

ORIGINAL ARTICLE

Non-functioning pancreatic endocrine tumors: eleven-year experience in a single institute

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Summary

Purpose: Non-functioning pancreatic endocrine tumors (NF-PETs) comprise the majority of pancreatic endocrine tumors. We present our experience from the management of 18 patients with NF-PET.

Methods: From May 2002 to June 2013, 18 patients were admitted in our hospital for the management of NF-PETs. We analyzed their clinical presentation, preoperative evaluation, surgical and postoperative management and the outcome.

Results: The tumor was located in the pancreatic head in 13 (72%) patients and in the body and tail of the pancreas in the remaining 5 (28%). Four patients (22%) had stage IIIa, 7 (39%) stage IIIb and 7 (39%) stage IV. Twelve (67%) patients with pancreatic head tumor underwent pancreatoduodenectomy (PD). In one case (5%), the tumor was deemed unresectable and the remaining 5 (28%) patients underwent distal pancreatectomy and splenectomy (DPSP).

Four (22%) patients with unilobar metastatic liver disease underwent hemihepatectomy or segmentectomy. Perioperative mortality was 0%. Postoperatively, all stage IV patients received peptide receptor radionuclide treatment (PRRT). The 5-year overall survival rate was 61%, with a median survival of 71 months, whereas the 5-year overall survival rate after diagnosis of hepatic metastases was 45%.

Conclusion: Surgical resection is the gold standard for the treatment of NF-PETs. A formal resection appears to be the standard procedure when malignancy is verified or suspected. Aggressive surgery should be undertaken in patients with locally advanced or metastatic NF-PETs, as it may prolong survival. In stage IV patients, intra-arterial PRRT, after super-selective catheterization of the hepatic artery, is a promising therapeutic modality.

Key words: distal pancreatectomy and splenectomy, non-functioning pancreatic endocrine tumors, pancreatoduodenectomy, peptide receptor radionuclide treatment

Introduction

NF-PETs, so termed due to the absence of symptoms of hormonal hypersecretion, comprise the majority (~60%) of the pancreatic endocrine tumors. Their prevalence has been estimated to be 0.4 to 1.5% in autopsy studies and clinically relevant NF-PETs have an incidence of 3.5 to 4 per million/year. Sixty to 80% of these tumors are well differentiated, low grade carcinomas [1,2]. Their histology and classification are the same as for functioning tumors and use of the WHO classification facilitates uniformity in reporting [3-5].

The primary tumors are usually discovered at an advanced stage as a huge mass and are localized mainly to the head of the pancreas. The presenting symptoms and signs are due to locoregional mass effects of the tumor or are related to distant metastases. Abdominal pain is the major presenting clinical symptom followed by weight loss, anorexia, bleeding and jaundice [6-8].

Prognosis is related to stage of the disease, tumor differentiation, patient age and the possibility of surgery. Ki-67 is an important prognostic factor with a cut-off level of 2%. The malignancy rate of NF-PETs is reported to range between

37.5 and 72% and the 5-year overall survival rate ranges from 60-80% [9].

In this study we present the results of 18 patients with NF-PETs who were admitted in our department during the last decade. We analyzed the clinical presentation, preoperative evaluation, surgical and postoperative management and finally the outcome of these patients.

Methods

From May 2002 to June 2013, 18 patients (11 male and 7 female), mean age 53 years (range 18-74), were admitted in our hospital for management of NF-PETs. Non-specific complaints, such as weight loss and vague abdominal pain were the main symptoms in 9 (50%) patients, whereas 1 patient presented with obstructive jaundice and 1 with gastrointestinal bleeding. The remaining 7 (39%) patients were completely asymptomatic (incidental finding). While in 16 (89%) patients the neoplasia was sporadic, 2 patients expressed Multiple Endocrine Neoplasia type 1 (MEN 1).

Preoperative imaging studies included computed tomography (CT) of the pancreas, magnetic resonance imaging with cholangiopancreatography (MRI/MRCP), transabdominal and/or endoscopic ultrasonography (US/EUS), as well as chromogranin-A (CgA) serum levels. Preoperative diagnosis of a NF-PET was based on imaging features such as calcification, cystic degeneration and a high degree of enhancement as well as increased levels of serum CgA or through bioptic material. Somatostatin receptor scintigraphy with octreotide (SRS Octreoscan) followed in order to delineate possible metastatic foci.

Liver metastases were present in 7 (39%) patients, in 3 of which metastatic disease was bilobar and constituted of microscopic foci evident on SRS and CT. None of the patients suffered from extra-hepatic metastatic disease at the time of diagnosis.

In patients with metastatic liver disease, in whom concomitant major hepatectomy was planned, preoperative evaluation of the future liver remnant (FLR) was performed with the Indocyanine Green (ICG) test.

Results

The tumor was located in the pancreatic head in 13 (72%) patients and in the body and tail of the pancreas in the remaining 5 (28%). The maximum diameter of the primaries ranged from 50 to 140 mm (median 78), based on imaging studies. Staging of NF-PET was as follows: 4 (22%) patients had stage IIIa, 7 (39%) stage IIIb and 7 (39%) stage IV.

Twelve out of 13 (67%) patients with pancreatic head tumor underwent PD. In one case, the tumor was deemed unresectable due to > 180° encasement of the superior mesenteric artery and thus palliative gastrojejunostomy was performed. The remaining 5 (28%) patients underwent DPSP. IOUS of the liver was carried out in all patients. Four (22%) out of 7 patients with unilobar metastatic liver disease underwent hemihepatectomy or segmentectomy.

In patients with bilobar metastatic liver disease who underwent DPSP, additional cholecystectomy was also performed. The reason for this was to obviate later adverse events related to the systemic or intra-arterial hepatic infusion therapy of somatostatin analogues, i.e. cholelithiasis or ischemic gallbladder necrosis, respectively.

Postoperative hospital stay ranged from 5 to 22 days (mean 9.8). Major complications included low-output pancreatic fistula in 2 patients, that resolved spontaneously and did not require intervention, and intra-abdominal abscess in 1 patient which was treated with percutaneous drainage

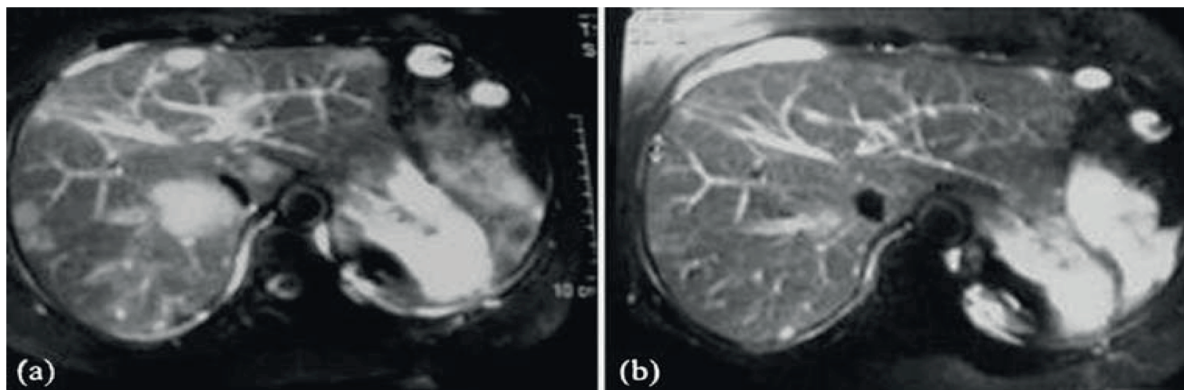


Figure 1. Multiple liver metastases from a NF-PET in a 54-year-old male. **(a)** MRI scan before selective catheterization of the hepatic artery (SCHA) and radionuclide infusions shows multiple hepatic metastases; **(b)** MRI scan obtained 8 months after SCHA and radionuclide infusions of ^{111}In -Octreotide shows almost complete disappearance of the metastatic lesions.

and antibiotics. Perioperative mortality was 0%.

Postoperatively, all stage IV patients received PRRT. Six (86%) of them via hepatic intra-arterial infusion of ^{111}In -Octreotide (110–190 mCi, repeated every 4–5 weeks with a maximum of 12 sessions), and one patient via intra-venous infusion of ^{177}Lu -DOTATATE (200 mCi repeated every 4–5 weeks based on white blood cell count for 6 cycles) demonstrating good outcome with respect to survival (Figure 1). The patient with the unresectable primary tumor received systemic chemotherapy with streptozotocin 500mg/m²/day and 5-fluorouracil 1000mg/m²/day for 5 consecutive days every 6 weeks for 6 cycles, but passed away 12 months after the operation.

The 5-year overall survival rate was 61%, with a median survival of 71 months, whereas the 5-year overall survival rate after diagnosis of hepatic metastases was 45%.

Discussion

NF-PETs have a silent course and present with the symptoms from mass effect, and local or distant metastases of the tumor. Liver metastases represent the main criterion for malignancy. However, malignant NF-PETs grow slowly and hence survival is longer than that of pancreatic adenocarcinoma [10]. In fact, the most important determinant of survival in these patients is the presence and extent of liver metastases.

NF-PETs often exhibit immunohistochemical positivity for hormones, neuropeptides or amines. While NF-PETs may secrete substances such as CgA, HCG α/β or PP, these products are not associated with hormone-related symptoms. However, the biochemical diagnosis requires assessment of general plasma markers including CgA, CgB, HCG subunits, PP, ghrelin and neurotensin [11]. Although NF-PETs may be part of hereditary tumor syndromes such as MEN1, vHL or tuberous sclerosis, their genetic background has not been elucidated [12,13].

Topographic imaging procedures include standard CT, MRI or US as well as functional molecular imaging including SRS and PET with specific tracers such as ^{11}C -5HTP and Ga^{68} [14].

The treatment of choice in NF-PET's is complete surgical resection. Following surgery, in case of disease progression or in symptomatic patients, a multimodal therapy ranges from biotherapy such as somatostatin analogues, IFN- α , tyrosine kinase inhibitors, m-TOR inhibitors and anti-angiogenic agents, up to systemic chemotherapy [15-18]. For unresectable tumors, systemic chemotherapy has been an important therapeutic modality with objective response rates of 35-40% (using streptozotocin + 5-FU or doxorubicin).

PRRT using Lu^{177} -Dota-Octreotide or Y^{90} -DOTATOC are considered novel treatment modalities [19]. Selective hepatic intra-arterial infusion of ^{111}In -Octreotide was used in 6 of our patients with metastatic liver disease. This technique delivers radioactive particles through the hepatic artery into the tumor rather than the normal hepatic parenchyma, resulting in a favorable tumor to normal uptake ratio and without liver or systemic complications.

Surgical resection is the gold standard for the treatment of NF-PETs. A formal resection appears to be the standard procedure when malignancy is verified or suspected [20]. Aggressive surgery should be undertaken in patients with locally advanced or metastatic NF-PETs, as it may prolong survival [17,21]. Surgery should be combined with lymph node dissection and/or hepatic resection [22,23]. In case of recurrence, repeated resections may improve survival. In stage IV patients, intra-arterial PRRT, after super-selective catheterization of the hepatic artery, is a promising therapeutic modality that may lead to more successful outcomes in these cases. Future therapeutic strategies are likely to be individualized based on delineation of the molecular genetics, tumor biology and disease stage.

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