Prognostic role of positive peritoneal cytology in patients with resectable gastric cancer

Valor prognóstico da citologia positiva no lavado peritoneal de pacientes com câncer gástrico ressecável

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A B S T R A C T

Objective: To evaluate the prognostic value of positive peritoneal lavage in patients with gastric cancer without signs of peritoneal or hematogenous spread. **Methods**: We evaluated patients with gastric adenocarcinoma treated with curative intent operation. The peritoneal lavage was classified as positive or negative for neoplastic cells. We obtained demographics, performance status, histology and type of surgery. The results were statistically compared and were considered significant for values of $p < 0.05$. **Results**: We included 72 patients with gastric adenocarcinoma. During a mean follow up of 26 months (one to 39 months) we observed 20 local or distant recurrences and 21 deaths. Only the presence of lymph node metastases and the need for resection of adjacent organs were associated with a significant reduction in relapse-free survival. There was a significant reduction in overall survival in patients with angio-lymphatic invasion, lymph node metastasis, requiring resection of multiple organs, need for total gastrectomy and greater invasion of the gastric wall. The presence of tumor cells in the peritoneal cavity was associated with worse overall survival, but without statistical significance. **Conclusion**: There was no statistically significant associations between positive peritoneal citology and recurrence-free survival or overall survival among patients with resectable gastric cancer.

Key words: Gastrectomy. Stomach neoplasms. Peritoneal neoplasms. Peritoneal lavage. Survival rate.

INTRODUCTION

The prognostic value of the presence of free tumor cells in the peritoneal cavity in patients with gastric cancer has been quite studied [1-4]. In the second edition of the Japanese Classification of Gastric Carcinoma, published by the Japanese Gastric Cancer Association, in 1998, the presence of tumor cells in the peritoneal lavage was already classified as stage IV [5]. The seventh edition of the Classification of Malignant Tumors – TNM, 2009, also began to classify this condition as distant metastasis[6]. The presence of malignant cells in the peritoneal lavage has been used to determine changes in therapeutic approach. Some studies suggest that these patients do not benefit from extended operations [7], or that radical gastrectomy only benefits the patients without lymph node metastasis[8]. Furthermore, several authors propose that patients with positive peritoneal lavage should receive additional treatment, either adjuvant [8,9] or neoadjuvant [10,11].

There is only one study on this topic published in Brazil [2], so that little is known about the profile of the spread of free cells in the peritoneum in our patients with gastric carcinoma. In this study, positive cytology was found in 6.8% of patients included, and in all of them tumor parietal invasion reached the serosa. Furthermore, the presence of malignant cells in the peritoneal lavage was associated with lower mean survival. Adequate knowledge of standard peritoneal dissemination is an important step, so that new therapeutic strategies, appropriate to our reality, are outlined.

The aim of this study was to evaluate the prognostic value of positive peritoneal lavage in patients with gastric cancer without signs of peritoneal or hematogenous spread.

METHODS

We evaluated patients with gastric adenocarcinoma undergoing surgery with curative intent between May 2007 and August 2008. We included: those who did not receive neoadjuvant chemotherapy, with

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resectable tumors, without signs of peritoneal dissemination and without distant metastases. The study was submitted to the Ethics Committee Researched In Araújo Jorge Hospital, being approved under number 13/2007.

In patients who met the inclusion criteria, the pelvic fornix was washed with 200ml of saline. Cytological analysis was performed with 20 ml of peritoneal lavage fluid fixed in 5ml of 92%ethanol. After centrifugation at 2000 rpm for five minutes, the sediment was stained by the methods of hematoxylin-eosin and Papanicolaou. The immunohistochemical evaluation of the sediment was made by the streptavidin-biotin immunoperoxidase method and the immunodetection, with specific antibodies (Berp4, p53, CK 20 and CK 7). The evaluation of neoplastic cells was performed by an experienced pathologist and the result was known one week after surgery.

We obtained data pertaining to demographics, performance status (PS)[12], histological type and operation performed. Histological evaluation of the resected specimen was made according to the rules of the second edition of the Japanese Classification of Gastric Carcinoma 5 and staging was done according to the sixth edition of the Classification of Malignant Tumors – TNM[13]. Patients with pathologic stage (TNM-UICC) II, III or IV were referred for adjuvant chemotherapy. Outpatient follow-up was performed every three months in the first year and every six from the second year on. The research of recurrence was made by clinical history, physical examination and laboratory tests, according to clinical indication (chest radiography, endoscopy, ultrasonography and computed tomography of the abdomen and/or chest).

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as absolute numbers and percentages. Proportions were compared using the Chi-square or the Fisher's exact test. Continuous variables were analyzed with the Student t test. Survival rates were estimated by the Kaplan-Meier method [14] and compared by log-rank test.B.

RESULTS

We included 72 patients with histologically confirmed gastric adenocarcinoma, aged 27-87 years (median 61.5), 46 of them were men (64%). Almost all (97%) had PS d" 2.0. All patients had resectable tumors and showed no signs of distant metastases pre or intraoperatively. Partial gastrectomy was performed in 42 patients, and in two it was also necessary to perform a segmental colectomy. The remaining 30 patients underwent total gastrectomy; of these, 15 had also at least one adjacent organ resected. In the latter group, the most frequently resected organ was the spleen (12), followed by distal esophagus (4), liver (3), colon (2), and pancreas (2). In 62 patients D2 lymphadenectomy was performed. D1 lymphadenectomy was performed in the remaining individuals. The average number of lymph nodes removed was 35.2 (SD = 18.9). Affected surgical margins observed under light microscopy were found in five patients (6.9%). Adjuvant chemotherapy was performed in 40 (55.5%). The peritoneal lavage cytology was positive in eight patients (11.1%). Clinical and histopathological features are presented in Table 1 and are equally distributed between the two groups. The operative morbidity was 12.5% and mortality of 5.5%.

In the postoperative follow-up of 26 months (range 1-39), 20 local or distant recurrences and 21 deaths occurred. The analysis of relapse-free survival for the different variables are listed in Table 2. The only statistically significant association was observed for the variables nodal metastasis and resection of adjacent organs. There was no association between the presence of tumor cells in the peritoneal lavage and relapse-free survival (Figure 1).

Table 3 shows the association between overall survival at three years and the variables listed. There was a significant reduction in overall survival of patients who required total gastrectomy, those who needed resection of adjacent organs and those who had greater gastric wall invasion, lymph node metastasis or angiolymphatic invasion in the resected specimen. Kaplan-Meier analysis showed a significant association between overall survival and gastric wall invasion (Figure 2) and the presence of nodal metastasis (Figure 3). The presence of malignant cells in the peritoneal lavage was associated with no significant reduction in overall survival (Table 3 and Figure 4).

DISCUSSION

The preoperative adoption of new imaging methods has greatly improved the locoregional staging of gastric cancer [15-17]. Nevertheless, the preoperative evaluation of peritoneal dissemination is still poor. A recent meta-analysis showed very low sensitivity, less than 34%, for detection of peritoneal metastases by radiological methods (conventional ultrasound, endoscopic ultrasound, computed tomography and positron emission tomography)[18].

The best method for diagnosis of peritoneal dissemination is still thorough inventory of the cavity during laparotomy or laparoscopy. Even if there are no macroscopic signs of involvement of the peritoneum, the presence of malignant cells in the peritoneal lavage has been reported by several authors, with rates ranging from 6.8 to 23% [2-4,10,11]. The present study revealed that 11.1% of patients with pre and intraoperative diagnosis of localized disease were already carriers of free malignant cells in the peritoneum, pointing to a more aggressive disease behavior. Progression beyond the muscle layer, lymph node metastasis and angiolymphatic invasion have been linked to the presence of malignant cells in the peritoneum [3,4,19], which was not observed in this series.

Table 1 – Clinical and pathological characteristics of patients.

Variable	Feature	Total (n=72)	NegativeCytology (n=64)	PositiveCytology (n=8)	*p*
Gender	M	46	43	3	0.21
	F	26	21	5	
Age	Average	60.4	60.8	57.5	0.52
	SD	13.3	13.3	13.5	
PS	0-1	64	59	5	0.08
	2-3	8	5	3	
Gastrectomy	Partial	42	36	6	0.54
	Total	30	28	2	
Resection ofadjacent organs	Not	55	48	7	0.78
	Yes	17	16	1	
Lymphadenectomy	D1	10	7	3	0.15
	D2	62	57	5	
Invasion ingastric wall	T_{1-2}	31	26	5	0.44
	T_{3-4}	40	37	3	
	T_X	1	1	0	
Nodal metastasis	N_0	25	22	3	0.99
	N_+	47	42	5	
Classificationof Lauren	Intestinal	41	36	5	0.99
	Diffuse	29	26	3	
	Not reported	2	2	0	
angiolymphatic Invasion	Absent	19	16	3	0.71
	Present	53	48	5	

SD, standard deviation; PS, performance status; D1, group 1 nodal dissection; D2, nodal dissection of the geoups 1 and 2; T_{1-2}, invasion into the subserosa; T_{3-4}, invasion of adjacent organs or serosa; T_x, invasion not evaluated; N_0, absence of nodal metastasis; N_+, presence of nodal metastasis.

Table 2 – Association between relapse-free survival and surgical and pathological features.

Variable	Feature	RFS 3a (%)	HR	95% CI	*p*
Gastrectomy	Partial	52.9	1		
	Total	56.1	1.98	0.78 - 5.01	0.15
Resection ofadjacent organs	Not	58.6	1		
	Yes	43.6	3.91	1.27 -12.07	0.02*
Lymphadenectomy	D1	71.4	1		
	D2	52.8	1.14	0.28 - 4.63	0.85
Invasion ingastric wall	T_{1-2}	78.5	1		
	T_{3-4}	29.9	2.21	0.92 - 5.35	0.08
Nodal metastasis	N_0	88.1	1		
	N_+	29.9	4.06	1.67 - 9.90	0.002*
Classificationof Lauren	Intestinal	62.0	1		
	Diffuse	47.4	0.77	0.31 - 1.88	0.56
Invasionangiolinfática	Missing	54.6	1		
	This	47.7	2.90	0.94 - 8.93	0.06
Cytology ofperitoneal lavage	Negative	53.3	1		
	Positive	72.9	1.48	0.27 - 8.09	0.65

RFS 3a, relapse-free survival rate in three years; HR, hazard ratio; D1, group 1 nodal dissection; D2, nodal dissection of the groups 1 and 2; T_{1-2}, invasion into the subserosa; T_{3-4}, invasion of adjacent organs or serosa; N_0, absence of nodal metastasis; N_+, presence of nodal metastasis. Statistically significant difference.*

In our study, only the presence of lymph node metastasis and the need for resection of adjacent organs were related to the reduction of relapse-free survival. Failure to demonstrate association between survival and gastric wall invasion and the presence of cells in the peritoneal fluid was certainly due to the small sample size,

Table 3 – Association between overall survival and surgical and pathological features.

Variable	Feature	OS 3a (%)	HR	95% CI	*p*
Gastrectomy	Partial	79.2	1		
	Total	45.7	3.04	1.23 - 7.51	0.01*
Resection ofadjacent organs	No	77.9	1		
	Yes	35.7	4.58	1.61 -13.03	0.004*
Lymphadenectomy	D1	68.6	1		
	D2	67.1	0.87	0.24 - 3.20	0.83
Invasion ingastric wall	T_{1-2}	79.7	1		
	T_{3-4}	58.2	2.60	1.07 - 6.33	0.03*
Nodal metastasis	N_0	91.5	1		
	N_+	53.6	3.50	1.43 - 8.56	0.006*
Classificationof Lauren	Intestinal	67.2	1		
	Diffuse	70.6	1.06	0.42 - 2.68	0.89
Angiolymphatic Invasion	Absent	75.9	1		
	Present	38.9	5.37	1.84 -15.72	0.002*
Cytology ofperitoneal lavage	Negative	68.7	1		
	Positive	48.6	1.88	0.41 - 8.48	0.41

OS 3a, overall survival rate in three years; HR, hazard ratio; D1, group 1 nodal dissection; D2, nodal dissection of the groups 1 and 2; T_{1-2}, invasion into the subserosa; T_{3-4}, invasion of adjacent organs or serosa; N_0, absence of nodal metastasis; N_+, presence of nodal metastasis. Statistically significant difference.*

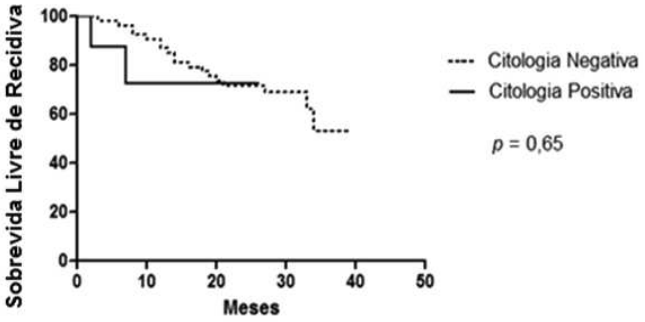

Figure 1 – *Kaplna-Meier curves of relapse-free survival according to the presence of tumor cells in the peritoneal lavage.*

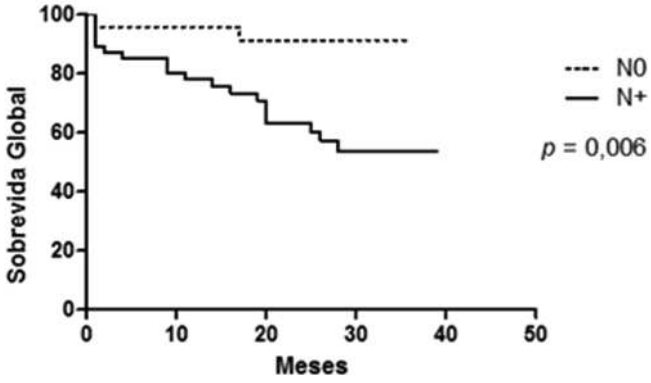

Figure 3 – *Kaplan-Meier curves of overall survival according to the presence of lymph node metastasis.*

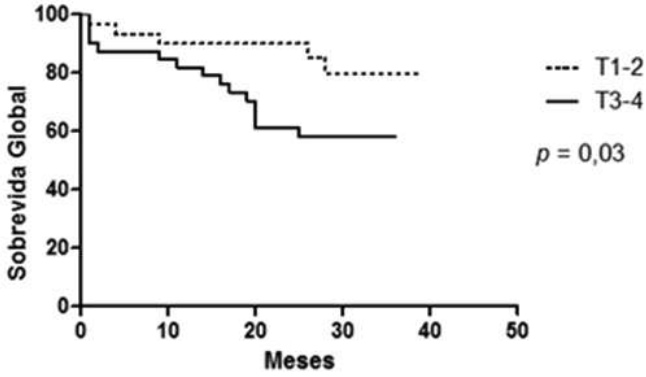

Figure 2 – *Kaplan-Meier curves of overall survival according to tumor invasion in the gastric wall.*

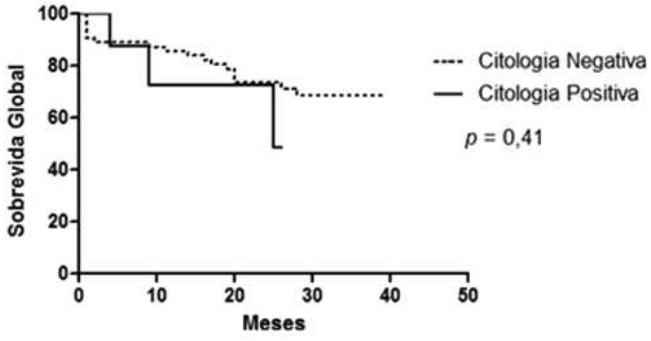

Figure 4 – *Kaplan-Meier curves of overall survival according to the presence of free tumor cells.*

since these prognostic factors are well known and universally accepted [20].

The reduction in overall survival has been associated with depth of infiltration of the gastric wall, to the presence of lymph node disease and various studies also have shown a positive association with positive peritoneal lavage [2-4,19,21]. In the present study, a significant reduction in overall survival at three years was observed in patients with greater tumor invasion in the gastric wall, lymph node metastasis, the presence of angiolymphatic invesion and also the need for total gastrectomy. It is a remarkable fact that overall survival at three years was lower among patients who had positive peritoneal lavage, but without statistical significance. The low number of this event in this sample is the cause of the failure to demonstrate the value of this important prognostic factor for overall survival.

In conclusion, this study showed no significant association between positive peritoneal lavage and overall survival or relapse-free survival in patients with resectable gastric cancer. However, these results confirm angiolymphatic invasion, lymph node metastasis, depth of invasion in the gastric wall, need for total gastrectomy and resection of adjacent organs as important prognostic factors.

R E S U M O

Objetivo: *Avaliar o valor prognóstico do lavado peritoneal positivo em pacientes com câncer gástrico sem sinais de disseminação peritoneal ou hematogênica.* ***Métodos:*** *Foram avaliados os pacientes com adenocarcinoma gástrico tratados com operação de intenção curativa. O lavado peritoneal foi classificado como positivo ou negativo para células neoplásicas. Foram obtidos dados demográficos,* performance status*, histológicos e tipo de operação realizada. Os resultados foram estatisticamente comparados e considerados significantes para valores de* p*<0,05.* ***Resultados:*** *Foram incluídos 72 portadores de adenocarcinoma gástrico. Durante seguimento médio de 26 meses (um a 39 meses) foram observadas 20 recidivas locais ou à distância e 21 mortes. Apenas a presença de metástases linfonodais e a necessidade de ressecção de órgãos adjacentes foram associados à redução significativa da sobrevida livre de recidiva. Houve redução significativa da sobrevida global entre os pacientes com invasão angiolinfática, metástase linfonodal, com necessidade de ressecção de múltiplos órgãos, necessidade de gastrectomia total e maior invasão da parede gástrica. A presença de células tumorais na cavidade peritoneal foi associada a pior sobrevida global, porém sem significância estatística.* ***Conclusão:*** *Não foi demonstrada associação significativa entre o lavado peritoneal positivo e a sobrevida livre de recidiva ou de sobrevida global entre pacientes com câncer gástrico ressecável.*

Descritores: *Gastrectomia. Neoplasias gástricas. Neoplasias peritoneais. Lavagem peritoneal. Taxa de sobrevida.*

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