

Duodenopancreatectomy: histopathological analysis of periampullary tumors

Duodenopancreatectomia: análise histopatológica de tumores periampulares

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Ferreira FERR, Araujo AG, Nobrega Junior BG, Araujo HG, Lima DL, Lima RNCL. Duodenopancreatectomy: histopathological analysis of periampullary tumors / *Duodenopancreatectomia: análise histopatológica de tumores periampulares*. Rev Med (São Paulo). 2020 July-Aug;99(4):366-73.

ABSTRACT: *Introduction:* Cephalic Gastropancreato-duodenectomy (CGDP) is the surgery of choice for the treatment of periampullary cancers. Patients with this disease have a 5-year survival rate of 20% to 50%, being related to the resection status, stage of the disease, and tumor location. To know the biological behavior of periampullary tumors allows to plan the treatment, and the follow-up of these patients. *Method:* The study analyzed 105 patients through histopathological results of surgical parts of CGDP. Data regarding origin, tumor size, lymph node status, perineural invasion, angiolymphatic invasion, surgical resection margins, and differentiation of tumor were collected, and compared with the current literature. *Results:* Patients with malignant neoplasms were 94 (89.5%) of those who went through CGDPs. Forty percent (42) of those were pancreatic tumors, 37% (39) were duodenal papillary tumors (Vater papilla), 4% (4) had duodenal origin and 2% were distal common bile duct tumors. The mean size of the tumors was 3.43cm (p = 0.049), with 85% of the tumors larger than 2cm and 46 (52.9%) of the adenocarcinomas were stage T3. Lymph nodes were positive in 27.6% of the adenocarcinomas and the margin was R0 in 87% of the patients. *Conclusion:* The biological behavior of periampullary tumors is of great importance for patients who have undergone CGDP. Better treatment planning and follow-up may be offered when the histological type of these tumors is known. The experience of the centers in this surgical procedure is of important relevance in the results.

Keywords: Pancreaticoduodenectomy; Abdominal neoplasms; Adenocarcinoma.

RESUMO: *Introdução:* A Gastroduodenopancreatectomia Cefálica (GDPC) é a cirurgia de escolha para o tratamento de tumores periampulares. Os pacientes portadores dessa doença possuem sobrevida de 5 anos estimada em 20% a 50%, estando relacionado com o status de ressecção, estágio da doença e a localização do tumor. Conhecer o comportamento biológicos dos tumores periampulares possibilita um melhor planejamento no tratamento e no seguimento desses doentes. *Método:* O estudo analisou 105 pacientes através do resultado histopatológico oriundo de peças cirúrgicas de GDPC. Dados sobre sítio de origem, tamanho do tumor, status linfonodal, invasão perineural, invasão angiolinfática, margens de ressecção cirúrgicas e grau de diferenciação do tumor foram coletados e comparados com a literatura vigente. *Resultados:* Os pacientes portadores de neoplasia maligna totalizaram 94 (89,5%) das GDPCs. Desses, 40% (42) eram tumores pancreáticos, 37% (39) eram tumores de papila duodenal (papila de Vater), 4% (4) eram de origem duodenal e 2% (2) eram de colédoco distal. O tamanho médio dos tumores foi de 3,43cm (p = 0,049), com 85% dos tumores maiores de 2 cm e 46 (52,9%) dos adenocarcinomas eram estágio T3. Os linfonodos foram positivos em 27,6% dos adenocarcinomas e a margem foi R0 em 87% dos pacientes. *Conclusão:* O comportamento biológico dos tumores periampulares é de grande importância para pacientes que foram submetidos a cirurgia de GDPC. Um melhor planejamento no tratamento e no seguimento dos doentes pode ser oferecido quando se conhece o tipo histológico desses tumores. A experiência dos centros na realização dessa cirurgia tem importante relevância nos resultados obtidos.

Descritores: Pancreaticoduodenectomia; Neoplasias abdominais; Adenocarcinoma.

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INTRODUCTION

Cephalic Gastroduodenopancreatectomy (CGDP) is the surgery of choice for the treatment of periampullary neoplasms, whether of pancreatic, ampular, biliary or duodenal origin. Only 10 to 20% of patients with periampullary tumors at diagnosis have resectable lesions due to locally advanced tumors or metastatic disease, and of these, the literature suggests that 23 to 30% are unresectable at the time of the surgical procedure¹. Survival of these patients is associated with resection status, disease stage, and tumor location^{2,3}.

In a three-decade study at the Johns Hopkins School of American Medicine, He et al.⁴ studied 2,564 specimens of periampullary tumors and found that the prevalence of pancreatic, ampular, biliary, and duodenal cancer was, respectively, 66%, 16%, 12% and 6%. To know the organ of origin and the histological pattern of these neoplasms predominating in each population is important to outline management protocols for the better care and treatment of patients, besides indicating the prognosis of these patients.

The presence of lymph nodes affected by neoplasia, perineural involvement, neoplasia-free resection margins, degree of tumor differentiation and tumor size greater than 2 cm are prognostic factors known in the literature. In the last decade, studies have shown that the ratio of lymph nodes affected by the total lymph nodes ratio (LN Ratio) is one of the most important independent predictors of survival, especially in patients with ductal adenocarcinoma of the pancreas^{5,6,7,8}.

It is important to know the biological behavior of tumors in patients undergoing this surgical procedure, due to the increase in the number of patients undergoing CGDP in the last decade by periampullary tumors, with 5-year survival estimated at 20% for patients operated with pancreatic adenocarcinoma and 50% for duodenum tumors.⁴ Thus, better planning in the treatment and follow-up of these patients can be offered.

METHOD

The study analyzed 105 patients through histopathological specimens from gastroduodenopancreatectomy

surgical specimens at *Getulio Vargas Hospital*, Recife - PE, from 2002 to 2016, retrospectively and descriptively, through absolute and percentage frequencies for categorical and mean variables, minimum and maximum for the numerical variable (tumor size). There was no exclusion of any report found. The study was approved by the Institutional Review Board (IRB), under the number 78883317.2.0000.5197.

Data on site of origin, tumor size, lymph node status, perineural invasion, angiolymphatic invasion, surgical resection margins and degree of tumor differentiation were collected. These data were compared with the current literature.

The tumor-node-metastasis (TNM) classification was used according to the 7th edition American Joint Committee on Cancer (AJCC)⁷. The Lymph Node Ratio (LN Ratio), a ratio between affected lymph nodes and the total number of lymph nodes found in the surgical specimen, was also investigated. Recent studies have shown that the LN ratio is a better predictor in univariate survival analysis than the simple lymph node involvement^{5,6,7,8}.

Grading of cancer (how abnormal, on the microscope, the cell appears to be) uses a scale from G1 to G3, with grade 1 cancers being cells similar to normal tissue and grade 3 cells being less undifferentiated^{10,11}.

As for surgical margins (AJCC 7th edition)⁷, R0: was designated when the entire lesion was resected and there are no visible or microscopic signs of cancer in the sample; R1: the entire visible tumor was removed, but laboratory tests showed compromised surgical margins; A2: The tumor cannot be removed completely^{12,10}.

Fisher's Exact test was used to verify the association between two categorical variables. The margin of error used in the decision of the statistical tests was 5%. The program used to obtain statistical calculations was IBM - SPSS in version 23.

RESULTS

The study analyzed 105 histopathological examinations of patients undergoing CGDP from 2002 to 2016. Of the patients submitted to CGDP, 59 (56.2%) were men and 46 (43.8%) were women (Table 1).

Table 1. Gender distribution of periampullary adenocarcinomas submitted to CGDP from 2002 to 2016 at *Getulio Vargas Hospital*

	Pancreas	Duodenal ampulla	Duodenum	Distal bile duct	All
	n = 42 (48.2%)	n = 39 (44.8%)	n = 4 (4.6%)	n = 2 (2.3%)	n = 87 (100%)
Gender					
Male	21 (50%)	25 (64,1%)	1 (25%)	2 (100%)	49 (56,3%)
Female	21 (50%)	14 (35,9%)	3 (75%)	0	38 (43,7%)

Eleven (10.5%) were operated for a benign disease: 8 (7.6%) for pancreatitis in its pseudo-tumour form and 3 (2.9%) for papillitis. Patients with malignant neoplasia totaled 94 (89.5%) of those who underwent duodenopancreatectomy.

Of these neoplasias, 40% (42) were pancreatic tumors, 37% (39) were duodenal papilla tumors (Vater's

papilla), 4% (4) were of duodenal origin and 2% (2) were distal tumors from the common biliary duct. Three patients (3%) were diagnosed with a pseudopapillary tumor of the pancreas (Frantz's tumor) and, of these, 2 were female and 1 was male. One, histopathologically, had had a condition with colon neoplastic origin, and two had gastric neoplasia, totaling 3% of the CGDP (Table 2).

Table 2. Distribution of histopathological characteristics of periampullary adenocarcinomas submitted to gastroduodenopancreatectomy (n = 87)

	Pancreas n = 42 (48.2%)	Duodenal ampulla n = 39 (44.8%)	Duodenum n = 4 (4.6%)	Distal bile duct n = 2 (2.3%)	All n = 87 (100%)
Perineural infiltration	27 (64,3%)	4 (10,3%)	1 (25%)	2 (100%)	34 (39%)
Angiolymphatic Infiltration	13 (30,9%)	8 (20,5%)	1 (25%)	2 (100%)	24 (27,6%)
Margin involved					
R0, R0	34 (80,9%)	37 (94,9%)	4 (100%)	1 (50%)	76 (87,3%)
R1, R1	8 (19,1%)	2 (5,1%)		1 (50%)	11 (12,6%)

Of all the CGDPs in this study (n=105), 87 were periampullary adenocarcinomas. Among the adenocarcinomas, it was found that 85% of the tumors (74 patients) were larger than 2 centimeters (p=0.049) and 26.4% (23 patients) already were larger than 5 cm. In the TNM evaluation, 52.9% (46 patients) were classified

as T3, 20.7% (18 patients) as T2, 20.7% (18 patients) as T1 and 5.7% (5 patients) as T4 (p<0.001). The degree of differentiation of tumors was well differentiated in 63 (72.4%), and moderately differentiated in 23 (26.4%) (p=0.005) (Table 3 and 4).

Table 3. Average size and number of tumors larger than 2 cm in patients with periampullary adenocarcinoma

	Pancreas n = 42 (48.2%)	Duodenal ampulla n = 39 (44.8%)	Duodenum n = 4 (4.6%)	Distal bile duct n = 2 (2.3%)	All n = 87 (100%)
Average tumor size, in cm (variation, in cm)	3.98 (1.5-9)	2.98 (0.6-8)	5.125cm (2.5-9)	1.65cm (1.5-1.8)	3,43 (0,6-9)
Tumors larger than 20mm	37 (88%)	33 (84,6%)	4 (100%)	0	74 (85%)

Table 4. Degree of differentiation of periampullary tumors operated at *Getulio Vargas Hospital* from 2002 to 2016

	Pancreas n=42 (48.2%)	Duodenal ampulla n = 39 (44.8%)	Duodenum n=4 (4.6%)	Distal bile duct n=2 (2.3%)	All n=87 (100%)
1 (2,3%)		0	0	0	1 (2,3%)
18 (42,9%)		4 (10,2%)	1 (25%)	0	23 (26,4%)
23 (54,8%)		35 (89,8%)	3 (75%)	2 (100%)	63 (72,4%)

Tumour size of >20 mm was associated with increased overall survival (OS) (RH 0.63, 95% CI 0.50e0.78, p 1/4 0.0001). Elberm et al.¹⁶, 1 and 9 through Fisher's exact test (p = 0.049*) with a significant difference at the level of 5.0%.

The resection margins were R0 in 88.3% (83 patients) and R1 in 11.7% (11 patients) (p=0.074) of the neoplasms in this study. Of the histopathological reports with margins affected by neoplasia after surgical resection, 9 pointed to the pancreatic margin as positive, 1 to the

choledocian and 1 to both the choledocian margin as positive and pancreatic margin as positive. Tumor invasion was found in 28 (29.8%) patients. There was perineura invasion in 35 cases (37.2%) (p=0.143) and angiolymphatic invasion in 30 (31.9%) patients.

In operated pancreatic tumors (42), 50% of the patients were men, the mean size of the tumors was 3.98 cm (1.5-9), 88% (37) were larger than 2 cm, 54.8% (23) were T3 and 42.9% (18) were T2. Thirty-three percent (33%) had positive lymph nodes. *The Lymph node Ratio* (LN Ratio)

was > 0.2 in 13 (92.8%) of the 14 (100%) patients evaluated with lymph nodes affected by neoplasia. Regarding the surgical margin, 80.9% (34) obtained R0 margin. Of the affected margins (8 or 9), in 7 patients the guilty margin was pancreatic and, in 2, it was in the common biliary duct.

In patients with duodenal ampullary neoplasia, the incidence between genders was 25:14 (Male:Female). The mean mass size was 2.98 cm (0.6 - 8) and 84.6% (33) of them were already larger than 2 cm. Almost all, 89.8%, of the tumors, were well differentiated, 43.6% (17) were T3 and 38.4% (15) were T1. 23.1% (9) of the patients had lymph node invasion and the LN Ratio > 0.2 in 55% (5) of the patients with affected lymph nodes. There was

perineural infiltration in 10.3% (4) and angiolymphatic infiltration in 20.5% (8) of the sample. R0 margin was obtained in 94.9% (37). The pancreatic margin was the compromised margin in the R1 samples, totaling 5.1% of the patients with ampullary tumor.

Samples of neoplasms of duodenal and distal bile duct (DBD) origin represent 4.2% (4) and 2.1% (2) of the sample, respectively. Only one (25%) of the patients with duodenal tumor had a positive lymph node with LN Ratio > 0.2. There was perineural invasion in both patients (100%) with DBD neoplasia and in one patient with the disease in the duodenum. There was an R1 margin in 1 patient (50%) with DBD tumor (Table 5 and 6).

Table 5. pT stage of periampullary adenocarcinomas operated from 2002 to 2016 at *Getulio Vargas Hospital*. (TNM - American Joint Committee on Cancer)

	Pancreas n = 42 (48.2%)	Duodenal ampulla n = 39 (44.8%)	Duodenum n = 4 (4.6%)	Distal bile duct n = 2 (2.3%)	All n = 87 (100%)
T1	2 (4,8%)	15 (38,4%)	1 (25%)		18 (20,7%)
T2	13 (30,9%)	4 (10,3%)	-	1 (50%)	18 (20,7%)
T3	27 (64,3%)	17 (43,6%)	1 (25%)	1 (50%)	46 (52,9%)
T4		3 (7,7%)	2 (50%)		5 (5,7%)

Table 6. pN stage of periampullary adenocarcinomas operated from 2002 to 2016 at *Getulio Vargas Hospital*. (TNM - American Joint Committee on Cancer)

	Pancreas n=42 (48.2%)	Duodenal ampulla n=39 (44.8%)	Duodenum n=4 (4.6%)	Distal bile duct n=2 (2.3%)	All n=87 (100%)
pN Stage					
N0, New Year	28 (66,6%)	30 (76,9%)	3 (75%)	2 (100%)	63 (72,4%)
N1, N1	14 (33,3%)	9 (23,1%)	1 (25%)		24 (27,6%)
N. of lymph nodes examined, mean (variation)	5,6 (0 - 18)	4,3 (0 - 30)	3,75 (3 - 5)	9 (9)	5, 01 (0-30)
N. of lymph nodes examined in patients with negative lymph nodes, mean (variation)	4,1 (0 - 18)	4,76 (0 - 11)	3 (3- 5)	9 (9)	4,32 (0- 18)
N. of lymph nodes examined in patients with positive lymph nodes, mean (variation)	8,5 (0 - 10)	2,11 (0 - 30)	3 (3)	0	5,2 (0 - 30)
LN Ratio > 0.2 N (variation) *	13 (0,2 - 1)	5 (0,2 - 0,71)	1	0	18

DISCUSSION

The Whipple procedure, or cephalic gastroduonepancreatectomy (CGDP), is one of the most complex surgeries of the digestive tract and the only form of cure for elective patients with periampullary tumors. However, this procedure involves high morbidity and mortality and patient survival can be assessed according to variables such as tumor origin, lesion size, stage of cell development, perineural invasion, LN Ratio and surgical margins. Therefore, a meticulous histopathological evaluation of the specimens resulting from CGDP is essential for surgical evaluation and oncological follow-up of these patients.

The prognosis of ampullary tumors depends on the histopathological type (which determines local growth and metastasis pattern). The pancreatobiliary type is associated with a more reserved prognosis than the intestinal type due to a more aggressive behavior. Histopathological differentiation should be seen as an independent predictor of survival and should have implications for the treatment of these patients¹³.

In our study, adenocarcinomas were found in 87 of the 105 patients. Of these, pancreatic adenocarcinoma (40%) and duodenal papillary type (37%) were the most common tumors found, followed by duodenal adenocarcinoma (4%) and distal bile duct tumors (2%). Sohn et al.¹⁴ and Yeo et al.¹⁵ in a study with 650 CGDP, found 43% cases of neoplasm of pancreatic origin, 11% of papillary origin, 10% DBD, and duodenal cancer in 4%.

The current literature^{16,17} points to tumor size, lymph node invasion (LN Ratio), perineural invasion, compromised surgical margins and presence of poorly differentiated tumor as independent variables which favor a lower survival rate. Elberm et al.¹⁶ found, in a multivariate analysis of 1,070 patients submitted to CGDP, the following factors: tumor size > 2 cm ($p=0.0001$), perineural invasion ($p=0.002$), independent status ($p=0.0001$) associated with survival.

Our study showed an average size of 3.98 cm (range 1.5-9 cm) in tumors of pancreatic origin and 2.98 cm (range 0.6-9) in tumors of papillary origin. Elberm et al.¹⁶ found an average size of 3 cm in their analysis. Winter et al.¹⁷, in their large series of 1,175 resected pancreatic tumors, demonstrated that as tumor smaller than 3 cm is one of the favorable survival factors in a multivariate analysis. In our study, the value of 2 cm as cut-off was used according to the 7th edition of the AJCC Classification. Lim et al.¹⁸, in a study at Harvard University, also demonstrated a better prognosis in tumors smaller than 2 cm. Our analysis showed that stage T3 was that of the tumors of half (52.9%) of operated patients, compatible with the current literature^{19,20}.

In the study by Winter et al.¹⁷, the incidence of

perineural invasion was 91% and that of angiolymphatic was 53%. In our study, perineural infiltration was observed in pancreatic tumors in 64.3% and angiolymphatic invasion in 30.9% and in papillary tumors, 10.3% presented perineural invasion and 20.5% presented angiolymphatic invasion. The presence of perineural invasion is associated with lymph node metastasis ($p<0.001$)²¹.

The surgical margins found in this study were clear (R0) in 80.9% of patients operated for pancreatic adenocarcinoma and 94.9% for duodenal ampullary adenocarcinomas. R0 margins were smaller also in pancreatic tumors (63%) when compared to the ampullary (93%) and DBD²² tumors (94%)²². Elberm et al.¹⁶ found R0 margin in 46.9% of the cases. Chandrasegaram et al.²² showed R0 margins in 46% of patients operated before 2010 and in 67% of patients after 2010. Verbeke et al.¹⁹, showed no relationship between tumor size and margin status ($p=0.732$). Yeo et al.¹⁵, at Memorial Sloan Kettering Cancer Center's in New York, showed 5-year survival, in patients with negative surgical margins, of 26% (mean survival of 18 months) and, in those with positive margins, of 8% (mean survival of 10 months).

We found lymph node metastasis in 27.6% of CGDP and LN Ratio > 0.2 in 18 patients. The mean number of lymph nodes found in our study was 4.9 lymph nodes per surgical specimen, low when compared to the world literature.

Hellan et al.²³ in a cohort study with 1,915 patients found better survival rates in patients with more than 11 lymph nodes in the surgical specimen ($p=0.0001$). Elberm et al.¹⁶, evaluating pancreatic cancer, observed that 81.1% of patients had lymph nodes, a factor with an impact on survival ($p=0.0001$), and found a mean number of lymph nodes of 17. Riediger et al., at the University of Friburg in Germany, found a mean number of lymph nodes of 16 and, in univariate analysis, a higher 5 years survival rate in patients with LN Ratio < 0.2 (6% vs. 19% with LN ratio < 0.2; $p=0.003$), which is a better factor than the analysis of simple lymph node involvement^{5,6,7,8}.

CONCLUSION

The biological behavior of periampullary tumors is of great importance for patients who have undergone CGDP surgery. To know the particularities of these neoplasms in the population is extremely important for the planning of treatment and postoperative follow-up of these patients and programming of health systems. The experience of the centers in performing this surgery has important relevance in the results obtained.

Authors' participation: We inform for due purposes that the article was prepared jointly by the group of authors with the following degree of participation: Data collection (*Ferreira FERR*). Organizational orientation and on the essence, argumentation and relevance of the work: (*Ferreira FERR, Araújo AG, N. Júnior BG and Araújo HG*). Analysis, research of articles, reading and exclusion of research not relevant to the involvement of the chosen theme: (*Ferreira FERR, Lima DL e Lima RNCL*). Reading and writing of the content: (*Ferreira FERR, Lima DL e Lima RNCL*). Revision of the text regarding integrity and veracity as to the sources used: (*Ferreira FERR, Lima DL e Lima RNCL, Araújo AG, N. Júnior BG e Araújo HG*) and translation of the article: (*Lima DL e Lima RNCL*). Thus, the group of authors certifies joint participation in the preparation of the article, hoping to contribute to the theme in question.

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Received: August 09, 2018

Accepted: April 30, 2020