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Original Article

T4B GASTRIC CARCINOMA: 12 YEARS OF EXPERIENCE AT AN UNIVERSITY HOSPITAL

Adenocarcinoma gástrico T4b: experiência de 12 anos em hospital universitário

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ABSTRACT – ***Background*:** Gastric neoplasia is a heterogeneous and multifactorial disease and its incidence and mortality vary widely based on geographic location. Approximately 60% of the diagnoses of patients from occidental countries were made on the stages III and IV. The best treatment still is to realize a surgical procedure. ***Aim*** **-** Identify the epidemiological aspects of the patients diagnosed with T4b gastric adenocarcinoma. ***Methods*** **-** The study was observational, transversal and retrospective; it was also based on secondary sources from patients diagnosed with T4b gastric adenocarcinoma, through pathologic stages. A total of 815 charts were analyzed and 27 patients studied. The variables were: demographic aspects, main symptoms, risk factors, access to health system, surgical aspects, morbidity, mortality and survival. ***Results*** **–** Were included 22 men (81,5%) and five woman (18,5%), in the age group between 38 and 87 years old - median age of 58. The time, in months, to access the health system varied from one to 120, average of 12,5 months. The most prevalent signs and symptoms were: weight loss 23 (85,2%), epigastric pain 22 (81,5%), vomit 16 (59,3%) and gastric fullness 12 (44,4%). The frequency of the affected adjacent body structures was: pancreas 8 (29,6%), liver 7 (25,9%), transverse colon 6 (22,2%), small intestine 6 (22,2%), mesocolon 3 (11,1%), spleen 1 (3,7%) and gallbladder 1 (3,7%). Postoperative morbidity occurred in 51, 85% of the patients. There were a significative association between surgical mortality and the occurrence of fistula/ dehiscence, septic shock and bleeding. The survival rate after six months was 63,27%. ***Conclusion*** **-** The mean time between onset of symptoms and access to specialized health services was high. More than half of the patients had postoperative morbidities. Patients who had fistula / dehiscence, bleeding and septic shock were significantly associated with surgical mortality. The survival rate after six months was 63.27%.

HEADINGS - Gastric cancer. Surgery, survival.

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RESUMO – ***Racional*:** A neoplasia gástrica é doença heterogênea e multifatorial, com incidência e mortalidade variando geograficamente. Aproximadamente 60% dos diagnósticos em pacientes de países ocidentais ocorrem nos estádios III ou IV. Nestes doentes, o melhor tratamento consiste na realização de procedimento cirúrgico. ***Objetivo*** **-** Identificar os aspectos epidemiológicos de pacientes diagnosticados com adenocarcinoma gástrico T4b. ***Métodos*** **-** Estudo observacional, transversal, retrospectivo, de fonte secundária, dos pacientes diagnosticados com adenocarcinoma gástrico T4b através de estadiamento patológico. Foram analisados 815 prontuários, sendo 27 pacientes estudados. As variáveis investigadas foram: aspectos demográficos, principais queixas, fatores de risco, acesso ao serviço de saúde, aspectos cirúrgicos, morbidade, mortalidade e sobrevida. ***Resultados*** **–** Vinte e dois eram homens (81,5%) e cinco mulheres (18,5%) com idade variando de 38 a 87 e média de 58,78 anos. O tempo de acesso ao serviço, em meses, variou de 1 a 120, com média de 12,5. Os sinais e sintomas mais prevalentes foram: perda de peso 23 (85,2%), epigastralgia 22 (81,5%), vômitos 16 (59,3%) e plenitude gástrica 12 (44,4%). A frequência de acometimento das estruturas adjacentes foi: pâncreas oito (29,6%), fígado sete (25,9%), cólon transverso seis (22,2%), intestino delgado seis (22,2%), mesocólon três (11,1%), baço um (3,7%) e vesícula biliar um (3,7%). Morbidades pós-operatórias ocorreram em 51,85% dos pacientes. Houve associação significativa entre mortalidade cirúrgica e ocorrência de fístula/deiscência, choque séptico e sangramento. A sobrevida ao final de seis meses foi de 63,27%. ***Conclusão*** - A média do tempo entre início dos sintomas e acesso ao serviço de saúde especializado foi elevada. Mais da metade dos pacientes apresentaram morbidades pós-operatórias. Os pacientes que apresentaram fístula/deiscência, sangramentos e choque séptico tiveram associação significativa com mortalidade cirúrgica. A sobrevida ao final de seis meses foi de 63,27%.

DESCRITORES - Carcinoma gástrico. Cirurgia, sobrevida.

INTRODUCTION

Gastric neoplasia is a heterogeneous and multifactorial disease. Its incidence and mortality varies geographically and shows higher rates in east Asia[14]. It is considered the fourth most common cause of cancer. More than 70% of the cases occur in developing countries. Moreover, the incidence rate is about twice as high in males than in females[3]. Several different countries, including Brazil have been showing a decrease in the incidence and mortality; however it is still one of the most frequent tumor sites[18].

The number of new cases of gastric neoplasia estimated in Brazil, in the year of 2012 is 20.090, 12.670 men and 7.420 women. These numbers correspond to an estimated risk of 13 new cases every 100,000 men and seven in women. Mortality in 2010 was 22.035[3].

Leaving aside non-melanoma skin tumors, stomach cancer in males is the second most frequent in the North (11/100,000) and Northeast (9/100,000) regions and the fourth in the South (16/100,000), Southeast (15/100,000) and Midwest (14/100,000) regions.

As to females, it occupies the fourth position in the Northern region (6/100,000), the fifth in the Midwest region (7/100,000) and the sixth in the Southeast (9/100,000), South (8/100,000) and Northeast (6/100,000) regions[3].

Locally advanced gastric cancer, classified as T4, is defined as one in which the tumor grows into the serosa (T4a) or into organs surrounding the stomach (T4b). It often has worse prognoses due to simultaneous metastasis, distant metastasis, peritoneal implants, liver metastasis and/or lymph node involvement[8].

Approximately 60% of the diagnoses in patients of western countries occur on the third and fourth stages. In these cases, the only effective treatment is surgery[19].

The main goal of this study is identify the epidemiological aspects of patients diagnosed with T4b gastric adenocarcinoma.

METHODS

It consists on a transversal, observational, retrospective study. The data collection was executed through the review of medical records available by the Department of Medical Files and Statistics, after approval by the Research Ethics Committee of the University Hospital João de Barros Barreto, Federal University of Pará, Belém, PA, Brazil.

The targeted population of this study was all the patients diagnosed with T4b gastric adenocarcinoma, through pathological staging during the period of January of 2000 and January of 2012. The definition of T4b gastric adenocarcinoma used was the one mentioned in the seventh edition of the UICC/TNM classification, which defined the T4b as the tumor that invades surrounding body structures. Furthermore, as proposed by Park et al.[17] and Kim et al.[10], the transverse mesocolon was included as adjacent structure in this study and its invasion by the tumor was considered as T4b.

A total of 815 medical records were made available; 86 of them were not found, 125 were not confirmed as gastric neoplasia and 604 were confirmed as gastric neoplasia. From this number 587 were adenocarcinoma, and 27 of these were T4b adenocarcinoma.

The investigated variables were: gender, age, occupation, origin, main complaints, risk factors, access time to the health system (period between onset of symptoms and first care in the health system), time between diagnosis and treatment, type of operation and lymphadenectomy performed, purpose of the surgical procedure, anatomical location of the tumor, adjacent structure affected, postoperative morbidity, surgical morbidity (30-day postoperative mortality) and survival.

The definition of curative surgery used was the performance of gastric resection, associated with D2 lymphadenectomy, with absence of residual neoplastic tissue, macroscopically and microscopically (free surgical margins).

Statistical analysis

It was showed descriptive analysis of the data, presenting the absolute frequency, relative frequency and measures of central tendency (arithmetic mean, median, minimum and maximum values) and measures of dispersion (standard deviation). It was also showed, inferential statistical analysis and analysis of effects through the exact and nonparametrical tests of Fisher e Mann-Whitney. Kaplan-Meier's survival analysis was performed to evaluate the denouement at the end of six months of monitoring.

In this study, were selected the variables that could be related to the outcome of interest in the bivariate analysis, to Log-Rank's survival analysis, without censoring (Collett method), with the main goal of evaluating their possible influence, individually, on survival at the end of the period of follow-up. For that analysis, the variables were reclassified dichotomously, according to the following coding: gender=male or female; age group=60 years old or ≥60 years old; surgical intent=curative or palliative; lymphadenectomy=D1 or D2; involvement of transverse colon, small intestine, liver, pancreas, involvement of two or more organs=yes or no. Numbers equal or lower than 0,05 (5%) were utilized as level α of significance to reject the null hypothesis and confidence interval at the level of 95%.

RESULTS

The Tables 1 e 2 show the distribution per gender, occupation, age and access time to health service.

TABLE 1 – Distribution per gender and occupation of patients with T4b gastric adenocarcinoma

Variables	Absolute frequency (n)	Relative frequency (%)
Gender		
Male	22	81,5
Female	5	18,5
Total	**27**	**100,0**
Occupation		
Agriculturist	4	14,8
Attendant	1	3,7
Bricklayer	1	3,7
Carpenter	1	3,7
Dock worker	1	3,7
Electrician	1	3,7
Farm caretaker	1	3,7
Fisherman	3	11,1
Foof handler	1	3,7
General Service worker	2	7,4
Housemaid	4	14,8
Retiree	1	3,7
Seafarer	1	3,7
Stockman	1	3,7
Tradesman	1	3,7
Watchman	1	3,7
Total	**27**	**100,0**

TABLE 2 – Distribution per age and access time to health service of patients with T4b gastric adenocarcinoma

Measures of central tendency and measures of dispersion	Age (years)	Access to health service (months)
Sample (N)	27	27
Average	58,78	12,50
Standard deviation	12,78	23,42
Minimum	38	1
Top quartile (25%)	47	3
Median	59	6
Third quartile (75%)	70	12
Maximum	87	120

Regarding the origin of the patients, it was observed that six (22,2%) were from Belém and 21 (77,8%) from other municipalities of the state of Pará, and one was Maranhão state.

The most prevalent signs and symptoms were: weight loss in 23 (85,2%), epigastralgia in 22 (81,5%), vomiting in 16 (59,3), gastric fullness in 12 (44,4%), dysphagia in five (18,5%), melena in five (18,5%), heartburn in five (18,5%), diahrrea in four (14,8%), nausea in four (14,85), asthenia in three (11,1%), pain in left flank in two (7,4%), pain in left hypochondrium in two (7,4%), hematemesis in two (7,4%) and fever in one (3,7%).

The risk factors were: smoking in 11 (40,7%), family history of gastric cancer in three (11,1%), previous gastric surgery in two (7,4%), infeccion by *H. pylori* in one (3,7%). In 13 patients (48,1%), risk factors were not found.

According to surgical and histopathological aspects, it was observed that the tumor affected the proximal gastric margin in five cases (18,5%), the distal margin in 12 (44,4%) and the whole organ in 10 (37,0%). As to the quantity of adjacent structures affected, 23 (85,2%) of the patients showed one, three (11,1%) showed two and one (3,7%) showed three.

The frequency of involvement of adjacent structures were: pancreas, eight patients (29,6%); liver, seven (25,9%); transverse colon, six (22,2%); small intestine, six (22,2%); mesocolon, three (11,1%); spleen, one (3,7%); and gallbladder, one (3,7%). Of 27 patients, 13 (48,1%) underwent total gastrectomy and 14 (51,9%) subtotal gastrectomy. Sixteen (59,3%) underwent D1 lymphadenectomy and 11 (40,7%) D2. Lymph node involvement was found in 26 patients (96,3%). Palliative surgery was performed in 17 (63%) and curative in 10 (37%) (Table 3).

TABLE 3 – Surgical and histopathological aspects of patients with T4b gastric adenocarcinoma

Surgical and histopathological aspects	Absolute frequency (n)	Relative frequency (%)
Tumor extension		
Proximal	5	18,5
Distal	12	44,4
Whole organ	10	37,0
Quantity of structures affected by contiguity		
1	23	85,2
2	3	11,1
3	1	3,7
Affected organs		
Pancreas	8	29,6
Liver	7	25,9
Transverse colon	6	22,2
Small intestine	6	22,2
Mesocolon	3	11,1
Spleen	1	3,7
Gallbladder	1	3,7
Type of Gastrectomy		
Total	13	48,1
Subtotal	14	51,9
Limphadenectomy		
D1	16	59,3
D2	11	40,7
Lymph node involvement		
Yes	26	96,3
No	1	3,7
Surgical intent		
Curative (R0)	10	37,0
Palliative (R1/R2)	17	63,0

Time between the diagnosis and treatment varied from 11 to 269 days, with an average of 57,88 days and median of 34. Two patients were excluded from the analysis, because the diagnostic confirmation was obtained after the surgery (Standard deviation: 55,35; top quartile: 25% - 23; third quartile: 75% - 82).

Surgical complications were: fistula/dehiscence in seven patients (25,9%), pneumonia in six (22,2%), septic

shock in five (18,5%), bleeding in three (11,1%), surgical site infection in three (11,1%), peritonitis in two (7,4%) and pleural effusion in one (3,7%) (Table 4).

TABLE 4 – Morbidity in patients with T4b gastric adenocarcinoma

Morbidities	Absolute frequency(n)	Relative frequency (%)
Fistula/ dehiscence	7	25,9
Pneumonia	6	22,2
Septic shock	5	18,5
Bleeding	3	11,1
Surgical site infection	3	11,1
Peritonitis	2	7,4
Pleural effusion	1	3,7

Regarding surgical mortality, seven (25,9%) of 27 died.

Analysing variables such as gender, affected structures, surgical intent, lymphadenectomy and morbidities with surgical mortality, there was significant association between surgical mortality and the occurrance of: fistula/dehiscence (p=0,0496), septic shock (p=0,0089) and bleeding (p=0,0120). There was a tendency of association between surgical mortality and peritonitis (p=0,0598) (Table 5).

TABLE 5 – Association of gender, affected structures, surgical procedure intent, lymphadenectomy and morbidities with surgical mortality in patients with T4b gastric adenocarcinoma

Variables	Mortalidade cirúrgica		p
	Sim n (%)	Não n (%)	
Gender			
Male	7 (100,0)	15 (75.0)	0,2834*
Female	-	5 (25,0)	
Affected organs			
Pancreas	2 (28,6)	6 (30,0)	1,00*
Liver	2 (28,6)	5 (25,0)	0,9953*
Transverse colon	-	6 (30,0)	0,1548*
Small intestine	2 (28,6)	4 (20,0)	0,9986*
Mesocolon	2 (28,6)	1 (5,0)	0,1556*
Spleen	-	1 (5,0)	1,00*
Gallbladder	-	1 (5,0)	1,00*
Surgical intent			
Curative (R0)	2 (28,6)	8 (40,0)	0,6784*
Palliative (R1/R2)	5 (71,4)	12 (60,0)	
Limphadenectomy			
D1	5 (71,4)	11 (55,0)	0,6618*
D2	2 (28,6)	9 (45,0)	
Morbidities			
Fistula/dehiscence	4 (57,1)	3 (15,0)	0,0496*
Pneumonia	2 (28,6)	4 (20,0)	0,9986*
Septic shock	4 (57,1)	1 (5,0)	0,0089*
Bleeding	3 (42,9)	-	0,0120*
Surgical site infection	-	3 (15,0)	0,5453*
Peritonitis	2 (28,6)	-	0,0598*
Pleural effusion	-	1 (5,0)	1,00*

Note: *Fisher's exact test.

The six-month survival demonstrated a number of 63,27% of the patients that did not die during the first month after the surgery (CI 95%= 39,90-86,63%).

In the study, there was not influence of gender, age, surgical intent, lymphadenectomy and involvement of adjacent structures in the survival at the end of six months (Table 6).

TABLE 6 – Survival analysis during the period of six months according to the variables studied in patients with T4b gastric adenocarcinoma

Variables	Initial frequency (N)	Final frequency n (%)	p ¥
Gender			0,5493
Male	14	9 (64,3)	
Female	4	3 (75,0)	
Age			0,4872
<60 years	10	6 (60,0)	
≥60 years	8	6 (75,0)	
Surgical intent			0,8579
Curative (R0)	7	5 (71,4)	
Palliative (R1/R2)	11	7 (63,6)	
Limphadenectomy			0,8579
D1	11	7 (63,6)	
D2	7	5 (71,4)	
Transverse colon involvement			0,1605
Yes	6	3 (50,0)	
No	12	9 (75,0)	
Small intestine involvement			0,1876
Yes	3	3 (100,0)	
No	15	9 (60,0)	
Liver involvement			0,6403
Yes	4	3 (75,0)	
No	14	9 (64,3)	
Pancreas involvement			0,3126
Yes	6	3 (50,0)	
No	12	9 (75,0)	
Involvement ≥ 2 organs			0,9552
Yes	3	2 (66,7)	
No	15	10 (66,7)	

Note: ¥Log-Rank survival analysis (Collett)

DISCUSSION

In Brazil, the incidence of gastric cancer is higher in males around 70 years old[3]. The male predominance (81,5%) and the average age of 58,78 are similar to the results of other publications[8].

Studies based on data of educational censuses, household income censuses and occupation censuses have shown, consistently, the association between stomach neoplasia and low socioeconomic status, demonstrating that the rates on people with low socioeconomic status can be twice or three times bigger than on people form higher income classes. The socioeconomic level, on its own, should not increase the risk of stomach cancer, it should be associated with several other risk factors, such as, salt intake and *H. pylori* infection. In this study, occupation was the only income indicator used. The most frequent were agriculturist (14,8%), housemaid (14,8%) and fisherman (11,1%), compared to another study[2].

The chances of cure of gastric cancer are directly related to an early diagnosis and clinical stage. Nevertheless, in Brazil, early detection is the exception, during either the asymptomatic phase or the initial symptoms. It is estimated that around 10 to 15% of gastric cancer cases in Brazil are diagnosed in an early stage, which makes a direct impact in the results, with low rates of survival[6]. In this study, the access time to health services varied from 1 to 120 months, with average of 12,5 months. Such wait could be justified by the difficulty of patients to access the specialized service, since 77,8% of them were from different municipalities; by late onset of symptoms, by the precariousness of basic health care. Moreover, the time between the diagnosis and treatment varied from 11 to 269 days, with an average of 57,88 days. The most frequent site of gastric cancer, which invades other structures surrounding the stomach (T4b), is variable. Published studies demonstrate that proximal gastric cancer is the most frequent[5,8]. However, in this study, in 44,4% of the cases there was distal impairment, agreeing with the studies shown on Lin et al.[13].

The evidences show that in most of the patients with T4b gastric adenocarcinoma, the tumor invades only one adjacent structure[8,16,12,9,4]. This fact was observed by the patients, in 85,2% the tumor invaded only one adjacent structure and in 14,8, two or more.

Among the invaded adjacent structures, it was found that the pancreas was the most frequent (29,3%), followed by the liver (25,9%), transverse colon 22,2%), small intestine (22,2%), transverse mesocolon (11,1%), spleen (3,7%) and gallbladder (3,7%).

The surgical treatment is the most indicated, because it contributes to increase, substantially, the survival time of patients. The question about which treatment is more indicated for antral stomach cancer, whether if it is total gastrectomy or subtotal gastrectomy, has been discussed by several different authors.

The clear consensus is that total gastrectomy is unnecessary in antral tumors, because it does not improve the patient's life after the surgery and it can, unnecessarily, increase postoperative morbidity and mortality[1]. In this study, subtotal gastrectomy was used in 51,9% of the cases, fact that is similar to the studies of Fukuda et al.[8] and Ozer et al.[16] The resection is considered curative when associated to D2 lymphadenectomy. In this study, however, 59,3% of the patients underwent D1 lymphadenectomy. The surgical intervention proposition was that the patients were submitted to a curative procedure based on preoperative diagnosis. Nevertheless, the curative resection was performed in 10 patients (37%) and palliative in 17 (63%).

A published study by Martin et al.[15] concluded that the resection of two or more adjacent organs in locally advanced gastric cancer is associated to a bigger risk of developing complications. Authors also suggest that R0 resection should always be the goal, but the additional resection of adjacent organs must be judicious. The main complications can vary, according to evaluated studies. Kunisaki et al.[12] show that the main complications are fistula and anastomosis dehiscence (45,7%) and pneumonia (2,6%), whereas to Carboni et al. are hemorrhage and sepsis.

In this study, 51,85% of the patients showed complications. There was significant association between surgical mortality and fistula/dehiscence occurrence (p=0,0496), septic shock (p=0,0089) and bleeding (p=0,0120). There was a tendency of association between surgical mortality and peritonitis (p=0,0598).

Most of the studies evaluate patients' survival at three years[16,9,5]. Although there is variation in this data, survival decreases along the years. The comparison of these results to the survival of patients could not be related to other studies due to a shorter follow-up.

CONCLUSION

The average time between onset of symptoms and access to the specialized health service was high. Over half of the patients showed postoperative morbidity. The patients that presented fistula/dehiscence, bleedings and septic shocks had significant association with surgical mortality. Survival ate the end of six months was 63,27%.

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