Neuroendocrine tumors of pancreas: a single center experience

Pankreas nöroendokrin tümörleri : Tek merkez deneyimlerimiz

Murat Arer, Hakan Yabanoglu, Kenan Caliskan

Baskent University Faculty of Medicine, Department of General Surgery, Adana, Turkey

Abstract

Background: Pancreatic neuroendocrine tumors (PNETs) are rare and only account for 12.1% of all gastroenteropancreatic neuroendocrine tumors. The peak prevalence for PNET is in 30-60 years and 50% are located in the head, 26.9% in the body and 23.1% in the tail of the pancreas. In the present study, we report 11 cases of PNETs treated at our hospital over the last 8 years.

Material and method: 11 patients with PNETs between 2011 and 2014 underwent pancreatectomy or enucleation were enrolled. All patients were pathologically classified according to the criteria established by the WHO 2010 classification of endocrine tumors. Patients were evaluated according to age, sex, co-morbidity, surgery type, tumor size, operation time, hospital stay and follow-up.

Results: Of 11 patients 6 (54.5%) were male and 5 (45.5%) were female with a mean age of 54.09 ± 15.8 years. 4 (36.4%) have functional tumors and preoperative diagnosis confirmed insulinoma. The mean tumor size was 3.05 ± 2.37 cm (range between 0.5-8 cm). The tumor was located in head (54.5%), body (27.3%) and tail (18.2%) of pancreas. Surgical magrin was negative for all patients. The average operation time was 174.54 ± 81.4 minutes. Mean hospital stay of patients was 6.54 ± 2.58 days. Mean disease free survival was 12.55 ± 13.76 months.

Conclusion: PNETs are rare and slow-growing tumors but can be malignant and associated with an expected survival. Large studies should be performed evaluating the results of surgical and conservative treatment for PNETs.

Key words: Neuroendocrine tumor, pancreas, insulinoma

Özet

Önbilgi: Pankreas nöroendokrin tümörleri (PNET) nadir görülür ve tüm gastroenteropankreatik nöroendokrin tümörlerin sadece %12.1'ini oluşturur. En yüksek prevalansı 30-60'lı yaşlarda görülür ve %50 oranında baş kısmında, %26.9 oranında gövdede ve %23.1 oranında pankreas kuyruk kısmında görülür. Bu çalışmada, 3 yıllık bir süre boyunca ameliyat edilen 11 adet PNET olgusunu sunmaktayız.

Gereç ve yöntem: 2011-2014 yılları arasında PNET nedeniyle pankreatektomi veya enükleasyon yapılan 11 hasta çalışmaya dahil edildi. Tüm hastalar WHO 2011 endokrin tümör sınıflamasına göre patolojik olarak sınıflandırıldılar. Hastalar, yaş, cinsiyet, ek hastalık, cerrahi tipi, tümör boyutu, ameliyat süresi, hastanede kalış ve takip süresi açısından değerlendirildi.

Sonuçlar: 11 hastanın 6'sı (%54.5) erkek, 5'i (%45.5) kadındı ve ortalama yaş 54.09 ± 15.8 idi. 4 hastada fonksiyonel tümör saptandı ve ameliyat öncesi tanı insülinoma olarak doğrulandı. Ortalama tümör boyutu 3.05 ± 2.37 cm (0.5-8 cm arasında) idi. Tümörler pankreasın baş (%54.5), gövde (%27.3) ve kuyruk (%18.2) kısmında yerleşmekteydi. Tüm hastalarda cerrahi sınır negatif saptandı. Ortalama ameliyat süresi 174.54 ± 81.4 dakikaydı. Ortalama hastanede kalış süresi 6.54 ± 2.58 gündü. Ortalama hastalıksız sağ kalım 12.55 ± 13.76 ay olarak saptandı. PNET nadir görülen ve yavaş büyüyen tümörler olsa da malign olabilmekte ve sağkalımı düşük olabilmektedir. PNET'in cerrahi ve konservatif tedavisini değerlendiren büyük çalışmalar yapılması gerekmektedir.

Anahtar kelimeler: Nöroendokrin tümör, pankreas, insülinoma.

Yazışma Adresi | Correspondence: Ilker Murat ARER,
Baskent University Adana Hospital Department of General Surgery Dadaloglu District 2591 Street No:4/A 01250 Yuregir Adana / TURKEY,
e-mail: igy1981@yahoo.com

Başvuru tarihi | Submitted on: 14.01.2015
Kabul tarihi | Accepted on: 28.06.2015

Introduction

Pancreatic neuroendocrine tumors (PNETs) are rare and only account for 12.1% of all gastroenteropancreatic neuroendocrine tumors[1]. They have an estimated incidence of 4 to 5 individuals per 100.000 per year though increasing rapidly in prevalence due to advancements and increased use of radiological and endoscopic investigations[2,3]. The peak prevalence for PNET is in 30-60 years and 50% are located in the head, 26.9% in the body and 23.1% in the tail of the pancreas[4,5]. However these tumors can produce symptoms, especially insulinoma or gastrinoma, most of them are non-functional and asymptomatic. Non-functional tumors are usually found incidentally or present with symptoms of mass effect or metastasis in very advanced stages and posses a higher malignant potential as they increase in size[4,6]. Therefore surgery should be considered for the treatment of PNETs once diagnosed[7].

Insulinomas are the most common functioning PNETs. The incidence of insulinoma is reported to be 4 cases per million population per year with a slight female predilection[8]. More than 90% insulinomas are small solitary lesions at diagnosis but multiple tumors can ocur[8]. All insulinomas 0.5 cm or greater are considered malignant[9]. However, most insulinomas are small at diagnosis, most patients with an insulinoma are treated by surgical resection.

In the present study, we report 11 cases of PNETs treated at our hospital over the last 8 years.

Material and method

Between 2011 and 2014, 11 patients with PNETs underwent pancreatectomy or enucleation at Baskent University Adana Hospital Department of General Surgery were included in our study. The diagnosis of PNET was established by histopathological examination and immunohistochemical staining of surgical specimens with chromogranin A and synaptophysin. Tumors were classified as "nonfunctioning" regardless of the plasma hormone levels or immune activity of the tissue if the patient lack the clinical symptoms that are typically caused by excess hormone secretion and "functioning" according to preoperative symptoms, clinical findings and hormone levels. The data was collected retrospectively. All patients were pathologically classified according to the criteria established by the WHO 2010 classification of endocrine tumors[10]. An immunohistochemical staining assay for Ki67 was performed for all patients. The tumor size was defined by the largest diameter of the tumor. A TNM stage group was assigned to each case based on the the American Joint Committee on Cancer (AJCC) staging classification for pNETs[11]. The postoperative follow-up included clinical examination, positron emission computed tomography (PET-CT) scanning. PET-CT scans were performed every 6 to 12 months in the first year, then annually thereafter.

This study was approved by Baskent University Institutional Review Board (Project No: KA15/41) and supported by Baskent University Research Fund.

Table 1: Demographic data of patients with PNETs

Male/Female	6/5
Age (years)*	54.09 ± 15.8
Functional / Non-functional	4/11
Blood group	
A Rh (+)	3 (27.3%)
B Rh (+)	2 (18.2%)
0 Rh (+)	2 (18.2%)

*Values are means±standard deviation.

Statistical analysis

Statistical analysis was performed using SPSS software (Version 17.0, SPSS Inc., Chicago, IL, USA). All numerical data are expressed as mean values ± SD or Median (Min-Max) and categorical data are expressed as proportions.

Results

A total of 11 patients with PNETs between April 2011 and December 2014 underwent pancreatic surgery were enrolled. Of 11 patients 6 (54.5%) were male and 5 (45.5%) were female with a mean age of 54.09 ± 15.8 years (range from 36 to 86). 4 (36.4%) patients presented with abdominal pain and 3 (27.3%) with symptoms of hypoglycemia. Demographic data of patients are listed in ***table-1.*** Serum CA 19-9 level was detected elevated in only 3 patients while other's lack. Maximum serum CA 19-9 level was 240 U/mL. Of 11 patients 4 (36.4%) have functional tumors and preoperative diagnosis confirmed insulinoma. A Rh(+) blood group was found in 3 (27.3%), B Rh(+) in 2 (18.2%) and 0 Rh(+) in 2 (18.2%) patients. Data of blood group of 4 patients was missing. Only 3 (27.3%) patients have comorbidity as coronary artery disease, hypertension, diabetes mellitus and cerebrovascular disease history. 3 (27.3%) patients had operations before like transurethral prostatectomy, laparoscopic cholecystectomy and cesarean section. Endoscopic ultrasound was performed in 2 (18.2%) patients. The mean tumor size was 3.05 ± 2.37 cm (range between 0.5-8 cm). The tumor was located in head (54.5%), body (27.3%) and tail (18.2%) of pancreas

Table 2: Characteristic features of PNETs

Tumor size (cm)	3.05 ± 2.37
Location of tumor in pancreas (%)	
Head	54.5
Body	27.3
Tail	18.2
Mitosis Number (cycles)	11.33
Chromogranin-A (n)	
Positive	9 (81.8%)
Negative	2 (18.2%)
Synaptophysin (n)	
Positive	10 (90.9%)
Negative	1 (9.1%)
Ki-67 (n)	
< 2%	9 (81.8%)
>2%	2 (18.2%)
Tumor Grade (n)*	
I	9 (81.8%)
II	1 (9.1%)
III	1 (9.1%)

*WHO 2010 classification of endocrine tumors

(Table-2). Surgical magrin was negative for all patients. 1 (9.1%) patient has preoperative metastasis to liver. The mean mitosis number of the tumor was 11.33 cycles (range between 2-21 cycles) that was detected in only 3 patients. Chromogranin-A was positive in 9 (81.8%) and negative in 2 (18.2%) patients. Synaptophysin was negative in only 1 (9.1%) patient. Ki-67 was <2% in 9 (81.8%) patients while other 2 (18.2%) patients have 8% and 10% Ki-67 positive tumor respectively. Lymph node excision was performed in 6 (54.5%) patients. The mean number of lymph nodes excised was 10.33 ± 9.45 (range between 1-31). Although the mean metastatic lymph node number was 1.16 ± 1.5 (range between 1-5), metastatic lymph node was observed in 3 (27.3%) patients. 9 (81.8%) patients have grade-I, 1 (9.1%) patient grade-II and 1 (9.1%) patient has grade-III tumor. Surgical treatment choice was; enucleation in 4 (36.4%), distal pancreatectomy in 3 (27.3%), total pancreatectomy in 2 (18.2%) and pancreaticoduodenectomy in 1 (9.1%) patient. The average operation time was 174.54 ± 81.4 minutes (range between 60-300 minutes). Mean hospital stay of patients was 6.54 ± 2.58 days (min. 3 days – max. 12 days). Follow-up of 1 patient was missing nevertheless no mortality was observed. Mean disease free survival was 12.55 ± 13.76 months ***(Table-3)***. Only 2 patients (18.2%) received adjuvant chemotherapy and radiotherapy. Mean follow-up of patients was 15.09 ± 14.02 months (range between 1-44 months). Recurrent disease was found in 2 (18.2%) patients. 5 patients have postoperative complication; 2 (18.2%) intra-abdominal abscess, 1 (9.1%) incisional hernia, 1 (9.1%) superficial incisional surgical site infection and 1 (9.1%) panreatic pseudocyst.

Table 3: Operation time, hospital stay, follow-up and disease free survival of patients

Operation time (minutes)	**174.54 ± 81.4**
Hospital stay (Days)	**6.54 ± 2.58**
Follow-up (Months)	**15.09 ± 14.02**
Disease free survival (Months)	**12.55 ± 13.76**

*Values are means±standard deviation

Discussion

However PNETs are not common tumors, they have an increasing trend in incidence[7]. Especially non-functional PNETs constitute about 65% of all PNETs, produce less symptoms that lead to late onset of diagnosis[12]. Compared with other pancreatic tumors, PNETs progress slowly and are associated with a better prognosis. However they have malignant potential, including local invasion, lymph node metastasis or distant metastasis[6]. The presence of liver metastases and incomplete resection of the tumor associates with poor prognosis[5,13,14]. Thus early diagnosis and surgical resection is essential for the accurate treatment. Under this circumstances non-functional PNETs should be the main target group.

Tumor size for surgery decision is one of the frequently asked questions of non-functional PNETs. Some studies demonstrate that tumor size less than 10 mm tend to have less malignant potential[6], others state contrary[15,16]. Eventhough tumor size and lymphoid invasion might have some impacts on the prognosis of non-functional-PNETs, surgery remains to play an important role in achieving a probably curative treatment[17]. In case of the treatment of functional PNETs like insulinoma, surgical treatment is curative in (85-95%) almost all patients[18-20]. Yang et al. encourages radical surgical treatment that can be explained by the mean tumor size 4.85 cm which is larger than literature average[17]. Despite all the contraversies about PNETs, surgery still seems to be the most effective treatment option even for the metastatic tumors[21,22]. Medical treatment with somatostatin analogs can be used in patients who do not benefit with surgery alone[23].

However radical resections are the preferred surgery type for treatment of PNETs, enucleation was the most common procedure performed in this study. But enucleation was performed only in patients with diagnosis of insulinoma. Thus distal pancreatectomy can be considered as the most common procedure with regard to tumor type that was also commonly performed by some authors[6,17].

The overall 5-year survival observed usually ranges between 60-70%[13,24-26]. However Lombardi et al. found higher survival rates (90%) than reported in previous series[27]. We observed no mortality in our study and it is not possible to mention about our survival rates. This can be due to small sample size and follow-up of 6 patients ranges between 1-9 months. Another finding of our study correlating with literature results is the common location of the tumor in the head of pancreas[4,17].

The present study is limited by small sample size, single center and retrospective design.

Conclusion

PNETs are rare and slow-growing tumors but can be malignant and associated with an expected survival. Surgery still remains the main treatment option. Large studies should be performed evaluating the results of surgical and conservative treatment for PNETs.

References

1. Frilling A, Akerstrom G, Falconi M, et al. Neuroendocrine tumor disease: an evolving landscape. Endocrine-related cancer 2012;19:163-85.
2. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26:3063–3072.
3. Chen M, Ness MV, Guo Y, Gregg J. Molecular pathology of pancreatic neuroendocrine tumors. J Gastrointest Oncol 2012;3:182-8.
4. Niederle MB, Niederle B. Diagnosis and treatment of gastroenteropancreatic neuroendocrine tumors: current data on a prospectively collected, retrospectively analyzed clinical multicenter investigation. Oncologist 2011;16:602-13.
5. Bettini R, Partelli S, Boninsegna L, et al. Tumor size correlates with malignancy in nonfunctioning pancreatic endocrine tumor. Surgery 2011; 150: 75-82
6. Furukori M, Imai K, Karasaki H, et al. Clinicopathological features of small nonfunctioning pancreatic neuroendocrine tumors World J Gastroenterol. 2014 Dec 21;20(47):17949-54.
7. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol. 2008;9:61–72.
8. Service FJ, McMahon MM, O'Brien PC, et al. Functioning insulinoma-incidence, recurrence and long-term survival of patients: a 60-year study. Mayo Clin Proc. 1991;66:711Y719.
9. Rindi G, Arnold R, Bosman FT, et al. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, et al, eds. WHO Classification of Tumours of the Digestive System. Lyon, France: IARC; 2010:13Y14.
10. National Comprehensive Cancer Network (NCCN): Neuroendcrine Tumors. 2012. Available from: URL: http://www. nccn.org
11. Edge, S. B. 2010. AJCC cancer staging manual. Springer, New York, NY
12. Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (PNETs): Incidence, prognosis and recent trend toward improved survival. Ann Oncol 2008;19:1727-33.
13. Ekeblad S, Skogseid B, Dunder K, Oberg K, Eriksson B. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. Clin Cancer Res 2008; 14: 7798-7803.
14. Sellner F, Thalhammer S, Stättner S, Karner J, Klimpfinger M. TNM stage and grade in predicting the prognosis of operated, non-functioning neuroendocrine carcinoma of the pancreas--a single-institution experience. J Surg Oncol 2011; 104: 17-21.
15. Higuchi R, Watanabe F, Horio Y, et al. A case of nonfunctioning minute malignant pancreatic endocrine tumor, showing regional stenosis of the main pancreatic duct. Nihon Shokakibyo Gakkai Zasshi 2000; 97: 358-361.
16. Ikenaga N, Yamaguchi K, Konomi H, et al. A minute nonfunctioning islet cell tumor demonstrating malignant features. J Hepatobiliary Pancreat Surg 2005; 12: 84-87
17. Yang M, Zeng L, Zhang Y, Su AP, Yue PJ, Tian BL. Surgical treatment and clinical outcome of nonfunctional pancreatic neuroendocrine tumors: a 14-year experience from one single center Medicine (Baltimore). 2014 Nov;93(22):e94.
18. Bonato FT, Coelho JC, Petruzzielo A, Matias JE, Ferreira GA Surgical treatment of pancreatic insulinomas Arq Bras Cir Dig. 2012 Apr-Jun;25(2):101-4.
19. Grant CS. Insulinoma. Best Pract Res Clin Gastroenterol, 2005, 19:783-798.
20. Zhao YP, Zhan HX, Zhang TP, et al. Surgical management of patients with insulinomas: result of 292 cases in a single institution. J Surg Oncol, 2011,103:169-174.
21. Hanazaki K, Sakurai A, Munekage M, et al. Surgery for a gastroenteropancreatic neuroendocrine tumor (GEPNET) in multiple endocrine neoplasia type 1. Surg Today 2013; 43: 229-236.
22. Mayo SC, de Jong MC, Pulitano C, et al. Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. Ann Surg Oncol 2010; 17: 3129-3136.
23. Detlef K, Volker F, Langer P. Outcome of Duodenopancreatic reseccions in patients with multiple endocrine neoplasia type 1. Annals of Surgery 2005;242.
24. Pape UF, Jann H, Müller-Nordhorn J et al. Prognostic relevance of a novel TNM classification system for upper gastroenteropancreatic neuroendocrine tumors. Cancer 2008; 113:256–265.
25. Scarpa A, Mantovani W, Capelli P et al. Pancreatic endocrine tumors: improve TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients. Mod Pathol 2010; 23:824–833.
26. Bilimoria KY, Talamonti MS, Tomlinson JS et al. Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors: analysis of 3,851 patients. Ann Surg 2008; 247:490–500.
27. Lombardi M, De Lio N, Funel N, et al. Prognostic factors for pancreatic neuroendocrine neoplasms (pNET) and the risk of small non-functioning pNET J Endocrinol Invest. 2014 Dec 12. PMID:25501604.