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Using chemotherapy against metastatic pancreatic neuroendocrine neoplasm: how aggressively do we treat it? Real world data from a Brazilian Cancer Center

Usando quimioterapia contra neoplasia neuroendócrina pancreática metastática: o quão agressivamente tratamos? Dados de mundo real de um Cancer Center brasileiro.

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ABSTRACT

Introduction: Pancreatic neuroendocrine neoplasms (pNEN) have poor prognosis. Available treatment options are limited. We aimed to evaluate the clinical characteristics and outcomes in patients with pNEN undergoing systemic chemotherapy. **Methods:** Retrospective study of patients with metastatic pNEN diagnosed between January 2000 and April 2018 in A.C. Camargo Cancer Center. We evaluated epidemiological characteristics and outcomes of patients who received systemic chemotherapy between the first and third-lines. **Results:** 35 patients with median age of 54.4 years; 51.4% had diabetes mellitus and 62.9% had smoking history. Most primary tumors were located in pancreatic body or tail and 34.3% were described as well or moderately differentiated, 40% were of high grade. Overall, chemotherapy from first to third-line was prescribed 50 times, 62% consisted of platin doublet, the chosen schema 50% of times when Ki-67<20%, 55.5% for Ki-67 between 20% and 55% and 66.7% for Ki-67>55%. The median PFS and RR were 7.8 months and 40.7%; 13 months and 33.3% and 3 months and 0% in the first, second and third-line, respectively. The estimated OS was 53.4 months. We found that female (HR 2.8, p=0.034), DM (HR 4.5, p=0.004), smoking (HR 3.5, p=0.017), high grade tumors (HR 3.8, p=0.025) and tumors localized in head/neck of the pancreas (HR 7.1, p<0.001) were negative prognostic factors for OS in univariate analysis. **Conclusion:** Our real world data shows that doublet platin is a preferred and active schema for treating pNEN, especially in first and second line. It brings the greatest benefit for undifferentiated tumors. Nevertheless, the prognosis remains poor and some factors may contribute to worse outcomes, such as female gender, silent tumors that do not manifest DM, poorly differentiated tumours, smoking and location in the head and neck of the pancreas.

Keywords: Neuroendocrine tumors; Pancreatic neoplasms; Drug therapy.

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RESUMO

Introdução: As neoplasias neuroendócrinas pancreáticas (pNEN) têm mau prognóstico. As opções de tratamento disponíveis são limitadas. Nosso objetivo foi avaliar as características clínicas e os resultados em pacientes com pNEN submetidos à quimioterapia sistêmica. **Métodos:** Estudo retrospectivo de pacientes com pNEN metastático diagnosticados entre janeiro de 2000 e abril de 2018 no A.C. Camargo Cancer Center. Avaliamos características epidemiológicas e desfechos de pacientes que receberam quimioterapia sistêmica entre primeira e terceira linha. **Resultados:** 35 pacientes com idade mediana de 54,4 anos; 51,4% tinham diabetes mellitus e 62,9% tinham história de tabagismo. A maioria dos tumores primários estava localizada no corpo ou cauda do pâncreas e 34.3% foi descrito como bem ou moderadamente diferenciados, 40% eram de alto grau. No geral, a quimioterapia de primeira a terceira linha foi prescrita 50 vezes, 62% consistiu em doublet de platina, esquema escolhido em 50% das vezes quando Ki-67<20%, 55,5% para Ki-67 entre 20% e 55% e 66,7% para Ki-67>55%. As medianas de SLP e TR foram de 7,8 meses e 40,7%; 13 meses e 33,3% e 3 meses e 0% de primeira, segunda e terceira linhas, respectivamente. A SG estimada foi de 53,4 meses. Encontramos que o sexo feminino (HR 2,8, *p*=0,034), DM (HR 4,5, *p*=0,004), tabagismo (HR 3,5, *p*=0,017), tumores de alto grau (HR 3,8, *p*=0,025) e tumores localizados na cabeça/colo do pâncreas (HR 7,1, *p*<0,001) foram fatores prognósticos negativos para SG na análise univariada. **Conclusão:** Nossos dados do mundo real mostram que a platina dupla é um esquema preferencial e ativo para o tratamento de pNEN, especialmente em primeira e segunda linha. Traz o maior benefício para tumores indiferenciados. Apesar disso, o prognóstico permanece ruim e alguns fatores podem contribuir para piores desfechos, como sexo feminino, tumores silenciosos que não manifestam DM, tumores pouco diferenciados, tabagismo e localização na cabeça e pescoço do pâncreas.

Descritores: Tumores neuroendócrinos; Neoplasias pancreáticas; Terapia medicamentosa.

INTRODUCTION

Neuroendocrine neoplasms (NENs) are a group of heterogeneous malignancies from neuroendocrine cells throughout the body, with an incidence of 2.5-5 per 100,000 people per year, corresponding to less than 0.5% of malignant neoplasms. The gastrointestinal tract (GIT) contains the majority of cases of NEN, 6% of which are located in the pancreas. Pancreatic neuroendocrine neoplasms (pNEN) represent approximately 1.3% of all pancreatic cancer cases but this incidence is increasing and this demands attention because the tumor is very rare, the diagnosis can be challenging and the prognosis is adverse.[1-6]

Several studies have already shown that the primary site is the main prognostic factor in metastatic disease and that pNEN is among the worst evolution, even in the case of the most well differentiated tumors, with a global survival between 24 and 27 months.[1] When compared to other primary GIT sites, the risk of death for pNEN is 3.7 times higher (95%CI 1.26-10.81, *p*=0.017). In this same analysis, another factor of worse important prognosis was described; the lowest degree of differentiation showed a 3-fold higher risk (95%CI 1.09-8.2, *p*=0.34) when compared to well-differentiated tumors.[7]

According to the most recent classification by the World Health Organization (WHO) and the European Neuroendocrine Tumor Society, pNEN are divided into four subgroups based on histological description, mitotic activity and Ki-67 immunostaining: neuroendocrine tumors (NET) are histologically well (WD) or moderately differentiated (MD) and can be G1 (mitotic count <2/10 high power fields [HPF] and/or Ki-67≤2%), G2 (mitotic count 2-20/10 HPF and/or Ki-67 3-20%) or G3 (mitotic count>20/10 HPF and/or Ki-67>20%). NETs are similar in terms of clinical course and molecular characteristics, such as mutations in MEN1 (44%) and DAXX/ATRX (43%). In contrast, G3 tumors described as poorly differentiated (PoD) are called neuroendocrine carcinomas (NEC). These tumors have a worse prognosis and frequently harbor TP53 (56%) and RB1 (72%) mutations, have small or large cell morphology, and often Ki-67>55%.[8-12]

Whether NET or NEC, unfortunately about 65% of pNEN cases are metastatic at diagnosis, with the liver being involved in 90% of these patients. This can be explained because these tumors are generally indolent and the minority are functioning, that is, few are associated with hormonal syndromes and, once silent, are diagnosed late.[1,13,14]

Among the various treatment options, the most commonly used are somatostatin analogues and tyrosine kinase inhibitors (TKI) based on phase III studies for well differentiated tumors with low response rates. (Table 1).[2,6,15-17] Regarding chemotherapy, most studies are retrospective analysis involving several primary sites, with response rates (RR) of up to 42% with platinum doublet for Ki-67>55% and 15% for Ki-67 between 20 and 55%.[18] A randomized phase II trial that was presented at the 2018 American Society of Clinical Oncology conference comparing temozolomide with its combination with capecitabine in patients with low-grade or intermediate (i.e., Ki-67 up to 20%) metastatic or unresectable pNETs. The combination group presented a significant improvement in median progression-free survival (PFS) of 8.3 months (22.7 vs. 14.4 months; HR=0.58 [0.36-0.93], p=0.023) and RR of 33.3%.[19,20]

Given the relative rarity and specificity of the disease, we believe that an analysis of an institutional cancer center experience elapsed with the difficulties of the real world can bring relevant information about the subject. Herein we report the results of a retrospective study including 35 patients with metastatic pNEN treated with chemotherapy in first through third-line settings. We aim to assess the efficacy and the institutional schema of chemotherapy in this setting.

METHODS

We performed a retrospective study in a single cancer-specialized Brazilian hospital. It was based on routinely collected data retrieved from the electronic charts of patients with pNEN submitted to palliative chemotherapy. Data were collected from January 2000 to April 2018. This study was approved by the A.C. Camargo Cancer Center internal ethics review board.

Patients

The patients harbor the following characteristics: age ≥18 years, with pathologically confirmed diagnosis of pNEN (mixed histology patients were excluded) from January 1st 2000 to April 30th 2018 and treated with any palliative chemotherapy on the first to third-line. Patients who underwent treatment outside A.C. Camargo Cancer Center were excluded.

Predictor variables

We collected data on the following baseline patients' characteristics: age, gender, number of comorbidities, smoking, previous diagnosis of diabetes mellitus (DM), body mass index (BMI), familial history of cancer, ECOG performance status, tumor site/neck vs. body/tail), presence of functional symptoms, histologic grade, mitotic index, pathological description (WD or MD vs. PoD or NEC), primary tumor surgery, number of metastatic sites, radiological response and PFS by the chemotherapy. Tumor response data were retrieved from charts registry and there was no independent radiological imaging or pathologic review. Despite recognizing the importance of a complete anatomopathological description including Ki-67 index, mitotic index and histological grade, only reports prior to 2010 were reviewed. Therefore, the classification used at the time of the study was the WHO 2010 classification. The missing data were not inferred from secondary descriptions in the medical records or pathological reports so we could evaluate the real world assistance and it fails.

Outcome variables

The primary outcome of the study was PFS (defined as radiological progression or death from the date of start of treatment). The secondary outcome was RR of patients diagnosed with pNEN and treated with palliative chemotherapy on first, second and third-line, overall survival of the entire population (defined as death from the date of start of treatment) and associated prognostic factors for all clinical and pathological characteristics available in the sample.

Patients were censored at the last follow-up visit in the absence of an event (radiological progression or death). The response rate was defined as partial response and complete response according to RECIST 1.1 criteria, as described in the patients charts.

Statistical analysis

To analyze the descriptive demographic characteristics, frequencies, means and medians were used; for comparison between the characteristics of the groups was made analysis of association between categorical variables using chi-square test or Fisher's exact test, when appropriate.

Table 1. Active target therapies for pNEN based on phase 3 trials.

Target therapy	Study	Population	Results
Everolimus	RADIANT-3 (6)	G1/G2 N = 410	PFS: 11m; RR: 5%
	RADIANT-4 (2)	G1/G2 N = 302	PFS: 11m; RR: 2%
Sunitinib	Raymond et al (15)	G1/G2 N = 171	PFS: 11,4m; RR: 9.3%
Surufatinib	Sanet-p (16)	G1/G2 N = 264	PFS: 10,9m; RR: 19%
Lanreotide	CLARINET (17)	G1/G2 N = 204	PFS: NR; RR: 0%

G: grade; RR: response rate; PFS: progression-free survival; NR: not reached

Survival analysis, disease control time, and evaluation of prognostic factors were estimated using the Kaplan-Meyer method and the analysis of the impact of the various variables by Cox proportional-hazards models to describe factors associated with survival. However, no multivariate analysis was performed given the small sample. We considered two-tailed *p*-values<0.05 as statistically significant. Statistical analysis was performed with SPSS software version 23.

RESULTS

We identified 83 patients with metastatic pNEN diagnosed in our institution from January 1st, 2000 through April 30th, 2018. There were 46 patients who received chemotherapy in the first, second or third-line setting. Patients were excluded due to mixed histology (8 patients) and treatment outside A.C. Camargo Cancer Center (three patients). As a result, 35 patients constitute the study population. Patients' characteristics are shown in Table 2. The median age was 54.4 years. Twenty-three (65.7%) patients were male and all patients presented ECOG 0 or 1 (1 missing data). The previous diagnosis of DM and overweight/obesity was present in 18 (51.4%) and 17 (48.6%) of the patients, respectively, and most have a previous smoking history (N = 22, 62.9%). Most primary tumors were located in the body or tail of the pancreas (N = 22; 62.9%) and only 5 (14.3%) were functioning. Although 80% (N = 28) of patients presented synchronic metastasis at diagnosis, 60% of these were submitted to surgery of the primary tumor. In description of pathological reports the number of WD or MD patients was 12 (34.3%), PoD was 5 (14.3%), NEC was 9 (25.7%) and 9 patients had missing report; 15 patients (42.9%) had Ki-67 index up to 20%, 16 (45.7%) had more than 20% and 4 patients had no Ki-67 index description.

Table 2. Demographic and clinical features of the study population

Age (years)	54.4 (24.9-76.9)	Site of the tumor	
		Head/neck	12 (34.2%)
		Body/tail	22 (62.9%)
		Missing	1 (2.9%)
Sex		Surgery of the tumor	
Male	23 (65.7%)	Yes	17 (48.6%)
Female	12 (34.3%)	No	18 (51.4%)
ECOG		Metastasis diagnosis	
0	26 (74.2%)	Synchronic	28 (80%)
1	8 (22.9%)	Metachronic	7 (20%)
Missing	1 (2.9%)		
DM		Smoking	
Yes	18 (51.4%)	Yes	12 (34.2%)
No	15 (42.9%)	No	22 (62.9%)
Missing	2 (5.7%)	Missing	1 (2.9%)
BMI		Functioning tumor	
≤24	15 (42.9%)	Yes	5 (14.3%)
>24	17 (48.6%)	No	30 (85.7%)
Missing	3 (8.5%)		
Pathological description		Ki-67 index	
WD/MD	12 (34.3%)	≤2%	4 (11.4%)
PoD/NC	14 (40%)	3-19%	11 (31.4%)
Missing	9 (25.7%)	≥20%	16 (45.8%)
		Missing	4 (11.4%)
Grade		Mitotic index	
1	3 (8.5%)	<2/10	7 (20%)
2	7 (20%)	2-20/10	5 (14.2%)
3	8 (22.9%)	>20/10	3 (8.5%)
Missing	17 (48.6%)	Missing	20 (57.2%)

ECOG - Eastern Cooperative Oncology Group. DM - diabetes mellitus. BMI - body mass index. WD - well differentiated. MD - moderately differentiated. PoD - poorly differentiated.
NEC - neuroendocrine carcinoma.

Unfortunately, almost 57% of pathological reports had no description of mitotic index and 17 (48.6%) had no grade described. Ten patients were grade 1 or 2 (28.6%) and 8 (22.9%) were grade 3.

Treatments

Overall, for the 35 patients chemotherapy from first to third-line was prescribed 50 times, and 62% consisted of platin doublet. In all lines, radiologic response was available for 44 treatments with an OR of 31.8%, higher when Ki-67>20% in PoD/NEC tumors but no response was seen in the third line setting. In the first-line, chemotherapy was used for 27 patients and about 70% consisted of platin doublet. The median PFS was 7.8 months (0.8-14.7) and the OR was 40.7%; for WD/MD was 33.3% and for PoD/NEC the RR was 57.2%. The RR was similar according to Ki-67 index intervals. In the second-line, chemotherapy was used for 13 patients and 53.8% of them received platin doublet. Previously, almost 31% received somatostatin analogue (SA) and the others received chemotherapy. In this line, the median PFS of 13 months (0.5-28.8) and 33.3% of OR, with no response when Ki-67 was <20%, 25% of RR when Ki-67>55% and all patients with Ki-67 between 20 and 55% responded. According to the description, half of the patients responded with PoD/NEC and for WD/MD, the RR was 25%. In the third-line, 10 patients received chemotherapy, half platin doublet, but no response was seen and the PFS was 3 months (1.8-4.6). In the previous line, 80% received some chemotherapy and 10% received SA. Table 3 contains the PFS, overall RR and responses according to Ki-67 intervals and pathological description in the three lines of treatment.

We assessed the chemotherapy schema according to the Ki-67 interval in three lines and the main combination was platin plus etoposide followed by capecitabine plus temozolomide (CAPTEM). It is depicted in Table 4. Platin double was chosen 50% of times when Ki-67<20%, 55.5% for Ki-67 between 20% and 55%, and 66.7% for Ki-67>55%.

The median follow-up was 51.5 months and 18 deaths occurred in the studied period. The estimated OS was 53.4 months (35.5-71.4) for the entire population. We found that female (HR 2.8, 95%CI 1.04-7.6, p=0.034), DM (HR 4.5, 95%CI 1.5-13.6, p=0.004), smoking (HR 3.5, 95%CI 1.2-10.3, p=0.017), PoD/NEC tumors (HR 3.8, 95%CI 1.1-13.5, p=0.025) and tumors localized in head/neck of the pancreas (HR 7.1, 95%CI 2.5-20.7, p<0.001) were negative prognostic factors for OS in univariate analysis (Table 5).

Table 3. Progression-free survival and response rate in all lines.

	1° line	2° line	3º line	All lines
Number of patients	27 (%)	13 (%)	10 (%)	50 (%)
Schema used				
Platin doublet	19 (70.4)	7 (53.8)	5 (50)	31 (62)
Others	8 (29.6)	6 (46.2)	5 (50)	19 (38)
Treatment in previous line				
Chemotherapy	-	8 (61.3)	8 (80)	-
SA	-	4 (30.8)	1 (10)	-
PFS	7.8m	13.0m	3m	-
Variation in months	0.8-14.7	0.5-28.8	1.8-4.3	
Best radiologic response	N=27	N=9	N=8	N=44
OR	11 (40.7)	3 (33.3)	0 (0.0)	14 (31.8)
CR	3 (11.1)	1 (11.1)	0 (0.0)	4 (9.0)
PR	8 (29.6)	2 (22.2)	0 (0.0)	10 (22.7)
SD	7 (25.9)	3 (33.3)	4 (50.0)	14 (31.8)
PD	7 (25.9)	3 (33.3)	4 (50.0)	14 (31.8)
RR according Ki-67	N=23	N=10	N=8	N=41
<20%	38.5%	0.0%	0%	25.0%
20-55%	40.0%	100%	0%	44.4%
>55%	40.0%	25.0%	0%	35.7%
RR according description	N=19	N=13	N=10	N=42
WD/MD	33.3%	25.0%	0%	27.8%
PoD/NEC	57.2%	50.0%	0%	41.2%

PFS - progression-free survival. OR - overall response. CR - complete response. PR - partial response. SD - stable disease. PD - progressive disease. RR - response rate. WD - well differentiated. MD - moderately differentiated. PoD - poorly differentiated. NEC - neuroendocrine carcinoma

Table 4. Chemotherapy schema according to Ki-67.

Schema	Ki67 <20%	Ki 67 20-55%	Ki 67 >55%	Total
Platin + VP	7 (35%)	5 (55.5%)	5 (41.7%)	17
Platin + Irinotecan	4 (20%)	-	3 (25%)	7
Irinotecan	1 (5%)	-	-	1
FOLFOX	2 (10%)	1 (11.1%)	-	3
Temozolomide	1 (5%)	-	-	1
CAPTEM	2 (10%)	3 (33.3%)	1 (8.3%)	6
Capecitabine	1 (5%)	-	1 (8.3%)	2
DTIC + 5-FU	2 (10%)	-	1 (8.3%)	3
Paclitaxel + Bevacizumab	-	-	1 (8.3%)	1
Total	20 (100%)	9 (100%)	12 (100%)	41 (100%)
Platin doublet	11 (55%)	5 (55.5%)	8 (66.7%)	

Table 5. Prognostic factors for overall survival.

Variable	HR	95% CI	p value	Variable	HR	95% CI	p value
Sex				Description			
Male	1	-	0.034	WD/MD	1	-	0.025
Female	2.8	1.04-7.6		PoD/NEC	3.8	1.1-13.5	
DM				Site			
No	4.5	1.5-13.6	0.004	Head/neck	7.1	2.5-20.7	<0.001
Yes	1	-		Body/tail	1	-	
Metformin use				Ki-67 index			
No	2.7	0.9-8.5	0.073	≤20%	1	-	0.356
Yes	1	-		>20%	1.7	0.5-5.6	
Surgery				Grade			
No	2.5	0.9-7.0	0.064	1/2	1	-	0.244
Yes	1	-		3	1.6	0.7-3.6	
Smoke				Functioning			
No	1	-	0.017	No	1	-	0.14
Yes	3.5	1.2-10.3		Yes	2.2	0.7-6.3	

An unplanned analysis was performed to show the relationship between primary site location and anatomopathological description. The majority of well differentiated tumors (81.3%) were located in the body and tail of the pancreas whereas 66.7% of the poorly differentiated tumors or neuroendocrine carcinomas were located at the head of the pancreas (p=0.031).

DISCUSSION

The treatment of pNEN varies according to its classification, with papers demonstrating the benefit of AS and TKI in lower grade tumors[15,17] and these drugs are often preferred as first line because of better tolerance and lower side effects. However, chemotherapy has efficacy studied in both well differentiated tumors[19] and higher-grade tumors.[18] To determine the best strategy, then, it is necessary for the oncologist the highest possible diagnostic accuracy, and it depends on the accomplishment of anatomopathological reports and test details, as has been recommended by the topic guidelines and classification according to WHO.[21] However, this information may be incomplete in the real world, as shown in our paper, which may hinder decision making. In our reports, the description was absent in about a quarter of cases, Ki-67 was not performed in 11.4%, the grade was not described in 48.6% and the mitotic index in about 57% of the patients. This may reflect the reality of many cancer centers but we must remember that we have data collected since 2000, when knowledge of the topic and guidelines were still under development. Therefore, it is often necessary to perform a pathology review. Despite this, our casuistry is consistent with historical data.[22]

The reason for choosing chemotherapy over targeted therapy for lower grade tumors was because of a high volume of disease or prominent symptoms that required higher response rates. Our study shows the preference for platinum doublet-based chemotherapy regimens in earlier lines, with the scheme being chosen more than 70% of the time in the first line and almost 54% in the second line. We observed, however, that the chance of prescribing such a scheme increases as the index increases, with 66.7% of schemes based on doublet platinum when Ki-67>55%.

The best evidence from the literature to treat high grade NEN comes from a retrospective study with 252 patients, 15% of which was pancreatic, which included tumors with Ki-67>20% receiving doublet platinum as the first-line in 78% of cases. This study showed that the Ki-67 cut of 55% had a better correlation with RR, with a 15% response and 14-month survival for Ki-67 of 20 to 55% and 42% of response and a 10-month survival for Ki-67>55%.[18] Our study, which consists exclusively of patients with pancreatic tumors, shows a similar RR (40%) for Ki-67>55% and PFS of 7.8 months, but suggests that pNEN has a greater platinum doublet response than others GIT NEN than pancreatic in the interval of Ki-67 between 20-55% (RR of 40%). Nevertheless, virtually all patients will experience disease progression after the first line and literature is very scarce regarding sequential lines of chemotherapy in NEN. For high-grade tumors, there is data showing that after progression to the platinum-based regimen, FOLFOX and FOLFIRI can provide RR of 29% and 31%, respectively, and PFS near 4 months both.[23,24] Our data showed RR of similar response for platinum doublet in the second line (33.3%) but PFS of 13 months, higher in pNEN when compared to NEN in general. A trial to evaluate CAPTEM or FOLFIRI as second-line therapy in NEC is open for recruiting.[25]

The present study then suggests that platinum doublet may be an appropriate scheme for pNEN, especially in the first and second-line. However, although platinum doublet may provide a PFS of 3 months in the third line setting, considerations should be made regarding toxicity and tolerance of the scheme and also consider that there was no radiologic response.

Our sample presented a high median OS, of 53.4 months, when compared with historical data,[1] due to a predominance of well-differentiated pNENs, although 40% were poorly differentiated or neuroendocrine carcinomas, 45.7% with Ki-67 greater than 20% and about 23% of grade 3.

Regarding the prognostic factors, our univariate analysis showed that, in addition to the classic factors of worse prognosis such as history of smoking (HR 3.5, $p<0.05$) and less differentiated tumors (HR 3.8, $p<0.05$), female gender, having no DM and tumors located in the head and neck region of the pancreas are related to lower survival (HR 2.8, 4.5 and 7.1 respectively, $p<0.05$).

There are case reports in the literature that show antiproliferative activity of hormone therapy in patients with NEN, with carcinoid syndrome control and regression of retroperitoneal fibrosis with tamoxifen, and a prospective study suggesting a clinical benefit with the use of medication in the disease.[26-29] So perhaps hormonal receptors signalling actually plays a role in NEN biology, which may justify the worst outcome for females in our study but the lower number of females in the study population is also a potential reason for this dismal outcome. We await results from a prospective ongoing study that aims to assess the role of tamoxifen in advanced NETs that express progesterone and estrogen receptors.[30]

The fact that patients without DM presented a worse outcome in relation to DM can not be attributed, in our study, to the use of metformin, which was not shown to be a prognostic factor. Impaired glucose tolerance or DM often occurs in pNEN patients as a consequence of hormonal hypersecretion by the tumor, specifically affecting glucose metabolism, or due to tumor mass or surgical and/or pharmacological treatment of the tumor itself may impair glucose tolerance. On the other hand, pre-existing DM may represent a risk factor for developing pNENs.[31] Perhaps, patients without DM can be diagnosed later and with more advanced tumors because they are then a quieter disease and not undergoing previous clinical treatment. Finally, we showed that tumors located in the head and neck of the pancreas have a worse prognosis and our unplanned analysis showed, with statistical significance, that in this location there were more poorly differentiated tumors or neuroendocrine carcinomas (66.73%), whereas in body and tail of the pancreas was located the most differentiated tumors (81.3%). In addition, we know that pancreatic head injuries can bring more complications such as obstructions and surgery, which can bring important comorbidities to these patients.

Our study presents limitations. It is a retrospective study with a relatively modest sample size. Also, most patients were treated before the studies that dictate the most current treatments, possibly hampering outcomes in these patients. There is missing data regarding pathological reports and no radiological review. Nonetheless, our study portrays the outcomes of a homogenous cohort of patients with a rare disease treated in a single center. We believe our study gives an example of real world approach and difficulties in neuroendocrine tumors and adds information to the current knowledge, especially regarding the role of female hormones in these cancer behaviors.

CONCLUSION

To summarize, patients with pNEN derive benefits from platin doublet chemotherapy, especially in the first and second-line. Numerically, the benefit seems to be greatest for undifferentiated tumors. Nevertheless, the prognosis remains poor and some factors may contribute to worse outcomes, such as female gender, silent tumors that do not manifest DM, poorly differentiated, smoking and location in the head and neck of the pancreas.

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