Review

Poorly Differentiated Neuroendocrine Tumors of the Pancreas: A Comparative Analysis of Primary Versus Secondary; Literature Review

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Review

Poorly Differentiated Neuroendocrine Tumors of the Pancreas: A Comparative Analysis of Primary Versus Secondary; Literature Review

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Abstract: Background: Poorly differentiated neuroendocrine tumors of pancreas (*pd*-PNETs) are very rare tumors. Differentiating primary *pd*-PNET from secondary *pd*-PNET can be difficult. This study evaluates the differences in incidence, clinical picture, outcomes, and treatment between primary and secondary *pd*-PNETs. **Methods:** A comprehensive search of the *pd*-PNETs database was performed to gather data on incidence, race, age, gender, clinical picture, and outcomes of primary and secondary *pd*-PNETs. The emphasis was on small cell lung cancer (SCLC) and Merkel cell carcinoma (MCC) due to their association with secondary *pd*-PNET. Additional data from the PubMed database were analyzed, and 12 case reports of primary *pd*-PNETs were added for clinical characteristics analysis. **Results:** Primary and secondary *pd*-PNETs exhibit highly similar profiles in terms of age, gender, race, and clinical features. However, treatment strategies are significantly different. Primary *pd*-PNETs are managed with tumor resection and platinum-based chemotherapy. Primary tumors usually have poor prognosis, with median survival of 12 months. Treatment for secondary *pd*-PNETs varies based on the primary tumor. The treatment strategy for metastatic MCC was changed to immune checkpoint inhibitors (ICI) and survival improved. Tarlatamab also recently showed a good response in the management of SCLC. These findings highlight the need for accurate and timely diagnosis to provide correct treatment. **Conclusion:** Patients with primary and secondary pd-PNETs exhibit similar clinical presentations and epidemiological characteristics. However, when a poorly differentiated neuroendocrine pancreatic mass is identified, it is critical to exclude MCC or Small cell lung carcinoma metastasis, as treatments may be different and prognosis may also be different.

Keywords: neuroendocrine tumors; pancreatic neuroendocrine tumors; poorly differentiated pancreatic neuroendocrine carcinoma; Merkel cell carcinoma; small cell lung cancer

1. Introduction

Pancreatic neuroendocrine tumors (PNETs) are rare tumors, with an incidence of one per 100, 000 individuals annually, and they account for 1-2% of all pancreatic neoplasms [1]. Well-differentiated pancreatic neuroendocrine tumors (wd-PNETs) are slow growing and have limited proliferative activity, thus usually have a good prognosis compared to poorly differentiated tumors [2]. They are usually asymptomatic and can be classified as functional and nonfunctional depending on hormone production [2]. Pancreatic neuroendocrine tumors which exhibit poor histologic differentiation can be referred to as Poorly differentiated pancreatic neuroendocrine cancer (pd-PNEC). These tumors are always high grade (G3) and have KI-67 index >20% by definition [3]. Histologically pd-PNETs can be classified according to cell type, either small cell type or large cell type [4]. It is very important to distinguish primary Poorly differentiated neuroendocrine tumors of pancreas (pd-PNETs) from pancreatic metastasis originating from other Neuroendocrine cancers (NECs), most notably small cell lung cancer (SCLC) and Merkel cell carcinoma (MCC). This article

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provides a comparative analysis of primary versus secondary poorly differentiated neuroendocrine tumors of the pancreas.

2. Materials and Methods

This study goal is to compare the incidence, clinical picture, treatment and prognosis of primary pd-PNETs with secondary pd-PNETs, given the absence of specific comparative data for poorly differentiated pancreatic neuroendocrine masses of varying origins. Case reports and case series from the published literature were used in a retrospective study. We concentrated on the poorly differentiated neuroendocrine advanced tumors, low grade pancreatic neuroendocrine tumors (G1-G2) and mixed tumors were not included in the study. PubMed and Google Scholar were used as the primary databases to find relevant case reports and case series for Primary pd-PNET and SCLC with pancreatic metastasis and MCC with pancreatic metastasis from 1970 to 2025. The search terms for pd-PNETs included "Poorly differentiated neuroendocrine cancer of the pancreas", "High grade neuroendocrine carcinoma of the pancreas", “Gastropancreatic high grade neuroendocrine carcinoma”, “Gastropancreatic neuroendocrine carcinoma”, “Aggressive Pancreatic Neuroendocrine Tumors”. We did not include case reports and case series not in English language. For primary pd-PNETs, we relied on the epidemiological insights from Gan et al. and the pathological analysis from the case series by Basturk et al [5,6]. We added clinical data from case reports to address the lack of clinical details in the databases from Gan et al. and Basturk et al. The case reports were summarized in Table 1. For secondary pd-PNETs we included data for MCC from the database by Pokhrel et al. and for SCLC we used data from Ugur Gonlugur et al. [7,8]. To determine incidence, clinical picture, and prognosis we examined the data from included case reports and case series. Also, the literature on treatment options was reviewed and analyzed.

Table 1. Case reports of primary poorly differentiated Pancreatic neuroendocrine tumors (pd-PNETs).

Case	Age	Sex	Metastasis sites	Clinical picture	Histology	Diagnosing method	Diagnosis confirmation method	Location	Treatment	Interval between disease establishment and death
Corrin B et al.[9]	50	Female	Liver	Fatigue, weakness, Weight loss	Small cell carcinoma	Technetium-99m	Autopsy	Tail	Palliative/ Supportive	Not Specified
Hobbs RD et al.[10]	66	Male	Liver, Gallbladder, mesentery. omentum, small and large bowel, adrenals, peritoneum, vertebrae	Weight loss. ascites, jaundice, flank pain, Hypercalcemia	Small cell carcinoma	CT	Autopsy	Head: 8-cm	Palliative/ Supportive	Not Specified
Morant R et al.[11]	54	Male	Regional lymph nodes, liver, and bone marrow	Abdominal pain radiating to the back, diarrhea and weight loss	Small cell carcinoma	CT	FNA	NA	Chemotherapy	Alive at 50 months
O'Connor TP et al.[12]	62	Male	Direct invasion to duodenum and anterior abdominal wall	Weight loss, vomiting, fever. symptoms of duodenal obstruction	Small cell carcinoma	CT	Endoscopic biopsy	Head: 9cm	Surgery + Chemotherapy	2 months
Nakasoneet al..[13]	51	Male	Liver and peripancreatic nodules	Abdominal pain, jaundice, pruritus, dark urine, weight loss	NA	CT	FNA	Head 3.4-cm	Chemotherapy + Surgical resection	Alive at 2 years
Van Fraeyenhove F et al.[14]	55	Female	Liver	Abdominal pain, Diarrhea, flushing	Small cell carcinoma	CT	CT-guided biopsy	Head	Chemotherapy + Surgical resection	2.4 months
Yamamoto M et al.[15]	42	Male	Liver	Abdominal pain and fullness	NA	CT	Tumoral tissue obtained by liver biopsy	Body: 5.6×2.5 cm	Chemotherapy	13 months
Kang NW.[16]	59	Male	Peripancreatic tissue and lymph nodes	Abdominal pain and fullness	Small cell carcinoma	CT	Pancreatectomy	Body: 3.3 cm	Chemotherapy + ICI + Surgical resection	Alive at 4 years

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Tohmatsu et al. [17]	72	Woman	No	Weight loss	Small cell carcinoma	CT	FNA	Head: 3.2 cm	Chemotherapy + Radiotheraoy + Surgical resection	Alive at 2 years
Fonseca et al [18]	34	Woman	Liver	Abdominal pain, Weight loss, nausea	NA	CT	Biopsy of the liver metastasis	Tail: 5 × 7-cm	Chemotherapy	33 months
Li et al [19]	63	Male	No	Abdominal pain	Small cell carcinoma	CT	Exploratory laparotomy.	Head: 6.5 cm x 8.3 cm	Chemotherapy + Surgical resection	Alive at 8 months
Elzein et al. [20]	29	Male	No	Epigastric pain radiating to back, nausea and mild weight loss	Small cell carcinoma	CT	Biopsy of the perigastric lymph node	Head: 3.7 × 2.9 cm	Chemotherapy + Surgery radiotherapy	Alive at 28 months

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3. Results

3.1. Primary Poorly Differentiated Pancreatic Neuroendocrine Cancers

3.1.1. Incidence

Primary *pd*-PNETs are rare and aggressive pancreatic neuroendocrine tumors, characterized by poor differentiation or undifferentiation. Due to their rarity, comprehensive data on the incidence in the United States remains limited. According to research by Ito et al., among all PNETs 7.5% are usually *pd*-PNETs [21]. We can estimate the incidence according to a study from the Netherlands Cancer Registry [22]. The incidence of G3 large cell neuroendocrine carcinoma between 2001 and 2010 was 0.13 per 100,000 persons per year, while G3 small cell neuroendocrine carcinoma had an incidence of 0.03 per 100,000/year[22]. Given total incidence of *pd*-PNETs 0.16 per 100,000/year.

3.1.2. Age, Sex and Race

This article utilizes the findings from a database of 485 confirmed pd-PNETs cases during the period 2004 to 2016 [5]. The data was further enriched with clinical findings from case reports presented in Table 1[9–20]. Among the 485 documented pd-PNETs cases over 61% of patients were older than 60 years, highlighting a predisposition among the elderly [5]. A small male predominance is observed, 55% of patients were males [5]. The cohort shows a significant predominance of White individuals, comprising 79% of cases [5]. The findings are also observed in the study conducted by Bastruk et al. revealing a mean patient age of 59 years and a male-to-female ratio of 1.4 [6].

3.1.2. Clinical picture

Comprehensive data on the clinical presentation of pancreatic metastases are scarce in existing databases, necessitating a reliance on case reports to demonstrate predominant symptoms. A review of literature from 1970 to 2025 identified 12 relevant case reports, presented in Table 1 [9–20].

Abdominal pain was the predominant symptom, reported in 75% (9 of 12), highlighting its role as a hallmark feature. Weight loss was also frequent, occurring in 66% (8 of 12) of cases. Additional symptoms included nausea, jaundice, pruritus, flank pain, and periumbilical pain. Epigastric pain radiating to the back was observed in some cases, a presentation that may mimic pancreatitis. SCLC metastasis to pancreas is also reported to present with symptoms of acute pancreatitis, complicating differential diagnosis [8]. Almost all masses were first identified on CT scan.

3.1.2. Outcome

The prognosis for *pd*-PNETs is generally unfavorable. A research conducted by Basturk, which examined 44 cases, revealed an overall median survival of 12 months[6]. This is similar with the overall survival rate for Gastroenteropancreatic neuroendocrine carcinomas (GEP NECs), which is 11 months, as reported by the NORDIC NEC study[23]. Among 44 patients 33 patients had a median survival of 11 months; 8 patients had a median follow-up of 19.5 months [6]. The 5-year survival rate was 16.1% [6]. In contrast, our case series includes patients who survived beyond two years post-diagnosis, highlighting extraordinary responders despite the typical poor prognosis [11,13,16–18,20].

3.2. Secondary Poorly Differentiated Pancreatic Neuroendocrine Cancers

3.2.1. Incidence

A variety of cancers can metastasize to the pancreas. Adsay et al. reported that the incidence of pancreatic metastases was 1.6% in a study of 4,955 postmortem cases[24]. The lung is the predominant source, comprising 42% of cases, followed by the gastrointestinal system at 24.7%[24]. Among pulmonary cancers spreading to the pancreas, SCLC accounts for 29% and large cell lung carcinoma

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(LCLC) - 26%.[24]. MCC comprises 2.6% of all secondary tumors [24]. Based on the evidence presented, it can be concluded that metastasis to the pancreas from SCLC, LCLC, and MCC represents the most common occurrence of secondary *pd*-PNETs. The incidence rate of MCC in the United States was 0.7 cases per 100,000 person-years in 2013, equating to 2,488 cases annually and expected to increase to 3,284 cases per year in 2025 due to the aging population[25]. The incidence of SCLC was 4.7 per 100,000/year in 2019[26].

3.2.2. Age, Sex and Race

An analysis of SCLC cases from 2000 to 2019 indicated that the median age at diagnosis varied between 60 and 69 years [26]. SCLC historically showed a male predominance, in a study conducted by Gonlugur et al., the male to female ratio was 48:22 and the average age was 59 years [8]. The prevalence of SCLC relative to all lung cancer types is consistently greater in the white population than in the black population[27]. MCC primarily affects elderly patients, in a case series of MCC with pancreatic metastasis most patients aged 60–80 years and the majority of patients were male - 68.19%[7]. Merkel cell carcinoma is identified in 95% of cases among white population [28].

3.2.2. Clinical Picture

Pancreatic metastases are generally asymptomatic, if symptoms develop the most common are jaundice and abdominal pain [29]. The tumors in the head of the pancreas can induce obstructive jaundice [8]. Acute pancreatitis due to metastasis typically caused by occlusion of the pancreatic duct by metastatic lesions [8]. Though most instances are asymptomatic, pancreatic metastases of Merkel cell cancer (MCC) can appear with abdominal pain and jaundice; sometimes accompanied by nausea, vomiting, or dyspepsia. [7].

3.2.2. Outcome

The prognosis for extensive-stage small cell lung cancer (ES-SCLC) is generally poor. In the study by Gonlugur et al., median survival was 8.25 months for patients without the other metastases and only 1.7 months for those with extensive metastatic disease [8]. Most individuals have widespread metastatic disease, isolated pancreatic metastasis are uncommon [8].

Historically, metastatic Merkel cell carcinoma (MCC) had a poor prognosis with 5-year overall survival (OS) of 14 % for metastatic disease [30]. According to SEER survival data from 2000 to 2018, the 2-year survival rate was 22.7% and the 5-year survival rate was 17.2% [31]. In the case series of pancreatic metastasis from MCC the average duration for the diagnosis of pancreatic metastases and subsequent mortality was 6.3 months, ranging from 1 to 24 months [7].

However novel therapeutic options have significantly changed the prognosis for MCC. Introduction of ICIs-based therapy has progressively improved the 2-year relative survival rate for metastatic MCC, rising from 23% (2010–2012) to 54% (2019–2021) [32]. We will further explore the treatment options and outcomes for MCC in the treatment section.

3.3. Differential Diagnosis

Differential diagnosis starts with evaluation of the clinical presentation. Most patients with Primary and secondary *pd*-PNETs are asymptomatic, with incidental findings often driving malignancy workup. When symptoms occur, abdominal pain is the most frequent complaint for both primary and secondary tumors, sometimes accompanied by less common symptoms such as weight loss, nausea, vomiting, jaundice, or epigastric pain radiating to the back. Differential diagnosis is complicated by similar epidemiological profile as patients have similar age, male gender and white population prevalence. Computed tomography (CT) is the main imaging modality for identification of the tumors[8]. Initially, pancreatic masses may raise suspicion for pancreatic adenocarcinoma, as this type of malignancy is more common[8]. However, when a biopsy shows a neuroendocrine tumor, precise differentiation between primary and secondary *pd*-PNETs is very important as it

 doi:10.20944/preprints202505.0465.v1

influences treatment strategies. MCC, SCLC and primary *pd*-PNETs have different immunohistochemistry characteristics: Merkel cell carcinomas are typically CK20-positive, this an indicator that distinguishes it from small cell lung carcinomas[33]. Unlike MCC, metastases of SCLC are CK20 negative but are positive for CK7, neuron-specific enolase, and thyroid transcription factor-1[33,34]. Consequently, CK20 staining is an important diagnostic step in evaluating *pd*-PNETs to confirm or exclude MCC metastasis.

3.4. Treatment

Primary and Secondary Poorly differentiated neuroendocrine carcinomas of the pancreas have different treatment approaches.

Treatment approaches for primary *pd*-PNETs are different, including combinations of surgery, chemotherapy, and radiation therapy. If patients with primary *pd*-PNETs are good candidates for surgery, they should undergo the procedure [35]. First-line systemic therapy treatment for primary *pd*-PNETs is a combination of Carboplatin/Cisplatin + Etoposide [36]. In our cohort of 12 primary *pd*-PNETs patients, treatment approaches included: Chemotherapy alone was used in 25%, Surgical resection plus chemotherapy - 33%, Surgical resection, chemotherapy, and radiation - 16%, Palliative/supportive care - 16%.

Immune checkpoint inhibitors changed the treatment strategies for MCC. Avelumab was the first ICI which showed improved and durable response in metastatic MCC for primary management and chemotherapy refractory tumors, FDA approved avelumab in 2017[37–41]. Pembrolizumab subsequently showed significantly improved progression free survival (PFS) and was approved by FDA in 2018 [42–44]. Retifanlimab also showed effective and durable response [45]. A study by Paulson et al. analyzing 453 patients with metastatic MCC showed significantly improved 2 years relative survival from 23% to 54% [32].

Platinum-based combinations are the standard of care for the initial systemic therapy for patients with SCLC [46]. Monoclonal anti-programmed death-ligand 1 (PD-L1) antibodies, such as durvalumab and atezolizumab, have demonstrated improved survival rates when combined with etoposide and a platinum agent during both induction and maintenance therapy [47–49].

Delta-like ligand 3 (DLL3) is highly expressed in SCLC[50]. Tarlatamab, a bispecific T-cell engager, has demonstrated encouraging results in patients who have relapsed on or got resistance to platinum-based chemotherapy [51,52]. Therapy achieved a 40% response rate, with a median progression-free survival of 4.9 months and an overall survival of 14.3 months[52]. In this extended follow-up objective response rate (ORR) was 35.3%, the median duration of response was 14.9 months, the median OS was 20.3 months [51]. Tarlatamab is approved only for ES-SCLC, however these results give promising options for therapy for other NECs such as primary *pd*-PNETs and MCC. There are several ongoing trials for Tarlatamab use in DLL3 positive tumors, including primary *pd*-PNETs and MCC: NCT04429087 and NCT04471727.

4. Discussion

This study provides a comprehensive comparison of primary pd-PNETs and secondary pd-PNETs based on case reports, case series and retrospective data from 1970 to 2025. Our analysis highlights the rarity, aggressive behavior, and similar clinical presentation of these tumors, which pose significant diagnostic challenges.

Primary and secondary pd-PNETs share similar demographic and clinical profiles: the age of the diagnosis is 59-80 years and male predominance is evident for both tumors. White ethnicity is most prevalent in both primary and secondary pd-PNETs. Both tumor types are often detected incidentally or present with common symptoms like abdominal pain and weight loss. Computed tomography (CT) is the primary modality for detecting pancreatic masses. A comparative summary of primary and secondary pd-PNETs is presented in Table 2.

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Outcomes for primary and secondary pd-PNETs were always poor. However, survival outcomes for secondary pd-PNETs are improved with novel treatment options highlighting the importance of accurate diagnosis.

Diagnosis of pancreatic neuroendocrine tumors should always include immunohistochemistry. MCC has positive staining for CK20, unlike SCLC and primary pd-PNETs [33,34]. This unique staining profile makes CK20 an essential marker for diagnosing MCC or excluding other tumor forms.

The introduction of ICIs has significantly improved the 2-year relative survival rate for MCC from 23% to 54% [32]. At the same time, Tarlatamab has demonstrated good results in treating metastatic SCLC, achieving a median overall survival of 20.3 months [51]. These therapeutic advancements emphasize the importance of accurately identifying tumor origin, since it guides the selection of correct treatment and increases chances for longer survival.

Table 2. Comparison of Primary and Secondary Poorly differentiated pancreatic neuroendocrine tumors (*pd*-PNETs).

	Primary *pd*-PNETs	Secondary *pd*-PNETs	
		SCLC	MCC
Origin	Pancreas	Lung	Skin
Incidence	≈0.16 per 100.000	Rare	
Age	59 years in Case series study, the data including 485 patients majority were >60 years	49-69 years	60-80 years
Gender	Male	Male	
Race	White	White	
Predominant Symptoms	Asymptomatic, Abdominal pain, Weight loss	Asymptomatic, Abdominal pain, Weight loss	
Other Symptoms	Nausea, Vomiting, Jaundice, Flank pain, Symptoms of acute pancreatitis	Nausea, Vomiting, Jaundice, Symptoms of acute pancreatitis	
Immunohistochemistry	CK20 negative	CK20 negative	CK20 positive
Treatment	Surgery, Radiotherapy or/and Platinum based Chemotherapy	Platinum based Chemotherapy + ICI (e.g., atezolizumab) Tarlatamab for relapsed/refractory disease	ICI (e.g., pembrolizumab, avelumab)
Prognosis	Poor prognosis with medial survival of 11-12 months after diagnosis	Better prognosis with therapy. Tarlatamab group achieving medical OS of 20.3 months	Better prognosis with therapy. ICI increase 2 years relative survival to 54%.

5. Conclusions

This study shows the need for differentiation between primary and secondary pd-PNETs, as they require different treatment approaches. Secondary pd-PNETs, especially those originating from MCC, demonstrate a significantly better prognosis with ICI. When a pancreatic tumor has poorly differentiated neuroendocrine histology distinguishing between primary and secondary pd-PNETs

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is challenging, as both tumors have similar clinical presentations and epidemiological characteristics. Thus, it is important to confirm or rule out MCC metastasis using CK20, enabling in time initiation of ICI therapy to improve survival outcomes.

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Abbreviations

The following abbreviations are used in this manuscript:

pd-PNECs	Poorly differentiated neuroendocrine tumors of pancreas
wd-PNECs	Well differentiated neuroendocrine tumors of pancreas
MCC	Merkel cell carcnima
SCLC	Small cell lung cancer
DLL3	Delta like ligand 3
ICI	Immune Checkpoint inhibitors
GEP NECs	Gastroenteropancreatic neuroendocrine carcinomas
LCLC	Large cell lung cancer
NEC	Neuroendocrine cancers
ICI	Immune Checkpoint inhibitors
pd-PNECs	Poorly differentiated pancreatic neuroendocrine cancer
LCLC	Large cell lung cancer

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