Pancreatic Neuroendocrine Tumors: Experience of a Tertiary Care Center in Lebanon

Sally Temraz, Mohamad Haidar, Rita Assi, Ayman Hakim, Elio Jabra, Maya Charafeddine, Ibrahim El Halabi, Deborah Mukherji, Ali Shamseddine

Department of Hematology – Oncology, American University of Beirut Medical Center, Beirut, Lebanon

Introduction

Pancreatic neuroendocrine tumors (p-NETs) are a group of functionally and biologically heterogeneous tumors which are clinically rare accounting for less than 2% of all pancreatic tumors and 1% of all malignancies. The incidence of p-NETs is <0.5 per 100,000 patients each year but has been on the rise recently largely due to physician awareness and improvements in diagnostic imaging. p-NETs are classified as two general categories, functional and nonfunctional, by means of the secretory activity of certain hormones and peptides, including insulin, gastrin, glucagon, vasoactive intestinal peptide (VIP), somatostatin, growth hormone-releasing factor and adrenocorticotropic hormone. Nevertheless, more recent clinical series describe the majority (between 50 and 75 percent) of p-NETs as nonfunctional, based on the assumption that even p-NETs secreting excessive amounts of hormones without consequent symptomatology are considered nonfunctional by many clinicians.

Keywords: Pancreatic Neoplasms; prognosis; neuroendocrine Tumors; general surgery; antineoplastic agents

(Received December 12, 2019; Accepted January 14, 2020)
classification\textsuperscript{17} and the American Joint Committee on Cancer (AJCC) staging system\textsuperscript{18}. The 2010 WHO grading scheme divided p-NETs into 4 main groups: neuroendocrine tumor G1 (NET G1), neuroendocrine tumor G2 (NET G2), neuroendocrine carcinoma G3 (NEC G3), and mixed adenoma and neuroendocrine carcinoma (MANEC)\textsuperscript{19}. The 2010 WHO classification system combined the differentiation and grading features to classify the biological aggressiveness of p-NETs based on the proliferative activity of the tumor as measured by mitotic count and the expression of Ki-67. The AJCC and ENETS both adopt a tumor-node metastasis (TNM) staging system for p-NETs; however, they differ in the definitions of T stage groupings. Thus the presence of these 2 staging systems for p-NETs might raise clinical concerns of potential confusions in patient management\textsuperscript{20}.

Despite a remarkable progress in understanding the molecular biology and classification of this disease, evidence-based research is still needed to develop treatment modalities that will improve overall prognosis. Large case series on outcomes are still scarce. In our study, we report the clinical features, treatment strategies and survival of p-NET patients treated at a tertiary care center—the American University of Beirut Medical Center (AUBMC), in Beirut, Lebanon.

Materials and Methods

Patient selection

The study was approved by the local institutional review board committee at AUBMC in accordance with ethical guidelines for biomedical research. Subjects gave their informed consent to participate. Data from medical records of twenty seven patients who were pathologically diagnosed as p-NETs at the American University of Beirut Medical Center from 2005 to 2015 were collected. The data included patient demographics, presentation, anatomic locations and imaging studies.

Tumor Characteristics

Tissue specimens from patients’ samples were collected during surgical resections and needle biopsies performed at our center. Features of the tumor (size, location, lymph invasion, distant metastasis, surgical margin, component, mitotic count, Ki-67 positive rate, etc.) were based on intra-operative findings and pathological diagnosis. By definition, patients who had symptoms related to secreted hormone(s) and elevated serum levels were considered as patients with functional p-NETs. The 2010 WHO NET and ENETS classification systems were used in concordance for all cases to determine staging. The pathological parameters in this series recognized the typical NET morphological findings along with the expression of neuroendocrine markers, including CgA, Synaptophysin and others. Additionally, the immunohistochemistry (MIB1 monoclonal antibodies against the Ki-67 antigen) cell proliferation index was used for grading of tumors.

Follow-up and Survival

The last date of follow-up was defined as a last contact marked in the patient records, or date of death upon follow up obtained from physicians’ clinic. Routine follow-up at AUBMC for p-NET patients is through evaluating markers and clinical assessment every 3 months and CT scanning every 6 months. Overall survival (OS) was defined as the number of months from the date of diagnosis to the time of death or last contact.

Statistical Analysis

Data are shown as median for quantitative variables, or as numbers and their frequencies as proportions (%) for categorical variables. Survival analyses using Kaplan-Meier were plotted using SPSS 23.0 (IBM). Differences with P < 0.05 were considered to be statistically significant.

Results

Patient Characteristics

Twenty-seven patients diagnosed with p-NET between 2005 and 2015 were identified. Median age of patients at diagnosis was 52 years (range 15–61). Out of the total 27 patients, there was a male predominance with 17 patients (63%) compared to 10 (37%) female patients. Baseline characteristics are shown in Table 1. Nine (33%) tumors were located in the head of the pancreas, 2 (7%) in the body, 5 (19%) in the tail, and 11 (41%) tumors were multifocal without any clear dominance of location.

Table 1 Baseline characteristics of sample patients

| Factor                  | n=27 (%) |
|-------------------------|----------|
| Sex                     |          |
| Male                    | 17 (63)  |
| Female                  | 10 (37)  |
| Age, years              |          |
| Median (range)          | 52 (15–61) |
| MEN1 syndrome           | 4 (15)   |
| Tumor size, cm          | Median (range) 4.5 (1.0–10.5) |
| Signs and symptoms*     |          |
| Abdominal pain          | 16 (59)  |
| Weight loss             | 13 (48)  |
| Nausea/Vomiting         | 7 (26)   |
| Diarrhea                | 5 (19)   |
| Jaundice                | 4 (15)   |
| Hypoglycemia            | 2 (7)    |
| Asymptomatic            | 4 (15)   |
| Tumor localization       |          |
| Head                    | 9 (33)   |
| Body                    | 2 (7)    |
| Tail                    | 5 (19)   |
| Multiple                | 11 (41)  |
| Functionality           |          |
| Functional              | 10 (37)  |
| Non-functional          | 17 (63)  |

*Total percentage greater than 100% as some patients presented with several symptoms.
Clinical Manifestation

Four patients (15%) had Multiple endocrine neoplasia type 1 (MEN I syndrome). Twenty-three patients (85%) were symptomatic before diagnosis, whereas in 4 patients (15%) the tumor was incidentally detected on imaging done for other clinical indications. The most common presentations were abdominal pain in 16 patients (59%), and weight loss in 13 patients (48%). Sixty-three percent of tumors were non-functional. Most functional tumors (50%) were multifocal within the pancreas, whereas most nonfunctional tumors (47%) were located exclusively in the head of the pancreas. Thirteen out of 27 (48%) patients had increased serum levels of CgA, 8 out of the 13 (62%) CgA positive patients had functional tumors; on the other hand, 12 out of 14 (86%) of the CgA negative patients had nonfunctional tumors (P=0.011). Although our study showed a significant difference in chromogranin levels between functional and non-functional tumors, the sample size is small and as per larger studies done across the literature there is no significant difference between the two14, 15).

Diagnostic workup

Twenty two patients (81%) had a multiphasic Computed Tomography (CT) done as the first step in diagnostic imaging and five (19%) had an Magnetic Resonance Imaging (MRI) abdomen done. This was done in conjunction with either a core biopsy (63%) or Endoscopic Ultrasound/ Fine Needle Aspiration (EUS/ FNA) (37%). For the patients who received Somatostatin analogues (SSAs), 12 of them (67%) underwent Ga-DOTATATE PET/CT and 2 of them (11%) underwent somatostatin receptor scintigraphy. Findings are summarized in Table 2.

Descriptions by the WHO Grading Systems

The proportion of patients who had grade 1, grade 2, and grade 3 (NEC) disease, (based on the WHO grading system), were 11 (41%), 13 (48%), and 3 (11%) out of all patients, respectively. According to the WHO 2010 classification (AJCC, American Joint Committee on Cancer/ UICC, International Union Against Cancer), the proportions of patients with pathologic TNM stages IA/B, II/ A/B, III, and IV disease were 18%, 22%, 4%, and 56% of all patients. Based on the ENETS classification, stages I, II/A/B, III/A/ B, and IV were 4%, 22%, 18%, and 56%, respectively. Ten patients (37%) had lymph node involvement according to surgical pathology reports. Cross tabulation of tumor grade with both staging methods is summarized in Table 3.

Table 2  Diagnostic workup of sample patients

| Factor                      | n=27 (%) |
|-----------------------------|----------|
| Diagnostic Imaging          |          |
| Multiphasic CT              | 22 (81)  |
| MRI Abdomen                 | 5 (19)   |
| Pathological assessment     |          |
| Core Biopsy                 | 17 (63)  |
| EUS/FNA                     | 10 (37)  |
| Assessment for SSA use      |          |
| Somatostatin receptor scintigraphy | 2 (11) |
| Ga-DOTATATE PET/CT          | 12 (67)  |

Table 3  Tumor characteristics according to the WHO 2010 grading system

| Factor          | G1 n=11 (%) | G2 n=13 (%) | G3 n=3 (%) |
|-----------------|-------------|-------------|------------|
| AJCC stage      |             |             |            |
| I A/B           | 3 (27)      | 2 (15)      | 0 (0)      |
| II A/B          | 3 (27)      | 2 (15)      | 1 (33)     |
| III             | 1 (9)       | 0 (0)       | 0 (0)      |
| IV              | 4 (36.5)    | 9 (69)      | 2 (67)     |
| ENETS stage     |             |             |            |
| I               | 0 (0)       | 1 (8)       | 0 (0)      |
| II A/B          | 4 (37)      | 2 (15.5)    | 0 (0)      |
| III A/B         | 3 (27)      | 1 (8)       | 1 (33)     |
| IV              | 4 (37)      | 9 (69)      | 2 (67)     |
| Lymph node invasion |           |             |            |
| Surgical resection | 6 (55)     | 8 (62)      | 2 (67)     |
| Chemotherapy    | 3 (27)      | 2 (15)      | 1 (33)     |
| Somatostatin analogues | 2 (18) | 3 (23)      | 0 (0)      |
| Initial treatment |           |             |            |
| Sandostatin only | 2 (18)     | 0 (0)       | 0 (0)      |
| Sandostatin + chemotherapy | 2 (18) | 5 (38)     | 1 (33)     |
| Surgery         | 5 (45)      | 4 (31)      | 0 (0)      |
| Surgery + Sandostatin | 0 (0)   | 3** (23)    | 1 (33)     |
| Sandostatin + chemotherapy and surgery | 2* (18) | 1 (8)       | 1 (33)     |

*One patient progressed and had chemotherapy
**2 patients progressed and received SSAs
AJCC: American Joint Committee on Cancer, ENETS: European Neuroendocrine Tumors Society.
Treatment

In our institution the cases of p-NET are managed in a multidisciplinary approach via weekly tumor board discussions among the various specialists. Surgical interventions were done in 17 out of 27 (63%) patients with 13 of these (77%) non-functional tumors (Fig. 1). All except one operation was performed with curative intent. The patient who underwent palliative surgery also received SSAs. Whipple procedure (pancreaticoduodenectomy) with peripancreatic lymph node dissection was performed for 12 out of 17 (70%) of the patients who underwent surgery. Two patients had porta-hepatis lymph node dissection, one patient had pericolonic lymph node dissection and one patient had peri common bile duct lymph node dissection. Two of the procedures (12%) were spleen-preserving distal pancreatectomies, and 3 of the 17 (18%) consisted of tumor enucleations.

Out of the total number of patients, during the course of treatment, eighteen patients received Somatostatin analogues (SSAs) and/or chemotherapy, 7 (39%) had regression in tumor size after first line therapy, 6 (33%) had stable disease, and 5 (28%) had disease progression despite therapy. Twelve patients received chemotherapy. All chemotherapy regimens are approved based on AJCC, ENET and ESMO guidelines. The chemotherapy regimens used and their response rate were monitored in 11 patients since one patient had missing information on his regimen. Nine patients (82%) were on capecitabine and temozolomide with a response rate of 67%, one patient (9%) was on doxorubicin and 5FU with a 0% response rate, and one patient (9%) was on cisplatin and etoposide with a 0% response rate. All 11 patients who received chemotherapy also received somatostatin analogues (octreotide).

Of the 15 patients with stage IV disease, 6 received chemotherapy and somatostatin analogues (SSA) initially, without surgical resection, an additional 2 patients received chemotherapy upon progression on SSAs. Out of the total 8 patients who received chemotherapy during the course of the disease; 2/8 (25%) responded with tumor regression, 4/8 (50%) with stable disease, and 2/8 (25%) progressed. In 5 patients, the primary tumor was surgically resected followed by chemotherapy and SSA; 2/5 had complete remission and 1/5 had a stable disease (Table 4).

![Diagram](image-url)

**Fig. 1** Initial treatment of primary and metastatic tumors based on Stage IV vs. Stages I, II, and III. Patients in our study either underwent surgery, chemotherapy, somatostatin analogues, or a protocol which included more than one of the p-NET treatment approaches. SSAs: Somatostatin Analogues

| Table 4 | Treatment stratified by staging systems |
|---------|---------------------------------------|
|          | Treatment all                        |
|          | AJCC stage                            |
|          | Sando only | Sando + chemo | Surgery | Surgery + Sando | Sando + chemo + surgery |
| I        | 1 | 0 | 4 | 0 | 0 |
| II       | 0 | 0 | 4 | 2 | 0 |
| III      | 0 | 0 | 0 | 0 | 1 |
| IV       | 1 | 8 | 1 | 2 | 3 |
| ENET stage | Sando only | Sando + chemo | Surgery | Surgery + Sando | Sando + chemo + surgery |
| I        | 0 | 0 | 1 | 0 | 0 |
| II       | 1 | 0 | 4 | 1 | 0 |
| III      | 0 | 0 | 3 | 1 | 1 |
| IV       | 1 | 8 | 1 | 2 | 3 |

AJCC: American Joint Committee on Cancer, ENETS: European Neuroendocrine Tumors Society, Sando: Santostatin, Chemo: Chemotherapy
Overall survival

Median survival of the whole cohort was more than 10.8 years while the median survival of patients diagnosed at stage IV was 6 years. The one and two-year survival rates for the entire cohort were 97% and 83%, respectively (Fig. 2). The one and two-year survival rates of stage IV were 93% and 70%, respectively (Fig. 3).

Discussion

In the present study, we have reported the clinical and diagnostic modalities as well as treatment outcomes of 27 patients with p-NET treated at a single cancer center over the past ten years. With an overall incidence of <0.5/100,000 per year, p-NETs generally are rare and contribute to about 1–2% of pancreatic tumors.

Males outnumbered females in this cohort contrary to other studies reporting a female predominance.

A large series investigation of p-NET was conducted to determine which staging system (the WHO or the AJCC) was superior in terms of performance in clinical practice. The authors report that both systems could consistently reflect the clinical outcome of patients with surgically resected p-NETs. Another report evaluating the clinical consistency of the new WHO 2010 grading system and the ENETS 2006 TNM staging system on surgical outcome revealed that both classifications accurately reflect the clinical outcome of p-NETs. Surgical margin, the WHO and ENETS may all be meaningful prognostic factors impacting the long-term survival of patients with p-NETs.

According to the AJCC system the percentage of patients with TNM stages IA/B were 18% compared to the ENETS stage I which was 4%. AJCC stage III patients comprised 4% compared to 18% of stage IIIA/B ENETS patients. We were unable to determine the prognostic implications of both staging systems because of the small size of our cohort.

The proportion of patients with p-NET grade 1, grade 2, and grade 3 were 41%, 48% and 11%, respectively. Our figures report higher rates of grade 1 and grade 2 p-NET cases which is different from those reported in the literature.

In the diagnostic workup of these patients, the majority (67%) of those who received SSAs underwent Ga-DOTATATE PET/CT. These results highlight the increasing diagnostic importance of Ga-DOTATATE PET/CT compared to other diagnostic modalities which is consistent with what other studies have reported.

Surgery is the only potentially curative first-line treatment of p-NETs if R0 resection of the primary tumor is achieved. Seventeen patients (63%) from our cohort underwent surgery with curative intent while ten patients had lymph node involvement. The percentages of patients with p-NET grade 1, grade 2, and grade 3 who underwent surgery were 55%, 62% and 67%, respectively.

During treatment, 12 patients received chemotherapy; the majority of which (9/12) received the oral alkylating agent temozolomide in combination with capcitabine. The response rate in those patients was 67%. In a series of 30 patients treated with temozolomide in combination with capcitabine, 70% of patients demonstrated a radiographic tumor response. However, the efficacy of temozolomide depended on O6-methylguanine-DNA methyltransferase (MGMT); a low expression of MGMT in tumor cells increases susceptibility to the temozolomide. Another retrospective trial has shown that the combination of capcitabine and temozolomide is effective in p-NETs especially in patients with metastatic tumors who were deemed unfit for surgical treatment modalities. The response rate in metastatic p-NETs was 20%.
The one- and two-year survival rates of our entire cohort were 97% and 83%, respectively. The reported one and two year survival rates range between 87%–94.6% and 70%–83%, which is similar to our reported survival.[12,31] The median survival time for the whole cohort including stages I, II, and III is more than 10 years whereas the median survival of stage IV patients was 6 years. Stage IV patients have significantly lower survival rates than those compared to stage I, II and III as reported by several studies.[21,22,30] In our cohort, and due to small population size, we were unable to compare survival between the different stages.

Conclusion

p-NETs still represent a significant clinical challenge and their management requires a coordinated multidisciplinary approach, because of their variable presentations and the non-standardized treatment plans, especially when surgery is not possible. The rarity of these malignancies precludes large scale randomized controlled trials to establish a gold standard treatment. Moreover, the paucity of data forces clinicians to rely on educated guessing and trends for the selection of management options. NETs are therefore a greater public health problem than previously appreciated and high-quality research as well as large population-based studies in the field appear imperative.

Abbreviations and units:

AJCC : American Joint Committee on Cancer
AUBMC : American University of Beirut Medical Center
CgA : Chromogranin A
CT : Computed Tomography
ENETS : European Neuroendocrine Tumors Society
ESMO : European Society for Medical Oncology
EUS : Endoscopic Ultrasound
FNA : Fine Needle Aspiration
MANEC : Mixed adeno and neuroendocrine carcinoma
MEN1 : Multiple Endocrine Neoplasia-type 1
MGMT : O6-methylguanine-DNA methyltransferase
MRI : Magnetic Resonance Imaging
NEC : Neuroendocrine carcinoma
OS : Overall survival
p-NETs : Pancreatic neuroendocrine tumors
PET : Positron emission tomography
SSAs : Somatostatin analogues
SYN : Synaptophysin
VIP : Vasoactive intestinal peptide
WHO : World Health Organization

References

1) Fraenkel M, Kim MK, Faggiano A, Valk GD. Epidemiology of gastroenteropancreatic neuroendocrine tumours. Best Pract Res Clin Gastroenterol. 2012; 26: 691–703. PMID: 23582913. doi: 10.1016/j.bpg.2013.01.006
2) Ito T, Sasano H, Tanaka M, Osamura RY, Sasaki I, Kimura W, et al. Epidemiological study of gastroenteropancreatic neuroendocrine tumors in Japan. J Gastroenterol. 2010; 45: 234–243. PMID: 20058030. doi: 10.1007/s00535-009-0194-8
3) Pape UF, Bohmig M, Berndt U, Tiling N, Wiedenmann B, Ploechinger U. Survival and clinical outcome of patients with neuroendocrine tumors of the gastroenteropancreatic tract in a german referral center. Ann N Y Acad Sci. 2004; 1014: 222–233. PMID: 15153439. doi: 10.1196/annals.1294.025
4) Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, 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. PMID: 18565894. doi: 10.1200/jco.2007.15.4377
5) Ehehalt F, Saeger HD, Schmidt CM, Grutzmann R. Neuroendocrine tumors of the pancreas. Oncologist. 2009; 14: 456–467. PMID: 19411317. doi: 10.1634/theoncologist.2008-0259
6) Turaga KK, Kvols LK. Recent progress in the understanding, diagnosis, and treatment of gastroenteropancreatic neuroendocrine tumors. CA Cancer J Clin. 2011; 61: 113–132. PMID: 21388967. doi: 10.3322/caac.20097
7) Falconi M, Ploechinger U, Kwakkeboom DJ, Manfredi R, Korner M, Kvols L, et al. Well-differentiated pancreatic nonfunctioning tumors/carcinoma. Neuroendocrinology. 2006; 84: 196–211. PMID: 17312380. doi: 10.1159/000098812
8) Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. Ann Oncol. 2008; 19: 1727–1733. PMID: 18515795. doi: 10.1093/annonc/mdn351
9) Ito T, Tanaka M, Sasano H, Osamura YR, Sasaki I, Kimura W, et al. Preliminary results of a Japanese nationwide survey of neuroendocrine gastrointestinal tumors. J Gastroenterol. 2007; 42: 497–500. PMID: 17671766. doi: 10.1007/s00535-007-2056-6
10) Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas. 2010; 39: 707–712. PMID: 20664470. doi: 10.1097/MPA.0b013e3181ec24a
11) Panzuto F, Nasoni S, Falconi M, Corleto VD, Capurso G, Cassetta S, et al. Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. Endocr Relat Cancer. 2005; 12: 1083–1092. PMID: 16322345. doi: 10.1677/erc.1.01017
12) Rindi G, Petrone G, Inzani F. The 2010 WHO classification of digestive neuroendocrine neoplasms: a critical appraisal four years after its introduction. Endocr Pathol. 2014; 25: 186–192. PMID: 24699927. doi: 10.1007/s12022-014-9313-z
13) Shiba S, Morizane C, Hiraoka N, Sasaki M, Koga F, Sakamoto Y, et al. Pancreatic neuroendocrine tumors: a single-center 20-year experience with 100 patients. Pancreatology. 2016; 16: 99–105. PMID: 26718527. doi: 10.1016/j.pan.2015.11.001
14) Zerbi A, Falconi M, Rindi G, Delle Fave G, Tomassetti P, Pasquali C, et al. Clinicopathological features of pancreatic endocrine tumors: a prospective multicenter study in Italy of 297 sporadic cases. Am J Gastroenterol. 2010; 105: 1421–1429. PMID: 20889735. doi: 10.1038/ajg.2009.747
15) Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. Gastroenterology. 2008; 135: 1469–1492. PMID: 18703061. doi: 10.1053/j.gastro.2008.05.047
16) Bosman F, Carneiro, F, Hruban, RH, Theise, ND. WHO Classification of Tumours of the Digestive System, Fourth ed: International Agency for Research on Cancer; 2010.
17) Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, et al. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. Neuroendocrinology. 2016; 103: 153–171. PMID: 26742109. doi: 10.1159/000434171
18) Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010; 17: 1471–1474. PMID: 20180029. doi: 10.1245/s10434-010-0985-4
19) Kloppe G, Rindi G, Perren A, Komminoth P, Klimstra DS. The
ENETS and AJCC/UICC TNM classifications of the neuroendocrine tumors of the gastrointestinal tract and the pancreas: a statement. Virchows Arch. 2010; 456: 595–597. PMID: 20422210. doi: 10.1007/s00428-010-0924-6
20) Ramirez RA, Beyer DT, Chauhan A, Boudreaux JP, Wang YZ, Woltering EA. The Role of Capecitabine/Temozolomide in Metastatic Neuroendocrine Tumors. Oncologist. 2016; 21: 671–675. PMID: 27226359. doi: 10.1634/theoncologist.2015-0470
21) Yang M, Ke NW, Zeng L, Zhang Y, Tan CL, Zhang H, et al. Survival Analyses for Patients With Surgically Resected Pancreatic Neuroendocrine Tumors by World Health Organization 2010 Grading Classifications and American Joint Committee on Cancer 2010 Staging Systems. Medicine (Baltimore). 2015; 94: e2156. PMID: 26632896. doi: 10.1097/md.0000000000002156
22) Yang M, Tian B, Zhang Y, Su A, Yue P, Xu S, et al. Epidemiology, diagnosis, surgical treatment and prognosis of the pancreatic neuroendocrine tumors: Report of 125 patients from one single center. Indian J Cancer. 2015; 52: 343–349. PMID: 26905133. doi: 10.4103/0019-509x.176746
23) Yang M, Tian BL, Zhang Y, Su AP, Yue PJ, Xu S, et al. Evaluation of the World Health Organization 2010 grading system in surgical outcome and prognosis of pancreatic neuroendocrine tumors. Pancreas. 2014; 43: 1003–1008. PMID: 24945681. doi: 10.1097/ mpa.0000000000000153
24) 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. PMID: 19047107. doi: 10.1185/1078-0432.Ccr-08-0734
25) Fischer L, Kleeff J, Esposito I, Hinz U, Zimmermann A, Friess H, et al. Clinical outcome and long-term survival in 118 consecutive patients with neuroendocrine tumours of the pancreas. Br J Surg. 2008; 95: 627–635. PMID: 18306152. doi: 10.1002/bjs.6051
26) Ito H, Abramson M, Ito K, Swanson E, Cho N, Ruan DT, et al. Surgery and staging of pancreatic neuroendocrine tumors: a 14-year experience. J Gastrointest Surg. 2010; 14: 891–898. PMID: 20224984. doi: 10.1007/s11605-010-1173-3
27) Mojtahedi A, Thamake S, Tworowska I, Ranganathan D, Delpassand ES. The value of (68)Ga-DOTATATE PET/CT in diagnosis and management of neuroendocrine tumors compared to current FDA approved imaging modalities: a review of literature. Am J Nucl Med Mol Imaging. 2014; 4: 426–434. PMID: 25143861.
28) Jarufe NP, Coldham C, Orug T, Mayer AD, Mirza DF, Buckels JA, et al. Neuroendocrine tumours of the pancreas: predictors of survival after surgical treatment. Dig Surg. 2005; 22: 157–162. PMID: 16043962. doi: 10.1159/000087148
29) Strosberg JR, Cheema A, Weber JM, Ghayouri M, Han G, Hodul PJ, et al. Relapse-free survival in patients with nonmetastatic, surgically resected pancreatic neuroendocrine tumors: an analysis of the AJCC and ENETS staging classifications. Ann Surg. 2012; 256: 321–325. PMID: 22415420. doi: 10.1097/sla.0b013e31824e6108
30) Strosberg JR, Fine RL, Choi J, Nasir A, Coppola D, Chen DT, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. Cancer. 2011; 117: 268–275. PMID: 20824724. doi: 10.1002/cncr.25425
31) 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; 93: e94. PMID: 25396335. doi: 10.1097/md.0000000000000094