							
Signet Ring		37	32,00	26,61	27,00	U = -0.38	0,704
Tub / Pap		11	30,55	28,26	21,00		
NE		4					
Degree of differentiation							
G1 / G2		10	22,10	24,65	11,50	U = -1.54	0,122
G3		42	33,71	26,72	29,00		
Lymphadenectomy							
D1		10	23,90	19,27	25,50	U = -0.87	0,384
D2		42	33,29	27,84	28,00		
Intrusion depth							
T2		3	18,33	16,44	12,00	U = -0.78	0,452
T3 / T4		49	32,29	26,91	27,00		
Metastasis linfonodal							
IN		7	50,43	17,11	44,00	# H = 15.18	0,002
Ni		16	32,00	26,89	22,50		
N2		15	38,27	31,75	31,00		
N3		14	14,14	11,45	11,50		
Lymphatic invasion							
Yes		32	24,78	27,28	18,00	U = -3.20	0,001
Not		20	42,20	21,79	36,00		
Venous invasion							
Yes		14	29,50	20,87	28,00	U = -0.07	0,942
Not		38	32,21	28,52	25,50		
Neural invasion							
Yes		45	30,93	27,62	24,00	U = -0.94	0,356
Not		7	35,00	19,04	33,00		
Stadium							
IB/II		8	45,63	20,87	41,50	H = 15.84	0,001
III		30	38,27	31,75	31,00		
IV		14	14,14	11,4-6	11,50		

**DP:** standard deviation; **U:** Mann-Whitney test; **TG:** gastrectomy total; **STG:** subtotal gastrectomy; **Tub/Pap:** tubular/papilliferum; **NE:** not specified; **H:** Kruskal-Wallis test.

were lost to follow-up and eight were alive with a survival rate of 37, 38, 39, 47, 53, 68, 73 and 132 months, all without evidence of disease.

## DISCUSSION

To analyze the various prognostic factors that affected the survival of our patients who underwent curative

surgical treatment and to compare them with other results found in literature is a daunting task. In most of these works, such variables were analyzed in groups of patients undergoing any type of gastric resection, without distinguishing curative from palliative approaches<sup>3,5,7,9,14-19</sup>, while a smaller number detained on the study of these factors solely in the curative operation<sup>8,11,20</sup>, similar to our series.

Like our study, several others confirmed that the B IV was associated with known factors of poor

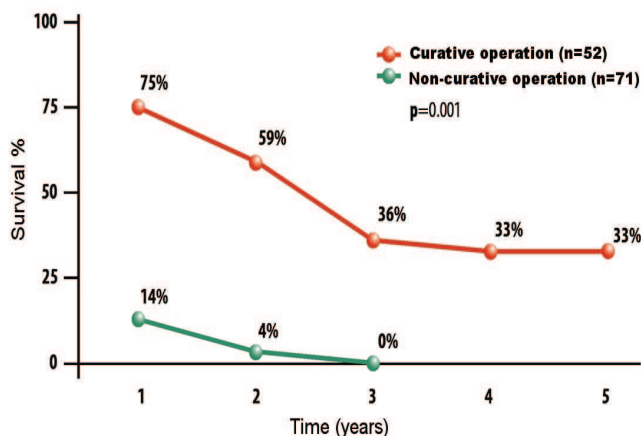


Figure 2 - Survival of patients submitted to curative and non-curative resection.

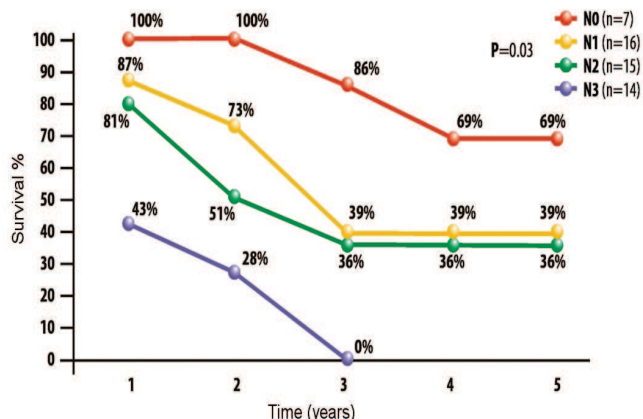


Figure 4 - Survival of patients submitted to curative resection according to lymph node involvement.

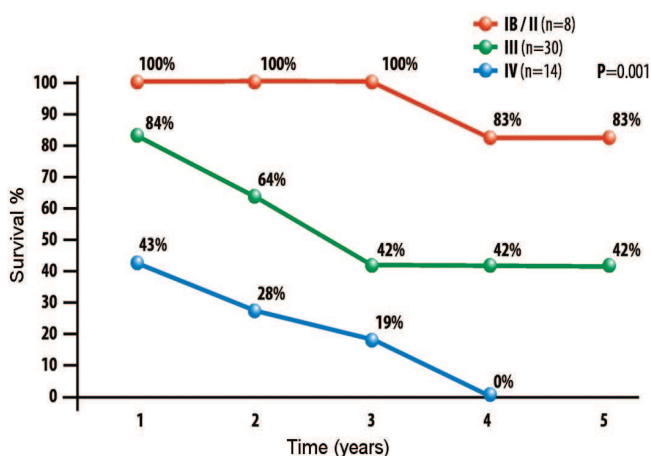


Figure 3 - Survival of patients submitted to curative resection according to pathological staging (pTNM).

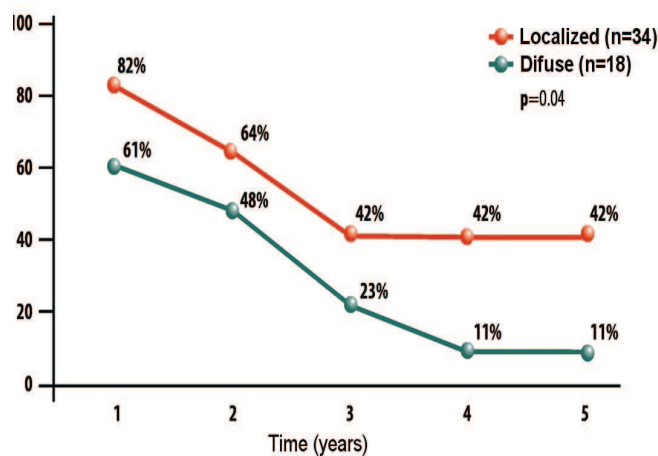


Figure 5 - Survival of patients submitted to curative resection according to tumor location.

prognosis<sup>5-7,11,14,16</sup>. Diagnosis in advanced stages, poorly differentiated histology, serosal invasion and high incidence of lymph node involvement are factors that directly influence the prognosis, causing lower rates of curative operations, which can vary between 31 and 52%<sup>3,5-8,20</sup> and are in agreement with our data, which was 42.3% (52/123). Some series have shown that up to 2/3 of these patients underwent non-curative operations<sup>17,20</sup>, which is why Aranha<sup>10</sup> states that *linitis plastica* is not a surgical disease. Moreover, there are other reports showing that gastrectomy should be avoided in B IV patients with positive peritoneal cytology<sup>21,22</sup>.

Despite advances in the treatment of gastric cancer, surgical results of B IV adenocarcinomas remain poor, the worst among all gastric carcinomas<sup>19</sup>. The survival rates at five years after curative gastrectomies rang from 11% to 33.4%<sup>5,7,17,19</sup>, confirming that they have lower rates compared to other Borrmann types<sup>6,7,9</sup>. In our patients, the overall survival at five years was 33%, similar to the ranges of variation found in the literature.

One of the main independent prognostic factors for survival in B IV gastric carcinoma was the depth of invasion of the lesion (pT)<sup>16,17,19,20</sup>. Analysis of 65 patients who underwent curative resection showed the absence of serosal invasion (T2 tumors) as the only variable of significant value, resulting in a five-year survival rate of 55.6% in this subgroup<sup>17</sup>.

Another report<sup>19</sup> showed that 100% of patients with T2 tumors were alive five years after tumor resection, whereas only 24% with T3 tumors survived five years after resection. As our sample consisted almost exclusively of tumors that had serosal invasion (49/52), we could not assess the real impact of this important prognostic factor on survival.

The presence of lymph node metastases was a significant prognostic factor for survival in our patients who underwent curative resection, these findings being similar to those found in other studies<sup>3,8,9,11,14,16,17,20</sup>. Moreaux<sup>3</sup> and Kodera<sup>8</sup> highlighted lymph node involvement as the only variable of significant value in their samples, which was considered, in other reports, an independent factor for

survival<sup>14,16,20</sup>. Our five-year survival rate in patients without lymph node involvement was 69%, while all others with more than 15 invaded lymph nodes (pN3) did not survive more than three years. Kikuchi<sup>11</sup> showed that all B IV patients with lymph node metastases beyond the level 2 (N2) submitted to curative resection died within two years. Still, there is potential for cure by radical operation with D2 lymphadenectomy in cases where the lymph node involvement is restricted to the level 2.

The TNM stage was another factor that significantly influenced survival in our sample of curative resection. We obtained a very expressive survival rate at five years in its earliest stages, i.e. IB / II (83%), satisfactory in stage III (42%) and poor in stage IV (0%), close to the results obtained by Kinugasa<sup>19</sup> (78%, 35% and 4%, respectively). These data show that stage IV behaves as a systemic disease, scarcely benefiting from the R0 resection with regard to overall survival.

The localized or diffuse presentation, as well as the presence or absence of lymphatic invasion, were other factors that were significantly associated with survival after curative resection, similar to other series<sup>11,17</sup>, notwithstanding Kunisaki<sup>20</sup> having demonstrated that the presence of lymphatic invasion had not altered survival. Our survival rate at five years was much higher when the tumor was localized (42% versus 11%), which allows us to characterize this subgroup as it was associated with greater benefit with radical surgery.

Just as in other series<sup>17,20</sup>, the type of surgery (TG versus STG) was not considered a significant prognostic factor after univariate analysis in our study. Our five-year survival rate after STG was higher compared to TG (44% versus 26%,  $p = 0.03$ ). This significant difference could be justified by the fact that STG has been used in tumors with a distal location and TG carried out in more proximal lesions or in cases of *linitis plastica*, tumors of known poor prognosis. These results are different from Hamy's<sup>18</sup>, who claims to be always necessary to apply TG to B IV tumors due to their intraparietal mode of spread in the stomach.

It is noteworthy that demographic variables such as age and sex were not statistically significant, like in other series with patients undergoing curative resection<sup>11,20</sup>.

Factors such as pathological grade and venous invasion were not associated with survival in our patients, as well as in those operated by Kunisaki<sup>20</sup>. Another factor, the histological pattern, was also not significant, just as in the reporting of Kinugasa<sup>19</sup>. Regarding the presence of neural invasion, it was not possible to compare our results with the literature, since none of the studies surveyed considered this variable after curative resection.

Although it was not the objective of our study to discuss the most suitable operation for treating B IV gastric adenocarcinoma, this topic generates great controversy. Aranha *et al.*<sup>10</sup> recommend TG when the disease is confined to the stomach or regional lymph nodes, but consider it

always palliative, according to a median survival of 13.6 months. Should there be a contiguous invasion of adjacent organs, the same authors contraindicate any type of resection.

Furukawa *et al.*<sup>23</sup>, based on high incidence of invasion of adjacent viscera and lymph node metastases in B IV stomach tumors have advocated the abdominal upper left quadrant evisceration, this procedure being called the Appleby procedure, which is the systematic resection of the entire stomach, spleen, body and tail of the pancreas, transverse colon, gall bladder and left adrenal gland, associated with extensive lymphadenectomy. They compared the findings of a group of 30 patients undergoing this procedure with other 30 patients undergoing TG with pancreatic-splenectomy, all patients with B IV adenocarcinoma. In addition to being able to demonstrate that mortality was similar in both groups, they observed that in stage IV cases no differences were found in survival rates over three years, unlike the stages II and III, which showed significant difference in benefits of the extended resection (83.3% vs 42.2%,  $p < 0.05$ ). Thus, they concluded that this procedure should be used routinely, except for cases in stage IV. However, there are contrary opinions<sup>16,20</sup> demonstrating that resection combined with other involved adjacent organs does not improve survival. Sharing the same impression, Chen<sup>9</sup>, in a retrospective study, showed similar survival rates when comparing enlarged resections such as TG associated with pancreatic-splenectomy versus STG or TG alone, suggesting that it is necessary to conduct a randomized clinical trial to determine the best operative strategy in B IV gastric carcinomas.

The type of lymphadenectomy, as a prognostic factor in B IV tumors subjected to curative gastrectomies, is very controversial, just as in gastric cancer in general. Yoshikawa<sup>17</sup> consider the D2 dissection a significant prognostic factor for survival, while Kunisaki<sup>20</sup> does not characterized it as a significant variable when compared to D1. In our series, median survival was 28 months in D2 lymphadenectomy and 25.5 months in D1, not representing a statistically significant difference.

A D2 lymphadenectomy was performed in most of our curative resections (42/52) and resulted in lower rates of morbidity and mortality in relation to D1. We believe that at least two factors contributed to these better results: the experience of surgeons with the D2 technique and the worst patients' clinical conditions in which the option was D1. While not proving to be a prognostic factor for improved survival in our study, we consider that D2 lymphadenectomy, depending on the clinical condition of the patient, should be routinely performed because it may allow a better assessment of nodal stations and eventually decrease the chance of stage worsening, the so-called Will Rogers phenomenon<sup>24</sup>.

As shown in our series and in other authors' findings<sup>5,6,8,15</sup>, peritoneal carcinomatosis was the most common pattern of recurrence in patients with B IV tumors

undergoing curative gastrectomy, observed in 61.2% of our relapses.

Serosal invasion, considered an important risk factor for peritoneal recurrence after radical surgery<sup>25</sup>, was present in 94.2% (49/52) of our curative resections. Otsuji *et al.*<sup>14</sup> Identified regional lymph node metastases as the only independent variable in predicting the development of peritoneal carcinomatosis in patients with B IV gastric carcinoma. It is noteworthy that 86.5% (45/52) of our sample had positive lymph nodes. These two factors, present in most of our patients, could justify deeming the peritoneum

the major site of failure after our gastrectomies with curative intent.

Resection remains the only curative treatment in gastric cancer, although most patients undergoing curative resection will develop locoregional or distant recurrence, so it is of great interest to develop strategies to prevent recurrences and improve global survival.

We conclude that the curative resection of B IV gastric adenocarcinoma had a positive impact on survival of patients with stages IB, II and III, with up to 15 lymph nodes (pN2) and localized type.

## R E S U M O

**Objetivo:** Avaliar o resultado obtido com a ressecção de intenção curativa do adenocarcinoma gástrico Borrmann IV(B IV), através da análise de variáveis clínicas, cirúrgicas e anatomopatológicas, identificando quais destes fatores prognósticos se associaram à sobrevida. **Métodos:** Foram analisados retrospectivamente, no período de janeiro de 1997 a dezembro de 2005, 123 pacientes com adenocarcinoma gástrico B IV submetidos ao tratamento cirúrgico no Serviço de Cirurgia Abdômino-Pélvica do Instituto Nacional de Câncer (INCA). O grupo submetido à ressecção curativa teve analisado diversos fatores prognósticos com relação à sobrevida global. **Resultados:** Dos 123 pacientes estudados, 68 foram submetidos à gastrectomia, 52 (42,3%) com intenção curativa e 16 (13%) como ressecção paliativa, enquanto 55 (44,7%) tiveram doença não passível de ressecção. Três óbitos no pós-operatório seguiram-se à ressecção curativa, configurando uma taxa de mortalidade de 5,76%. Em nove (17,3%) pacientes ocorreram complicações técnicas, sendo a fístula esofagojejunal com sete casos, a mais frequente. Todos os óbitos e complicações técnicas ocorreram após gastrectomias totais, que foi o tipo de ressecção curativa mais realizada nesta série. O padrão de recidiva mais comum foi a carcinomatose peritoneal. A localização do tumor, metástase linfonodal, invasão linfática e estadiamento patológico foram considerados fatores prognósticos significantes. O tempo de sobrevida mediano foi de 29 meses, com taxa de sobrevida em cinco anos de 33% nos pacientes submetidos à ressecção curativa. **Conclusão:** A ressecção com intenção curativa do adenocarcinoma gástrico B IV apresentou um impacto positivo na sobrevida dos pacientes com a doença nos estágios IB, II e III; com até 15 linfonodos comprometidos (pN2) e no tipo localizado.

**Descritores:** Estômago. Prognóstico. Adenocarcinoma. Neoplasias gástricas/cirurgia. Avaliação de resultados (cuidados de saúde).

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