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# Clinical presentation and outcome of nonfunctional pancreatic neuroendocrine tumors in a modern cohort

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**Abstract**

**BACKGROUND:** The natural history of nonfunctional pancreatic neuroendocrine tumors (NF-PNETs) is largely unstudied due to its rarity. The primary goal of this study was to characterize clinical features and outcomes of incidental NF-PNETs.

**METHODS:** An institutional review board–approved retrospective study of patients with NF-PNET evaluated by the Surgical Oncology of University of Nebraska Medical Center was performed. Patients were evaluated with dedicated pancreatic and liver imaging using multiphasic computed tomographic scan and dedicated magnetic resonance imaging protocols.

**RESULTS:** Forty-six patients (male, 47.8%) were evaluated, and 35 ultimately resected. Of these, 16 tumors were discovered incidentally. The median age was 62 and 59 years in incidental and symptomatically discovered, respectively. Incidental median size was 2.4 cm vs 6 cm in the symptomatic group, with a $P$ value of .037. The presence of lymphatic and liver metastases was 10% and 25% incidental and 45% and 67% for those with symptoms (lymphatic involvement, $P = .05$; liver metastases $P = .07$). Median overall survival was 45 and 76 months ($P = .03$).

**CONCLUSIONS:** Incidentally discovered NF-PNETs represent a malignancy with more questions than answers. Our series indicates that these cancers are more indolent than previously believed.


Pancreatic neuroendocrine tumors (PNETs) are rare neoplastic masses of islet cell origin, classically divided into tumors presenting with symptoms of hormonal excess (functional) and those without syndromic symptoms (nonfunctional). These tumors represent a small proportion of all pancreatic masses, with recent epidemiologic studies demonstrating an incidence of 1 to 5/million/year and accounting for 3% of pancreatic cancers.[1–4] Relative instance of the 2 categories have changed in the last 3 decades. Before the ubiquitous use of computed tomography (CT), functional tumors represented the more common subtype, with nonfunctional pancreatic neuroendocrine tumors (NF-PNETs) accounting for one third of all PNETs.[5] The NF-PNETs that were found during this period presented at late stage with symptoms of either mass effect or metastatic disease. With increased use of abdominal imaging, incidence of

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**Table 1** Demographics and clinical data of total population

| Patient characteristics | n = 46 |
|---|---|
| Age | |
| Median | 59 |
| Range | 23–84 |
| Sex, % | |
| Male | 48 |
| Female | 52 |
| Location | |
| Head | 15 (33%) |
| Body/tail | 31 (67%) |
| Size, cm | |
| Median | 4.85 |
| Range | .05–19 |
| Nodal status | |
| Node positive | 11 (37%) |
| Synchronous liver metastases | |
| Positive metastases | 24 (52%) |

NF-PNETs has increased, and the subtype, now, represents 50% to 75% of all PNETs diagnosed.[6] As many as 50% of these tumors are identified on imaging for an unrelated problem and are asymptomatic at diagnosis.[6–8] Treatment for such incidental masses is generally surgical with few studies reporting malignant potential in 60% to 90% of NF-PNETs.[9] However, because to the rarity of diagnosis, the clinical history of incidentally discovered tumors is largely unknown. The primary goal of this study is to characterize NF-PNETs of both incidental and symptomatic discovery in terms of clinical, pathologic, and surgical features; as well as to identify trends in the presentation of symptomatic tumors.

## Methods

Patients undergoing surgical evaluation for pancreatic mass by the surgical oncology service at the University of Nebraska Medical Center (UNMC) from January 1, 2002, to December 31, 2013 were identified through a pre-existing database, and retrospectively recruited pancreatic cancers of neuroendocrine origin based on pathologic examination and no clinical evidence of hormonal excess at presentation were selected. Patients with genetic syndromes, such as multiple endocrine neoplasia or von Hippel-Lindau, as well as mixed adenoneuroendocrine carcinoma were excluded. The patients underwent evaluation at UNMC with a high-resolution pancreatic protocol CT scan or magnetic resonance imaging of the pancreas and liver. Pathologic analysis was performed on either surgical or biopsy specimens, and histopathologic findings were characterized according to the World Health Organization classification scheme for PNETs.[10] Data points were retrieved through institutional record and social security index review, and included demographics, presenting symptoms, tumor size and location, extent of metastasis, pathology, disease progression, and overall survival. The cohort of patients was divided into 2 groups: NF-PNETs discovered on imaging in the absence of jaundice or abdominal complaints or during surgical intervention for an unrelated problem (incidental tumors) and NF-PNETs that presented with any of the following: jaundice, pancreatitis, abdominal pain, or unexplained weight loss (symptomatic tumors). The 2 groups were compared using chi-square analysis. Patients with symptomatic tumors were also segregated based on tumor location, head, and body and/or tail. Rates of presenting symptoms listed previously were compared between the 2 groups using chi-square analysis. Overall survival was calculated as the time in months from diagnosis with tissue biopsy to date of death. Survival curves were calculated by the method of Kaplan and Meier.[11] Histologically, poorly differentiated tumors were included for all analysis excluding survival. This study was approved by the Institutional Review Board (IRB) at the UNMC.

## Results

During the study period, 46 patients were evaluated, and 35 ultimately received surgical resection (Table 1). Of the total population, 16 tumors were discovered incidentally. When compared with symptomatic patients, there was no difference in age (62 years vs 59 years in symptomatic), sex (63% male vs 40% male), or surgical resection rate (73% vs 81%; Table 2). Surgical pathology data points differed between the 2 groups. Incidental tumors were more commonly found in the body of the pancreas, ([head = 4, body = 16] vs [head = 11, body = 19], $P = .42$), but the difference was not statistically significant.

**Table 2** Operative resection and tumor examination

| Patient characteristics | Incidental | Symptomatic | *P* value |
|---|---|---|---|
| n | 16 | 30 | |
| Tumor size (cm) | 2.4 | 6 | .04 |
| Age, median, (y) | 57 | 64 | .57 |
| Location | | | |
| Head | 4 (25%) | 11 (37%) | — |
| Body/tail | 12 (75%) | 19 (63%) | .42 |
| Resection of the primary tumor | 13 (81%) | 22 (73%) | .55 |
| Positive nodes (resected patients) | 1 (10%) | 10 (45%) | .05 |
| Liver metastases | 4 (25%) | 12 (55%) | .07 |