

# Resection of liver metastasis from neuroendocrine tumors: evaluation of results and prognostic factors

## *Ressecção de metástases hepáticas de tumores neuroendócrinos: avaliação dos resultados e fatores prognósticos*

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### A B S T R A C T

**Objectives:** to determine the prognostic factors that may impact on morbidity and mortality and survival of patients undergoing surgical treatment of liver metastases from neuroendocrine tumors. **Methods:** We studied 22 patients undergoing liver resection for metastases from neuroendocrine tumors between 1997 and 2007. Epidemiological and clinical data were correlated with morbidity and mortality and overall and disease-free survivals. **Results:** twelve patients were male and ten female, with a mean age of 48.5 years. Bilobar disease was present in 17 patients (77.3%). In ten patients (45.5%) the primary tumor originated in the pancreas, terminal ileum in eight, duodenum in two, rectum in one and jejunum in one. Complete surgical resection (R0) was achieved in 59.1% of patients. Eight patients (36.3%) developed complications in the immediate postoperative period, one of them dying from septicemia. All patients undergoing re-hepatectomy and/or two-stage hepatectomy had complications in the postoperative period. The overall survival at one and five years was 77.3% and 44.2%. The disease-free survival at five years was 13.6%. The primary pancreatic neuroendocrine tumor ( $p = 0.006$ ) was associated with reduced overall survival. Patients with number of metastatic nodules  $< 10$  ( $p = 0.03$ ) and asymptomatic at diagnosis ( $p = 0.015$ ) had higher disease-free survival. **Conclusion:** liver metastases originating from pancreatic neuroendocrine tumors proved to be a negative prognostic factor. Symptomatic patients with multiple metastatic nodules showed a significant reduction in disease-free survival.

**Key words:** Neuroendocrine Tumors. Hepatectomy. Survival Analysis. Neoplasm Metastasis.

### INTRODUCTION

Neuroendocrine tumors (NETs) are a heterogeneous and unusual group of neoplasms, with variable natural history, slow-growing and often indolent evolution. They are characterized by the ability to synthesize, store and secrete hormonal substances and vasoactive amines, which are directly related to clinical manifestations<sup>1</sup>. The exact incidence of neuroendocrine tumors is variable between different studies, involving 1-7 cases / 100,000 individuals<sup>2</sup>, representing 0.49% of all cancers<sup>3</sup>. Over the past 30 years there has been an increased incidence of this tumors at a rate of 6% per year, possibly due to improvement in diagnostic methods and greater awareness of the disease by doctors<sup>3,4</sup>.

Although neuroendocrine tumors are generally indolent, slow-growing compared to carcinomas, metastases can occur, making the prognosis poor. Neuroendocrine tumors series show that 17% to 27% have regional disease, and 17% to 74%, distant metastatic

involvement<sup>1</sup>. The liver is the organ which is most affected by distant metastases and it is estimated that 75% of patients with small bowel TNE and 30% to 85% of those with TNE of pancreatic origin develop liver metastases, of whom 80% die within five years<sup>3,5</sup>. The liver is often the only organ affected by distant metastases<sup>6</sup>. The TNE five-year survival in the presence of liver metastases ranges from 13% to 35%<sup>5,7-9</sup>, and from 77% to 99% in the absence of hepatic involvement<sup>2</sup>.

There is no consensus on how best to treat patients with NET liver metastases despite several attempts of systematization<sup>10,11</sup>. Due to the rarity and clinical and biological heterogeneity of such neoplasms, there is a paucity of published randomized studies. Surgical resection is the only potentially curative therapy. While in patients with untreated liver metastases survival is 20% to 40% in five years<sup>3,12</sup>, in patients undergoing resection of the metastases this rate reaches 50% and 90%<sup>13</sup>. Furthermore, the alleviation of symptoms is achieved in 90% of cases.

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Due to the heterogeneity of results, it is important to evaluate the possible prognostic factors for survival in an attempt to predict the evolution and treatment planning.

This study aims to determine the prognostic factors that may impact mortality, morbidity and survival of patients undergoing surgical treatment of liver metastases from neuroendocrine tumors.

## METHODS

We conducted a retrospective study with patients with liver metastases from neuroendocrine tumors who underwent surgical resection with curative intent. Data were prospectively collected in the period between January 1997 and December 2007. Twenty-two patients were eligible, according to the following inclusion criteria: patients with liver metastases originating from neuroendocrine tumor, histologically confirmed, submitted to hepatic resection with curative intent; availability of material in appropriate conditions for histological evaluation in the Department of Pathology.

Demographics, primary tumor characteristics and metastases, as well as surgical and pathological findings were used to define the following parameters for prognosis analysis: age; gender; symptoms; extent of hepatectomy; Full (R0) or incomplete (R1) liver resection; need for perioperative blood transfusion; presence of immediate postoperative complications; presence of extrahepatic disease; clinical presentation of liver metastases (synchronous X metachronous); distribution of metastases (bilobar X unilobar); number and size of liver metastases; location of the tumor; histological grade; tumor staging; number of operations; morbidity and mortality; and recurrence.

Patient characteristics, tumor tissue and surgical procedures were evaluated and correlated with: morbidity and mortality, overall survival and disease-free survival.

The size, number, location and extent of liver metastases were defined by computed tomography and/or magnetic resonance imaging of the abdomen, isotopic mapping with labeled octreotide (octeoscam). Careful palpation of the liver and intraoperative ultrasonography were performed in all patients for the evaluation of metastases not detected by preoperative imaging studies, and for defining surgical strategy. The surgical reports were reviewed to determine the location, extent of liver involvement and type of liver resection performed.

Patients were considered to have synchronous disease when the identification of liver metastasis and primary tumor was simultaneous or when detected up to six months after diagnosis of the primary tumor. Metachronous disease was defined if the metastasis became apparent after a period of six months after the detection of the primary tumor.

The classifications of the location and type of liver resection were based on Brisbane classification<sup>14</sup>. Liver resection was ranked as major when three or more segments were resected - right hepatectomy (segments 5, 6, 7 and 8); left hepatectomy (segments 2, 3 and 4); trisegmentectomy right (segments 4, 5, 6, 7 and 8); left trisegmentectomy (segments 2, 3, 4, 5 and 8). Segmentectomies, enucleations, wedge resections were classified as minor liver resection. The primary tumor was resected simultaneously to metastases in 11 patients.

Patients with negative margins and no evidence of macroscopic residual disease were considered to have undergone complete resection (R0); resection margins coincident with the section area or microscopic residual disease were classified as R1.

Liver resection was performed in two stages in patients with bilobar metastases not amenable to resection in only one surgical procedure. In these we performed in the first procedure, the resection of liver nodules of one of the sides associated with ligation of the portal vein of the contralateral lobe for the purpose of causing hypertrophy of the remaining liver, allowing the removal of all liver metastases. This technique was used in two patients.

Re-hepatectomy was performed in patients evolving with hepatic recurrence for whom the preoperative evaluation proved possible the complete resection of secondary lesions. Four patients have undergone this type of resection.

Patients who developed non-resectable recurrences and those with disease progression were treated with somatostatin analogues, hepatic artery chemoembolization, chemotherapy or radiation therapy.

Complications were considered all events that required any medical intervention or prolonged hospital stay. Postoperative complications were classified as immediate when occurred until the 30th day after surgery.

Survival was calculated from the first liver resection. Overall survival (OS) was defined as period of time in months elapsed between the date of the first liver resection and the date of death or last follow-up. Disease-free survival (DFS) was defined as the period of time in months elapsed between the date of first liver resection and date of diagnosis of recurrence or last follow-up.

We used the distribution of absolute and relative frequencies to describe categorical variables. We applied central tendency and dispersion in the analysis of numerical variables. We used the chi-square test for the correlation between categorical variables. In cases where the expected values in the contingency table were smaller than 5 by more than 20% of barriers and / or less than 1, the Fisher's exact test was performed. We used the Kaplan-Meier technique for the analyses of global and disease-free survival and the significance was evaluated by the log-rank test. We considered statistical significance when  $p < 0.05$ .

## RESULTS

Twelve patients were males and ten females. The mean age was 48.5 years, ranging from 32 to 69. In six patients (27.3%) the diagnosis was incidental, the other 16 patients (72.7%) being symptomatic at diagnosis. Liver metastases were diagnosed synchronously with the primary tumor in 17 cases (77.3%). In 17 patients (77.3%) metastases were distributed in a bilobar fashion in the liver parenchyma, and unilobar in five (22.7%). Eleven patients had less than ten nodes. The liver parenchyma presented involvement greater or equal to 50% in eight (36.4%) patients, and less than 50%, in 14 (63.6%).

The primary tumor was resected simultaneously to metastases in 11 patients. Although resection with curative intent have been designed in all 22 patients, in only 13 (59.1%) was achieved radical or R0 resection; for the other nine (40.9%) the procedure was R1. Among the 22 patients, 20 underwent single-time liver resections, those being: 13 minor liver resections; two left side sectionectomies; two right hepatectomies; two left hepatectomies; and one right posterior sectionectomy. In two patients we opted for the realization of two-stage hepatic resection: in one patient, on the first time we performed a segmentectomy of segment 7, enucleations in segments 4, 5 and 8, and ligation of the left branch of the portal vein; on the second time, a left trisegmentectomy was performed. The other patient was submitted to segmentectomy of segment 3, with enucleation in segment 4 and ligation of the right branch of the portal vein; on the second time we carried out a right hepatectomy.

Four patients developed hepatic recurrence and underwent re-hepatectomy; one of them had two more recurrences in the liver, which were resected. Three minor liver resections were performed, one left trisegmentectomy, one right hepatectomy and one left hepatectomy.

The mean duration of surgical procedures was 337 minutes, ranging from 65 to 840. The mean hospital stay was 7.2 days (2-17). Eight patients (36.4%) received blood transfusion, with an average of 360ml per transfusion.

Ten patients (45.5%) had the primary neuroendocrine tumor located in the pancreas, eight (36.4%) in the terminal ileum, two (9.1%) in the duodenum; one in (4.5%) in the rectum and one (4.5%) in the jejunum. The average size of the resected metastatic lesions was 48,3mm, with a median of 42.5mm, ranging from 6 to 150 mm. The average number of resected metastatic nodules was 3.4, ranging between one and 11. Eleven patients (50%) had involvement of lymph nodes regional to the primary tumor.

Eight patients (36.3%) developed postoperative complications, two with pneumonia, one urinary tract infection, one septicemia, one liver failure, one intraperitoneal abscess, one pleural effusion and one cardiac arrhythmia. The patient with peri-hepatic abscess needed percutaneous drainage, all the others having been treated

medically. All patients undergoing liver resection in two stages or re-hepatectomy had postoperative complications. One patient (4.5%) submitted to re-hepatectomy developed sepsis and died in the postoperative period.

The mean follow-up was 37 months (12-107). Among the thirteen patients who underwent complete resection, six (46.15%) had recurrences in the liver, two showed bone relapse, and one, in bone and central nervous system. At the end of the study, five patients (22.7%) were alive without neoplastic disease; eight were alive with disease (35.4%) and nine had died (40.9%).

On statistical analysis of patients who developed complications in the immediate postoperative period, the only factor correlated with the occurrence of complications was the performance of more than one hepatectomy (two stages or re-hepatectomy) ( $p = 0.028$ ). The other variables showed no significant statistical correlation with the occurrence of postoperative complications.

Overall survival was 77.3% at three years and 44.2% at five years. The disease-free survival at five years was 13.6%. No variable related to patient characteristics or treatment had any influence on overall survival (Table 1). Among the variables related to the tumor, the location of the primary tumor showed a statistically significant difference in the overall survival curve; the five-year survival for patients with the primary tumor originating in the pancreas was 15%, and 91.7% for patients who had the primary tumor originating in the digestive tract ( $p = 0.006$ ) (Figure 1).

Among the variables related to patient characteristics, the number of liver metastases was statistically significant; patients with less than ten metastatic nodules showed 9.1% disease-free survival versus 0% for patients with greater than or equal to ten metastatic nodules ( $p = 0.03$ ). The presence of symptoms at diagnosis was also statistically significant, since patients without symptoms to diagnosis showed 18.8% of disease-free survival versus 0% for symptomatic patients ( $p = 0.015$ ) (Table 2). No variable relative to treatment or tumor characteristics had a significant impact on disease-free survival.

## DISCUSSION

Neuroendocrine tumors, although considered slow growing tumors and mildly aggressive, tend to develop distant metastatic disease with relative frequency, and the liver is the most affected organ. The development of liver metastasis results in a significant reduction in survival and quality of life of patients. There is some doubt in the management of patients with liver metastases from neuroendocrine tumors: what is the goal of treatment (curative or palliative)? When should treatment be start? How to treat best?<sup>15</sup>

The goals of treatment when there is metastatic disease are improved quality of life by relieving symptoms

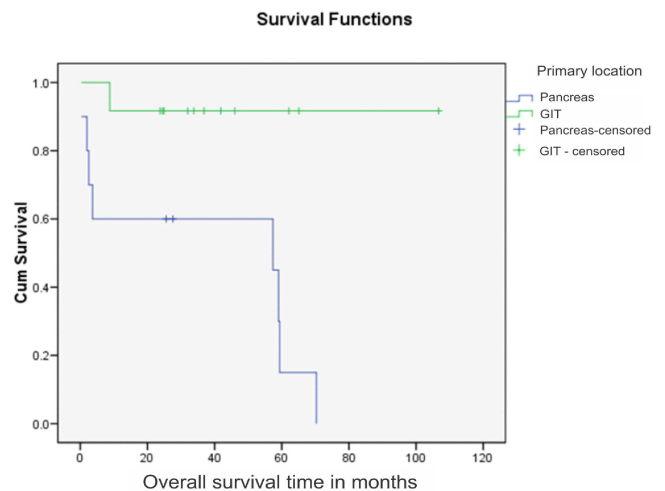
**Table 1 -** Overall survival rates (SR) in five years by the Kaplan-Meier method.

Variable	Category	n	SR(%/5 anos)	p(Log rank)
Presentation of metastases	Synchronous	17	38.2	0.565
	Metachronous	5	80	
Age	< 50 years	13	67.7	0.069
	> 50 years	9	0	
Symptoms	Asymptomatic	6	66.7	0.598
	Symptomatic	16	32.5	
Distribution of metastases	Unilobar	5	40	0.75
	Bilobar	17	45.9	
Number of metastases	< 10	11	49.1	0.394
	> 10	11	36.4	
Gender	Female	10	23.3	0.138
	Male	12	62.5	
Treatment intent	R0	13	38.50	0.610
	R1	9	46.70	
Relapse	Yes	6	42.90	0.9
	No	16	43.80	
Re-hepatectomy	Yes	4	25	0.444
	No	18	72.2	
Postoperative complication	Yes	10	20	0.219
	No	12	75	
Prior resection of primary	Yes	7	85.7	0.2
	No	15	29.3	
Blood transfusion	Yes	8	42.9	0.876
	No	14	43.8	
Primary Location	Pancreas	10	15	0.006
	TGI	12	91.70	
Regional lymph node disease	Yes	11	81.80	0.15

and increased survival. Surgical resection is the only potentially curative treatment.

Other forms of treatment have been employed with intra-arterial chemoembolization and systemic treatment, with results poorer than resection<sup>13</sup>. Due to the indolent behavior and less aggressive evolution when compared with other metastatic diseases to the liver, patients with liver metastases deemed unresectable have undergone liver transplantation. The result of the transplant for this group of patients was very heterogeneous, with five-year survival ranging from 14 to 90%, being much better for patients with non-pancreatic tumor metastasis<sup>3</sup>. For patients with restricted but unresectable liver disease, transplantation appears to be the best therapeutic alternative<sup>16</sup>.

In our study, complete surgical resection (R0) of liver metastases was achieved in 13 patients (59.1%), although the operation with curative intent has been intended in all patients. Our data are consistent with the literature, which describes a complete resection rate ranging between 20% and 54%<sup>13,17-19</sup>. This high percentage of incomplete resection is due to the low sensitivity of preoperative diagnostic methods<sup>20</sup>, the thorough

**Figure 1 -** Overall survival curve according to the location of the primary tumor.

Legend: Cum: cumulative; GIT: Gastrointestinal Tract.

examination of the cavity, with detailed palpation of the liver and the use of intraoperative ultrasonography being of great importance.

**Table 2** - Disease-free survival rates (DFS) in five years by the Kaplan-Meier method.

Variable	Category	n	DFS(%/5 years)	p(Log rank)
Presentation of metastasis	Synchronous	17	17.6	0.155
	Metachronous	5	0	
Age	< 50 years	13	19.2	0.162
	≥ 50 years	9	11.1	
Symptoms	Asymptomatic	6	18.8	0.015
	Symptomatic	16	0	
Distribution of metastases	Unilobar	5	0	0.121
	Bilobar	17	17.6	
Number of metastases	< 10	11	9.1	0.03
	≥ 10	11	0	
Gender	Female	10	0	0.966
	Male	12	25	
Re-hepatectomia	Yes	4	0	0.796
	No	18	27.8	
Blood transfusion	Yes	8	0	0.319
	No	14	21.4	
Postoperative complication	Yes	10	0	0.676
	No	12	33.3	
Prior resection of primary	Yes	7	14.3	0.621
	No	15	0	
Primary location	Pancreas	10	0	0.052
	TGI	12	41.7	
Regional lymph node disease	Yes	11	36.4	0.347
	No	11	9.1	

Because of the rarity of these neoplasms, most studies are retrospective and composed of small case series, ranging between 13 and 47 patients, especially when only analyzing patients who underwent surgical treatment of metastases<sup>17,20-22</sup>.

In our study, the overall five-year survival after liver resection was 44.2% over a mean follow-up of 37 months. Although superior to historical controls of patients who did not receive surgical treatment<sup>23-25</sup>, our results were relatively lower than those of more recent studies<sup>13,24-26</sup>. These overall survival rates can be explained by the characteristics of our study population, comprised of 45.5% of patients with primary tumor originating in the pancreas; bilobar involvement of hepatic parenchyma in 77.3% of cases; average size of metastases 48,3mm; synchronicity between the primary tumor and liver metastasis in 77.3% of patients; and half of patients with over ten metastatic nodules.

In our study, liver metastases originating from pancreatic neuroendocrine tumors showed significant differences in overall survival. Patients with pancreatic primary tumor showed an overall five-year survival of 15%, this being 91.7% for those with primary tumors originating in the digestive tract. Neuroendocrine tumors of the pancreas and cecum are those with the highest percentage of non-localized disease, 71.9% and 81.5%, respectively<sup>2</sup>. The

pancreatic neuroendocrine tumors develop liver metastases from 30% to 85% of cases<sup>27</sup>. Several studies have demonstrated adverse movement in neuroendocrine tumors originating in the pancreas<sup>3,17,28-3</sup>.

Patients with liver metastases from TNE have high recurrence rate<sup>28,30-32</sup> and less than 15% are cured<sup>6,13</sup>. In this study, relapse occurred in 46.1% of patients who underwent complete resection of liver metastases. Disease-free survival was 13.6%. A multi-institutional study of 339 patients undergoing liver resection for TNE metastases reports AN overall survival of 74% and 51% in five and ten years, respectively. However, despite the good results in terms of survival, the authors reported 94% of recurrence<sup>33</sup>.

The number of metastatic lymph nodes showed significant influence on disease-free survival; patients with a number higher than or equal to ten metastatic nodules had lower disease-free survival. The presence of symptoms at diagnosis also had a significant influence on disease-free survival, and symptomatic patients had lower disease-free survival.

In the past, liver resections were considered highly complex operations. Nevertheless, with the development of surgical and anesthetic techniques and perioperative management, these operations have become safer, especially if performed in specialized centers. In our study, eight patients (36.3%) had complications within 30 days

after surgery and, of these, one was fatal. In the analysis of predictive factors for the occurrence of postoperative complications, the highlights were the performance of multiple hepatectomies and other procedures associated with the liver resections. Likewise, S oreide et al.<sup>34</sup> demonstrated that patients submitted to aggressive surgical treatment, including the re-hepatectomy and operations in two stages, had gain in overall survival, but displayed high complications (33%) and mortality (9%).

The sample size of several published studies is invariably small. The rarity of neuroendocrine tumors enables few institutions to collect large series, making it difficult for a single center to have sufficient numbers of patients to allow the conduction of studies on the clinical course of the disease for long periods.

Despite the great heterogeneity of presentation and clinical behavior of TNE, it is clear that surgical treatment plays an important role in addressing these patients. It is worth noting that, in symptomatic patients with multiple nodules, surgical treatment in isolation is not able to provide cure. In this situation, and also in those patients with TNE metastases of pancreatic origin, of known worse prognosis, other forms of treatment deserve to be studied. Efforts should be taken to the selection of patients seeking surgical treatment and new therapeutic approaches.

In conclusion, liver metastases originating from pancreatic neuroendocrine tumors proved to be a negative prognostic factor. Symptomatic patients with multiple metastatic nodules showed a significant reduction in disease-free survival.

## R E S U M O

**Objetivos:** determinar fatores progn sticos com poss vel impacto na morbimortalidade e sobrevida de pacientes submetidos ao tratamento cir rgico das met stases hep ticas de tumores neuroend crinos. **M todos:** foram estudados 22 pacientes submetidos   ressec o hep tica por met stases de tumores neuroend crinos entre 1997 e 2007. Dados epidemiol gicos e cl nicos foram correlacionados com morbimortalidade e sobrevidas global e livre de doen a. **Resultados:** doze pacientes eram do sexo masculino e dez do feminino com m dia de idade de 48,5 anos. Doen a bilobar esteve presente em 17 pacientes (77,3%). Em dez pacientes (45,5%) o tumor prim rio se originou no p ncreas, em oito no  leo terminal, em dois no duodeno, em um no reto e em um no jejuno. Ressec o cir rgica completa (R0) foi alcan ada em 59,1% dos pacientes. Oito pacientes (36,3%) evolu ram com complica es no p s-operat rio imediato, com um paciente evoluindo ao  bito por septicemia. Todos os pacientes submetidos   re-hepatectomia e/ou hepatectomia em dois tempos evolu ram com complica es no per odo p s-operat rio. A sobrevida global em um e cinco anos foi 77,3% e 44,2%. A sobrevida livre de doen a em cinco anos foi 13,6%. O tumor neuroend crino prim rio do p ncreas ( $p=0,006$ ) foi associado   redu o na sobrevida global. Os pacientes com n mero de n dulos metast ticos <10 ( $p=0,03$ ) e os assintom ticos ao diagn stico ( $p=0,015$ ), apresentaram maior sobrevida livre de doen a. **Conclus o:** met stases hep ticas oriundas de tumores neuroend crinos pancre ticos demonstraram ser um fator progn stico negativo. Pacientes sintom ticos e com m ltiplos n dulos metast ticos apresentam redu o significativa na sobrevida livre de doen a.

**Descritores:** Tumores Neuroend crinos. Hepatectomia. An lise de Sobrevida. Met stase Neopl sica.

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