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Pancreatic Neuroendocrine Tumors: The Experience of The "A" Visceral Surgery Department in The Light of the New Who 2017 Classification

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1. Abstract

1.1. Introduction: PNETs represent 1-5% of all NET and about 1% of pancreatic tumors. The object if of this study is to firstly introduce the update of the new WHO 2017 classification and to report epidemiological, clinical, paraclinical, therapeutic, anatomopathological and evolutive characteristics of cases of PNETs treated in our service.

1.2. Material and Method: It is a retrospective study conducted in the department of visceral surgery "A" of the Avicenne Hospital of Rabat including all the patients diagnosed with the PNETs histologically proven. Over 10 years from January 2009 to December 2018. All clinical, paraclinical, therapeutic and evolutionary parameters were collected and studied.

1.3. Results: 17 cases of PNETs were collected. Mean age was 48,47 +/- 15,82 years with a Sex-Ratio of 1.12. The cases were divided into 5 functional PNETs revealed by the symptoms of hypoglycemia and 12 non-functional PNETs were by a tumor syndrome.

The cephalic pancreaticoduodenectomy was the most common operative procedures performed (46,7%), followed by the left sided splenopancreatectomy (33,3%) and surgical enucleation (20%). In 17,7% of cases, the treatment was supplemented by an adjuvant chemotherapy.

After reclassification according to the new WHO 2017 classification: 35.3% of tumors were classified as NET G1, 23.5% of tumors NET G2, 5.9% of tumors NET G3 and 5.9% of tumors NEC G3 with 29.4% of undifferentiated NETs. In general, the evolution was favorable with a 4year overall survival rate of 40%.

1.4. Conclusion: The better knowledge of the clinical, biological and histopronostic characteristics, there have been many improvements in treatment options over the past few years, allowing better management of PNETs.

2. Introduction

Pancreatic neuroendocrine tumors (P-NETs) are tumors defined as rare. They represent less than 2% of all pancreatic carcinomas [1] and between 7 and 36.5% of digestive neuroendocrine tumors, behind intestinal NETs [2,3]. A large portion of these tumors exhibit benign behavior, while other lesions exhibit a profile comparable to pancreatic malignancies with the risk of metastases (mainly hepatic and locoregional lymph nodes) and significant recurrence. Even if their evolution is generally slow, the little symptomatic nature of these lesions explains why certain p-NETs are discovered on considerable masses in size, or even metastatic. They are, however, associated with prolonged survival rates.

The heterogeneity of the clinical presentation of p-NETs and their evolving profile makes it difficult to classify them reproducibly, hence the regular reissue of new systems by WHO, ENETS, AJCC and UICC to obtain an adapted histo-prognostic classification [4,5].

The WHO classification of tumors of endocrine organs has under-

gone several modifications and enhancements, the last of which was published in July 2017 [5] introduced substantial modifications in the classification of p-NETs, the previous version of which dated back to 2010 as part of the WHO classification of digestive tumors [4].

In front of the interesting finding on the one hand the well-differentiated NETs which are grade 1 or 2 (G1 OR G2) and on the other hand the poorly differentiated NETs which are grade 3 (G3), recently a proportion of well-differentiated NETs presenting a high proliferation rate (defined either by a mitotic index or Ki67 index >20%) and whose prognosis is more reserved than for G2 NETs, was identified and thus necessitated the creation of a new category: NETs well differentiated G3 [4].

The other changes concern: [4] The threshold used to separate neuroendocrine tumors G1 and G2, now set at 3%. And the terminology proposed to designate mixed tumors associating a neuroendocrine contingent and non-neuroendocrine contingent: the term mixed adeno-neuroendocrine carcinoma (MANEC) is abandoned in favor of mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN).

The aim of our work is to determine the different characteristics of these tumors by including the new WHO classification 2017 through a retrospective study of a series of cases of p-NETs.

3. Materials and Methods

It is a retrospective study conducted in the department of visceral surgery "A" of the Ibn Sina Hospital of Rabat including all the patients diagnosed with the p-NETs histologically proven on a resection or biopsy piece, for a total of 17 cases, from January 2009 to December 2018.

The diagnosis was made on the histological study of the biopsy samples or of the resection piece with an immunohistochemical study.

The tumors were classified according to the WHO classification 2010 and after a re-reading of the anatomopathological reports, they were reclassified according to the new WHO classification 2017 of the p-NETs.

Clinicopathologic characteristics, imaging study results, follow up surveillance data, and outcome of these patients were retrospectively analyzed. Relevant demographic and clinicopathological data were harvested and compiled from existing medical records. We analyzed the following outcome variables: Date of diagnosis, patient gender, age at diagnosis, presence of symptoms, preoperative imaging characteristics, imaging size by various modalities, presence of lymph nodes and distant metastases, margin status and type of surgical intervention.

The main diagnostic tools used were Abdominal Ultrasound (US) and Computed Tomography (CT). Other diagnostic imaging tools implemented included endoscopic ultrasound (EUS) and magnetic resonance imaging (MRI). The recurrence and disease survival data were collected for prognostic stratification.

The surgical strategy was based on the anatomical location of the tumor and oncologic criteria. The types of surgery performed included atypical pancreatic resections such as enucleation, and more typical forms of resection such as pancreaticoduodenectomies, median and spleno-pancreatectomies. In patients with synchronous liver metastases, simultaneous hepatic resection was performed when the tumor was considered resectable.

All histo-pathological classification and grades were revised. All of the pNETs were reclassified according to the World Health Organization (WHO) classification, 2017 version. According to the WHO classification, all well-differentiated neoplasms are called "neuroendocrine tumors" (NETs) and designated Grade 1 (G1) (mitotic count, <2/10 HPF and/or <3% Ki-67 index) or G2 (mitotic count, 2-20/10 HPF and/or 3-20% Ki-67 index) or G3 (mitotic count, >20/10 HPF and/or >20% Ki-67 index). All poorly differentiated neoplasms are called "neuroendocrine carcinomas" (NECs) and designated G3 (mitotic count, >20/10 HPF and/or >20% Ki-67 index).

Patients were followed up every three to six months for the first three years postoperatively, and then annually thereafter. The actual follow-ups included clinical re-evaluations and abdominal ultrasound. The diagnosis of recurrence was based on imaging findings, with histological confirmation as deemed clinically appropriate.

Quantitative variables are expressed as mean with standard deviation or median or IQ, and compared using Student's t test. Qualitative variables are expressed as numbers with percentages, and compared with the Chi2 or Fisher's exact test, as appropriate. Overall survival rate was calculated from the day of surgery to the date of death or the end of follow-up period. Disease-free survival was calculated using the date of death or recurrence as the time of terminal event. To estimate the association between eligible variables and mean survival time, the Kaplan-Meier test was applied. All variables with P<0,05 was considered statistically significant. Statistical analyses were performed in SPSS statistics version 13.00 (biostatistics, clinical research and epidemiology laboratory of the faculty of medicine and pharmacy of Rabat).

4. Results

Over 10 years, our study collected a total number of 30 cases of digestive NETs with a representative number of 17 cases of pNETs. These 17 cases represented 57% of digestive NETs, but only 8.80% of all pancreatic tumors.

The clinicopathologic results of these patients are summarized in (Table 1 and 2). The mean age of patients was 48.47 ± 15.82 years. No patient was diagnosed incidentally; all patients were symptomatic (100%). The most frequently reported symptoms were respectively: a tumor syndrome (70.6%) represented by an abdominal pain and/or other symptoms of abdominal discomfort (64.7%) were the symptoms most frequently reported. Weight loss and jaundice were documented in 52.9% and 23.5% of patients. And an endocrine syndrome documented in 29.4% of patients (sweating episodes, intense hunger, asthenia, headaches, tremors). Distant metastasis rate at diagnosis was 17.6%. The median postoperative tumor size (N=15) was 4,38cm (range 1.20-12.0) and proportion of tumors measuring < 1cm, 1-2cm, and ≥ 2cm was 0%, 20% and 80% respectively. These findings are summarized in (Table 1).

Table 1: Clinical characteristics of 17 patients diagnosed with pNETs.

Clinical characteristics	No. (%)
Age (years)	48.47±15.82
Age < 50	8 (47.1%)
Age ≥ 50	9 (52.9%)
Gender	
Female	9 (47.1%)
Male	8 (52.9%)
Medical history	
Tabacco use	2 (11.8%)
HTN	5 (29.4%)
Diabetes	4 (23.5%)
GERD	0 (0%)
PUD	0 (0%)
PPIs medication	0 (0%)
NEM 1	0 (0%)
Symptom	
Asymptomatic	0 (0%)
Abdominal pain or discomfort	11 (64.7%)
Jaundice	4 (23.5%)
Weight loss	9 (52.9%)
Palpable abdominal mass	2 (11.8%)
Endocrine syndrome	5 (29.4%)
Deterioration of clinical state	8 (47.1%)
Tumor Location	
Head	8 (47.1%)
Body only	1 (5.9%)
Tail only	2 (11.8%)
Body and tail	5 (29.4%)
Isthmus	1 (5.9%)
Distant metastasis at initial diagnosis	3 (17.6%)
Bilobar liver metastases	2 (11.8%)
Unilobar liver metastases	1 (5.9%)
Surgical treatment method	
No surgery	2 (11.8%)
Palliative surgery	1 (5.9%)
Cephalic duodenopancreatectomy	7 (41.3%)
Spleno-pancreatectomy	5 (29.4%)
Enucleation	3 (17.6%)
Postoperative measured tumor size (cm)	4.38cm (1.20-12cm)
< 1cm	0 (0%)
1-2cm	3 (20%)
≥ 2cm	12 (80%)
[2 patients not operated : tumors size N=15]	
Functioning pNETs (Insulinoma)	5 (29.4%)
Nonfunctioning pNETs	12 (70.6%)

Table 2: Pathological characteristics of 17 patients diagnosed with pNETs.

Pathological characteristics	No. (%)
Histological differentiation	
Well differentiated	15 (88.2%)
Poorly differentiated	2 (11.8%)
TNM : (N=15)	
T stage	
T1	2 (13.33%)
T2	2 (13.33%)
T3	2 (13.33%)
T4	1 (6.67%)
N stage	
Nx	1 (6.67%)
N0	5 (33.33%)
N1	1 (6.67%)
M stage	
Mx	2 (13.33%)
M0	4 (26.66%)
M1	1 (6.67%)
2010 WHO classification	
Well differentiated	
NET G1	7 (41.2%)
NET G2	2 (11.8%)
Poorly differentiated	
NEC G3	1 (5.9%)
MANEC	0 (0%)
Not determined	5 (29.4%)
Tumors classified according to WHO 2017 (from the start)	2 (11.8%)
2017 WHO Classification: reclassification of the anatomopathological reports:	
Well differentiated	
NET G1	6 (35.3%)
NET G2	4 (23.5%)
NET G3	1 (5.9%)
Poorly differentiated	
NEC G3	1 (5.9%)
MiNEN	0 (0%)
Not determined	5 (29.4%)
Functioning pNETs (Insulinoma)	5 (29.4%)
Nonfunctioning pNETs	12 (70.6%)

NET : neuroendocrine tumor NEC : neuroendocrine carcinoma MANEC : Mixed adenoneuroendocrine carcinoma MiNEN : Mixed neuroendocrine non-neuroendocrine neoplasm Not determined : indefinite grade on the pathology report received

Table 3: Summary table of the reclassification of the different tumors in our series from anatomopathological reports from WHO 2010 to the WHO classification 2017.

OMS 2010	STATUTE	OMS 2017
7 NET G1	6 unchanged	6 NET G1
	1 changed	**1 NET G2**
2 NET G2	Unchanged	2 NET G2
1 NEC G3	Unchanged	1 NEC G3
5 not determined	Unchanged	5 not determined

Seven out of 15 operating pieces (46.67%) were classified according to the TNM classification [4, 5], the results were found on the anatomopathological reports. Two tumors (13.33%) were classified as pathologic T1 stage, 2 tumors (13.33%) as T2, 2 tumors (13.33%) as T3 and 1 tumor (6.67%) as T4. In pathological N staging, 6.67% (n=1) had unknown lymph node (LN) metastasis status (Nx), 33.33% (n=5) had no pathological documented LN metastasis (N0) and 6.67% (n=1) had LN metastasis (N1). There were 4 tumors (26.66%) without metastasis (M0) and only one tumor (6.67%) with distant metastasis which were all liver metastasis.

Pathologic analysis showed that of 17 pNETs, 5 tumors (29.4%) had undetermined grade on the anatomopathological reports, 10 tumors (70.6%) with identified grade based on the 2010 WHO classification and 2 tumors (11.8%) were classified directly according to the 2017 WHO classification.

The reclassification of the tumors in our case series (N = 10) from the different data recorded through the anatomopathological reports: the mitotic index, the proliferation index and the degree of differentiation, based on the new classification WHO 2017. These are summarized in (Table 3).

After the reclassification of the 10 tumors from the WHO 2010 based on the classification of the WHO 2017: One tumor was found NET G2 according to the WHO 2017 while it was classified NET G1 according to the WHO 2010 while the other categories have not undergone a change of grade.

The median overall survival (OS) was 29 ± 8.41months. The overall 6-month survival was 86.67%, 2 years 60%, 4 years 40% and 8 years 13.33% (Figure 1).

The median of disease-free survival (DFS) was 24 ± 4.67months. The disease-free survival rate was 86.67% at 6 months, 60% at 1 year, 53.33% at 2 years, 33.33% at 4 years, 20% at 6 years and 6, 67% at 8 years old (Figure 2).

In our study, among the 15 patients who underwent curative surgery, a third of them recurred: 2 patients recurred within 1st post-operative year (7 months and 8 months) and 3 patients recurred between the 3rd and 6th post-operative year (26 months, 44 months and 73 months) (Figure 3).

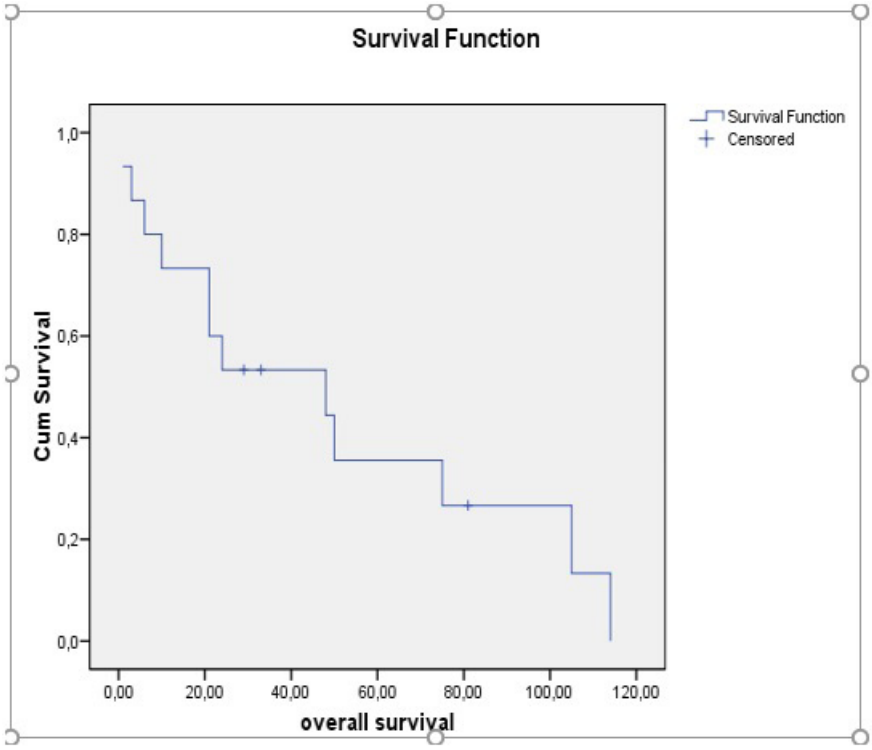

Figure 1: The overall survival curve for the 15 patients in our series receiving curative surgery.

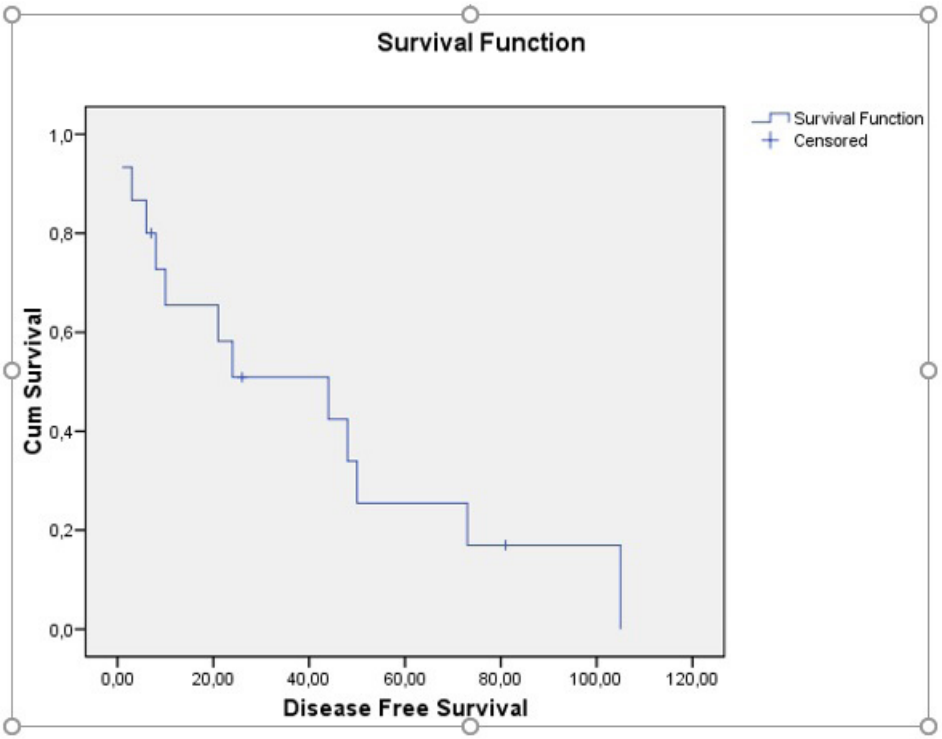

Figure 2: The disease-free survival curve for the 15 patients in our series receiving curative surgery.

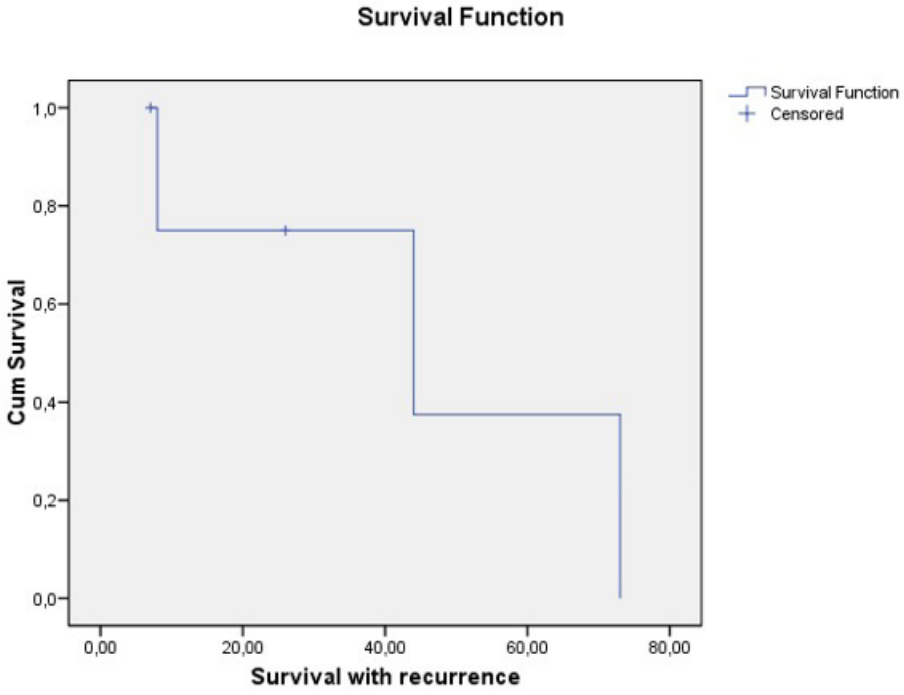

Figure 3: The survival with recurrence curve for the 15 patients in our series receiving curative surgery.

5. Discussion

The natural history of p-NETs is not fully understood, making it difficult to predict the malignant potential of these tumors. In addition, the slow growth of p-NETs and the incomplete establishment of accurate prognostic factors makes the management of these tumors even more problematic. So, there is no standard strategy for p-NETs in particular yet [6]. Our series includes a total number of 17 patients with p-NETs, various functional and non-functional, of different malignancies over a period of 10 years.

Ten patients had their tumors classified according to WHO 2010. After the reclassification of their tumors according to the new classification of WHO 2017: only one case of these tumors changed grade from NET G1 according to WHO 2010 to NET G2 according to WHO 2017. The other categories have not undergone any change

of grade.

In our study, only 10 cases were classified according to the WHO 2010 classification (the only classification set up before the appearance of the WHO 2017 classification) and 2 cases were straight away classified according to the new WHO 2017 classification, which has already been established in this period. In three situations: the mitotic index and the Ki67 index were discordant, each indicating a different grade, in these cases the higher of the two values was used to establish the final grade.

We obtained 9 cases of well-differentiated NETs distributed as follows: 7 cases of NET G1, 2 cases of NET G2. Only one case of poorly differentiated NEC and no case of mixed adeno-neuroendocrine carcinoma (MANEC) was found.

In our department, we confronted the new criteria of the WHO classification of 2017 to a retrospective analysis in order to assess the prognostic interest of this classification by separating the patients into 4 groups (NET G1, NET G2, NET G3 and NEC G3).

Only one in 10 cases changed grade from NET G1 according to the WHO 2010 to NET G2 according to WHO 2017. The other categories did not undergo a change in grade.

In total: This new classification WHO 2017 involved a total of 12 tumors from our series with a final distribution as follows: 6 NET G1, 4 NET G2, 1 NET G3 and 1 NEC G3.

Many studies have endeavored to find and identify prognostic factors of p-NETs. There are many reports on prognostic factors but with much diversity. Tumor size, differentiation grade, Ki-67 index, and lymph node metastases are some examples of frequently noted prognostic factors [7,8].

It is difficult to find consistent prognostic factors (because of the slow growth of the p-NETs, the malignant potential of non-functional p-NETs which is difficult to predict and their natural history which is not fully understood), but histologic grade, especially the WHO grade is an often indicated prognostic factor. In an analysis of 128 patients of at four institutions, identified age over 55, higher WHO histologic grade, and distant metastasis to be significantly associated with worse survival outcome [9].

In our current study, for the new category NET G3 added at the new WHO 2017. We found only one tumor in this class which was immediately classified according to WHO 2017. Therefore, we could not benefit in our study from a follow-up to assess the prognostic interest of this classification. Due to the small number of our series, as well as the low incidence of these tumors and the recent application of this new classification, we could not take advantage of this classification. His interests can be summed up in the improvement of therapeutic management but also in the assessment of prognostic survival factors for the validation of this new WHO 2017 classification.

A multivariate analysis based on a retrospective single-center study of 74 cases [10] on overall survival highlighted all the stages of the new classification, compared with G1 NETs, as prognostic factors for survival. This does not emerge with the WHO 2010 classification where only the NEC G3 stage was an independent factor influencing survival.

Comparisons of survival curves found significant survival for NET G1 and NET G2 lesions compared to the other stages. NET G3 lesions did not show a significant difference in the comparison of survival curves with NEC G3 lesions [10].

Regarding the analysis of recurrence-free survival, low-grade lesions (NET G1 and NET G2) have a lower risk of recurrence than grade 3 lesions [10]

In addition, lesions classified as NET G3 had significantly better recurrence-free survival than NEC G3 lesions [10].

These results reinforce the prognostic interest of tumor differentiation in addition to the ENETS grades [5] and seems to suggest that the WHO 2017 classification is more discriminating. The small number of patients in the NET G3 and NEC G3 groups require caution on its results, which must be confirmed by a larger study [10].

Patients with p-NETs generally have a better prognosis than patients with adenocarcinoma of the pancreas [11,12]. Several prognostic factors are determined among which, the site of the primary tumor, the tumor volume and stage at the time of diagnosis as well as the grade and degree of differentiation are the major prognostic factors common to NETs [13-15].

The size of the primary tumor is an important part of the prognosis. The size of non-metastatic neuroendocrine tumors is smaller than the size of tumors with secondary locations [16]. This criterion cannot be used alone to predict with certainty the benign or malignant nature of p-NETs [16].

The presence of metastases is associated with a poor prognosis. The most common sites of metastasis are the liver, followed by regional lymphadenopathy, peritoneum (17-33%), bone (4-15%) and lung (5-14%) [17,18].

The presence and the type of tumor hormonal secretion are important to take into account for the prognostic classification of these tumors, as well as the existence of an NEM1 [19]. Insulinomas are benign in over 90% of cases. Non-functional p-NETs also frequently metastasize at diagnosis, due to their late clinical translation [19].

Tumor differentiation is a major criterion involved in the prognosis of neuroendocrine tumors. The 2017 WHO classification of neuroendocrine tumors separates well-differentiated neuroendocrine tumors from poorly differentiated neuroendocrine carcinomas. Poorly differentiated NETs are rare, they correspond to malignant tumors with an unfavorable prognosis. Median survival is approximately 223 months in patients with localized forms, 111 months for regional forms and 33 months for metastatic forms [13]. For poorly differentiated NECs, median survival is 34-38 months, 15-16 months and 5-6

months, respectively, in cases of localized, regional and metastatic stage [13, 20].

The Ki67 proliferation index is inversely correlated with survival. Indeed, a low Ki67 index would be linked to slow tumor progression with a favorable prognosis. And the reverse is true: a high Ki67 index indicates rapid tumor proliferation and therefore a poorer prognosis [21-23].

Mitotic index is also an independent prognostic factor for p-NETs, according to Liangtao Ye [24], high mitotic levels were statistically appropriate for poorer survival.

An epidemiological study carried out in the Netherlands on NETs of all locations found survival strongly associated with histological grade: survival at 5 years was 80%, 63%, 20% and 6% for G1, G2, G3 large cells and G3 small cells respectively [25].

6. Conclusion

Pancreatic NETs are rare tumors, but their incidence has increased markedly in recent years. This would be due to a better knowledge of these tumors, the diagnosis of which is becoming easier with the advent of new morphological and biological techniques. The place of anatomopathology remains essential for the diagnosis of NETs. Surgical excision of the primary tumor is classically recommended for localized well-differentiated p-NETs. For poorly differentiated metastatic p-NETs with a poor prognosis, the standard chemotherapy is cisplatin-VP16 (etoposide). The main prognostic factors include tumor stage, metastatic volume, histological differentiation and proliferation index. The new classification proposed by the WHO in 2017 appears to be a strong prognostic tool, more discriminating than the previous classifications, in the stratification of survival of p-NETs.

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