Prognostic factors and characteristics of pancreatic neuroendocrine tumors: single center experience

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ABSTRACT

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Purpose: Pancreatic neuroendocrine tumors (PNET) are a rare subgroup of tumors. For PNETs, predictive factors for survival and prognosis are not well known. The purpose of our study was to evaluate the predictive factors for survival and disease progression in PNETs. **Material and Methods:** We retrospectively analyze 37 patients who were diagnosed as PNET at Severance Hospital between November 2005 and March 2010. Prognostic factors for survival and disease progression were evaluated using the Kaplan-Meier method. **Results:** The mean age of the patients was 50.0±15.0 years. Eight cases (21.6%) were described as functioning tumors and 29 cases (78.4%) as non-functioning tumors. In univariate analysis of clinical factors, patients with liver metastasis (p=0.002), without resection of primary tumors (p=0.002), or AJCC/UICC III/IV stage (p=0.002) were more likely to show shorter overall survival (OS). Patients with bile duct or pancreatic duct invasion (p=0.031), larger than 20mm sized-lesions (p=0.036), liver metastasis (p=0.020), distant metastasis (p=0.005), lymph node metastasis (p=0.009) or without resection of primary tumors (p=0.020) were more likely to show shorter progression-free survival (PFS). In multivariate analysis of clinical factors, bile duct or pancreatic duct invasion [p=0.010, hazard ratio (HR) =95.046], and tumor location (non-head of pancreas) (p=0.036, HR=7.381) were confirmed as independent factors to predict shorter PFS. **Conclusion:** Patients with liver metastasis or without resection of primary tumors

were more likely to show shorter OS. Patients with bile duct or pancreatic duct invasion or tumors located at body or tail of pancreas were more likely to show shorter PFS.

Key words : pancreatic neuroendocrine tumor, prognostic factor, liver metastasis, bile duct invasion, pancreatic duct invasion, location of tumor

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I. INTRODUCTION

Pancreatic neuroendocrine tumors (PNETs), one of the rarest neoplasms, occurs in fewer than one in 100,000 people per year and represents 1~2% of all pancreatic tumors.[1] PNETs arise in all ages with a peak incidence between 30 and 60 years.[1] Their incidence is thought to be increasing over the past 20 years.[2] During the 1980s and 1990s, the term ñcarcinoidò was used, but this term was confusing for pathologists and clinicians. Since 2000, the terms ñneuroendocrine tumorò and ñneuroendocrine carcinomaò have been introduced to describe neuroendocrine tumors of the gastroentero-pancreatic system.[3]

PNETs can be classified as functional or non-functional tumors based on symptoms and endocrinologic laboratory tests.[4] Functional PNETs secrete biologically active peptides, such as insulin, gastrin, glucagon, somatostatin, and vasoactive intestinal polypeptides (VIP).[4] Most functional tumors cause glycemic symptoms, such as hypoglycemia, but most non-functional tumors are found by chance. PNETs can be sporadic or may be part of genetic syndrome, such as multiple endocrine neoplasia (MEN) type 1 syndrome, von Hippel-Lindau disease, neurofibromatosis type 1, and tuberous sclerosis.[3]

Approximately 60% of patients with PNET have been reported to have liver metastasis at presentation. However, the slow growth pattern of PNET, along with

improvement in the methods of pre- and intra-operative tumor localization, more aggressive treatments, including surgical interventions, have lead to better outcomes.[3] Even though patients with PNET often have liver metastasis, 5-year survival can exceed 80% with liver resection or resection of the primary tumor and multimodal medical therapy.[5] On the other hand, a much poorer 5-year survival of 29% has been reported among groups in which primary tumors were not resected.[6]

There have been some reports about the prognostic factors for predicting survival and disease progression of PNETs. Functional status, primary mass size, resectability, lymph node metastasis, distant metastasis, and location of tumor have been reported as prognostic factors.[7-9] Up to now, prognostic factors have been inconclusive, because there is no consistent prognostic factors.

The aim of our study was to evaluate the prognostic factors for predicting survival and disease progression in PNETs.

II. MATERIAL AND METHODS

1. Patients

Thirty seven patients diagnosed with PNET at Severance Hospital, Yonsei University, in Seoul, South Korea, between November 2005 and March 2010, were enrolled in this study. The clinical and laboratory data of patients were obtained from a retrospectively enrolled database of the patients. As candidate predictive factors for survival or disease progression, clinicopathological parameters, including patient gender, age, tumor size, location, endocrine function, duct invasion, resection of primary tumor, distant metastasis, lymph node metastasis, were investigated from a database of the enrolled patients. Diagnosis of PNET was confirmed by pathologists, using immunohistochemical staining (chromogranin A, synaptophysin), based on a surgical specimen or biopsy sample.

2. Data analysis and statistical considerations

The primary end points were overall survival (OS) and progression-free survival (PFS). OS was calculated from the date of diagnosis until death from any cause or the patientôs last visit to the hospital. PFS in cases of resected tumors was calculated from the date of operation until the date of recurrence or the day of the last radiological evaluation (computed tomography or magnetic resonance imaging). PFS in cases of unresected tumors was calculated from the date of diagnosis until the date of radiological evaluation, demonstrating tumor size increase, or the day of the last radiological evaluation.

In a univariate analysis, OS and PFS were calculated using Kaplan-Meier methods. In a multivariate analysis, OS and PFS were calculated using the Cox regression method with a 95% confidence interval. All analyses were performed with the SPSS statistical program (version 18.0; SPSS Inc.). $p<0.05$ was considered statistically significant.

III. RESULTS

1. Baseline characteristics of patients

The baseline demographic and clinical characteristics are summarized in Table 1. The patient population included 17 men and 20 women, and the mean age of the patients was 50.0±15.0 years. The most common clinical symptom was hypoglycemia (62.5%) in functioning tumors, but in non-functioning tumors, 69.0% had no specific symptoms. Tumor size ranged from 6 to 100 mm (average 28.08±19.29). Eight cases (21.6%) were listed as functioning tumors and 29 cases (78.4%) as non-functioning tumors. Five patients (14%) had bile duct or pancreatic duct invasion, confirmed by imaging study (4 patients) or pathologic findings (1 patient). A total of 13 patients (35.1%) had distant metastasis. Among them, 10 patients (27%) had liver metastasis. Twelve patients (32%) were positive for lymph node metastasis. There were 25 patients (68%) with tumors located at the head of the pancreas. According to American Joint Committee on Cancer (AJCC) staging, stages I, II, III, and IV were 21

(56.8%), 6 (16.2%), 0 (0%), 10 (27.0%). According to European Neuroendocrine Tumors Society (ENETS) staging, stages I, II, III, and IV were 16 (43.2%), 6 (16.2%), 5 (13.5%), 10 (27.0%). The mean follow-up period was 23.3±16.6 months (Table 1).

Table 1. Demographic and Clinical Characteristics of the Study Population

Characteristics (n=37)	Total (%)
Age (Mean±SD)	50±15
Gender	
Male	17 (45.9%)
Female	20 (54.1%)
Symptom	
Functioning group (n=8)	
Asymptomatic	2 (25.0%)
Hypoglycemia	5 (62.5%)
Galactorrhea	1 (12.5%)
Non-functioning group (n=29)	
Asymptomatic	20 (69.0%)
Abdominal pain	4 (13.8%)
Weight loss	2 (6.9%)
Jaundice	1 (3.4%)
Diarrhea	1 (3.4%)
Constipation	1 (3.4%)
Size (mm) (Mean±SD)	28.08±19.29
Location	
Head	25 (68%)
Body	7 (18.9%)
Tail	5 (13.5%)
Distant metastasis	13 (35.1%)
Site of metastasis	
Liver	10 (27%)
Peritoneum	1 (2.7%)
Stomach	1 (2.7%)
Adrenal gland	1 (2.7%)
Ductal invasion	5 (14%)
Bile duct invasion	2 (5.4%)
Pancreatic duct invasion	3 (8.1%)
Multicentricity	4 (10.8%)

Metastasis to LN	12 (32%)
AJCC stage	
I	21 (56.8%)
II	6 (16.2%)
III	0 (0%)
IV	10 (27%)
ENETS stage	
I	16 (43.2%)
II	6 (16.2%)
III	5 (13.5%)
IV	10 (27%)

2. Prognostic factors related to overall survival (OS)

As of March 2010, 5 patients (13.5%) died. The cumulative survival rate was 94.6% at 1 year and 91.9% at 2 years. Univariate analysis of clinical factors showed that primary tumor without resection (p=0.002), with liver metastasis (p=0.002), or AJCC/UICC III/ IV stage (p=0.002) were more likely to show shorter OS (Table 2). Without liver metastasis, the 5-year survival rate was 96.3%, but it was 60% for the group with liver metastasis (Figure 1-A). If the primary tumors were resected, the 5-year survival rate was 96.3%, where as it was 60% for the group in which primary tumors were not resected (Figure 1-B).

Table 2. Univariate Analysis of Clinical Factors Associated with Overall Survival

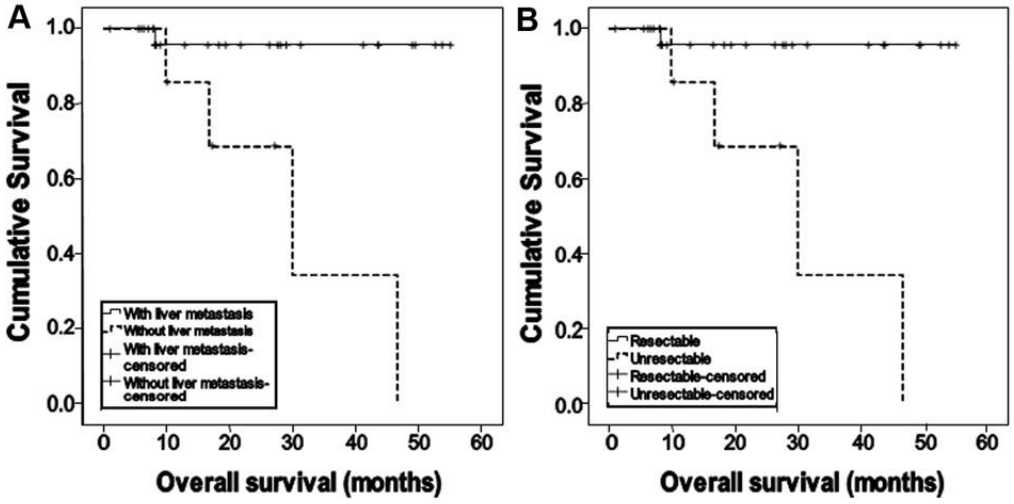
Factor	OS	*p*-value
Age (%)		0.623
Age>50	44.935	
Age<50	47.698	
Gender (%)		0.785
Male	46.951	
Female	45.835	
Size (%)		0.318
Size Ó20mm	42.745	
Size <20mm	51.219	
Location (%)		0.621
Head	45.811	
Non-head	49.327	
Function of tumor		0.136
Function	NA*	
Non-function	NA*	
Ductal invasion		0.691
Yes	NA*	
No	NA*	
Treatment of primary tumor		0.002
Resection	53.091	
No resection	30.575	
Liver metastasis		0.002
Yes	30.575	
No	53.091	
Distant metastasis except liver		0.325
Yes	30.000	
No	48.331	
Lymph node metastasis		0.071
Yes	51.290	
No	35.257	
AJCC/UICC stage		0.002
I/ II	53.091	
III/ IV	30.575	
ENETS stage		0.050

I/ II	52.524
III/ IV	38.149

OS, Overall survival; NA, Not applicable.

*OS could not be available because survival rate was 100% in the group with functioning tumor and the group without duct invasion.

Figure. 1. (A) Disease-specific survival comparing patients with liver metastasis and those without liver metastasis (p=0.002, univariate analysis). (B) Disease-specific survival comparing patients who underwent definitive resection of the primary tumor and those who did not (p=0.002, univariate analysis).



3. Prognostic factors related to progression-free survival (PFS)

As of March 2010, 9 patients (24.3%) showed disease progression. The cumulative progression free survival was 89.2 % at 1 year and 81.1 % at 2 years. Median progression free survival could not be calculated because patients who experienced disease progression did not amount to 50% of all patients. Univariate analysis of clinical factors showed that patients with bile duct or pancreatic duct invasion (p=0.031), tumor size larger than 20mm (p=0.036), liver metastasis (p=0.020), distant metastasis (p=0.005), lymph node metastasis (p=0.009), without resection of primary tumor (p=0.020), AJCC/UICC III/IV stage (p=0.020), or ENETS stage III/IV stage (p=0.009) were more likely to show shorter PFS (Table 3). Multivariate analysis for prognostic factors demonstrated that bile duct or pancreatic duct invasion (p=0.010, HR=95.046), and tumor location (non-head portion of pancreas) (p=0.036, HR=7.381) were significant factors for predicting shorter PFS (Table 4, Figure 2).

Table 3. Univariate Analysis of Clinical Factors Associated with Progression Free Survival

Factor	PFS	*p*-value
Age (%)		0.891
Age>50	34.848	
Age<50	36.127	
Gender (%)		0.389
Male	31.190	
Female	39.195	
Size (%)		0.036
Size Ó20mm	29.038	
Size <20mm	47.133	
Location (%)		0.126
Head	40.187	
Non-head	26.857	
Function of tumor		0.354
Function	38.740	
Non-function	34.569	
Ductal invasion		0.031
Yes	11.683	
No	38.637	
Treatment of primary tumor		0.020
Resection	42.404	
No resection	24.178	
Liver metastasis		0.020
Yes	42.404	
No	24.178	
Distant metastasis except liver		0.005
Yes	15.389	
No	40.057	
Lymph node metastasis		0.009
Yes	20.508	
No	42.070	
AJCC/UICC stage		0.020
I/ II	42.404	
III/ IV	24.178	

ENETS stage		0.009
I/ II	45.407	
III/ IV	25.555	

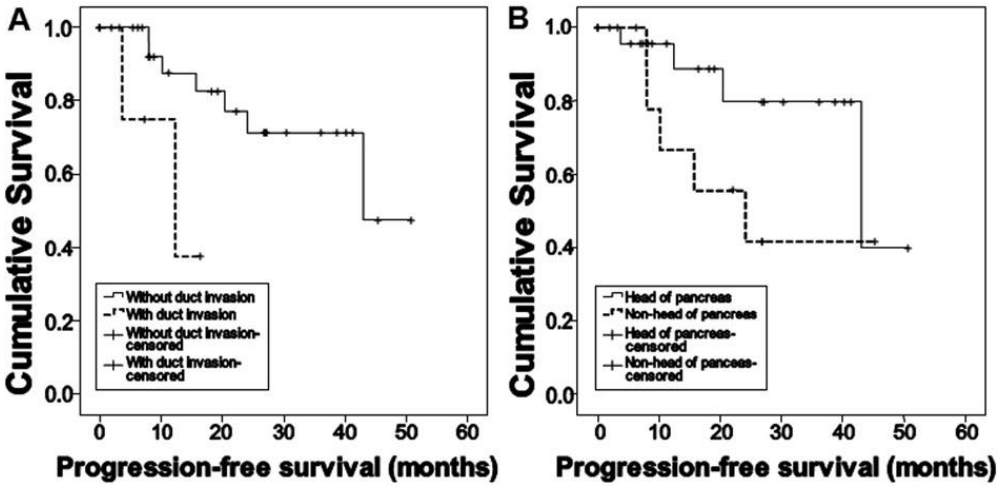
PFS, progression free survival.

Table 4. Multivariate Analysis of Risk Factors for Progression Free Survival

Variables	*p*-value	HR	95% CI	
			Lower	Upper
Size	0.273	4.769	0.291	78.035
Ductal invasion	0.005	95.046	3.857	2341.986
Treatment of primary tumor	0.597	1.906	0.174	20.850
Distant metastasis except liver	0.350	3.421	0.259	45.130
Location (Non-head of pancreas)	0.036	7.381	1.143	47.652
Lymph node metastasis	0.099	4.915	0.742	32.563

HR, hazard ratio; CI, confidence interval.

Figure. 2. (A) Disease-specific recurrence or progression comparing patients with duct invasion and those without duct invasion (p=0.010, HR=95.046 (3.857~2341.986), multivariate analysis). (B) Disease-specific recurrence or progression comparing patients with tumors in the head of pancreas and those within the non-head of the pancreas (p=0.036, HR=7.381 (1.143~47.652), multivariate analysis).



4. Treatment modality

Surgical resection was performed in 27 patients. Among them, R0 resection was performed in 24 patients, which were still alive without recurrence. Surgical methods consist of PPPD (pylorus preserving pancreatoduodenectomy) (n=7), distal pancreatectomy (n=9), enucleation (n=8), central pancreatectomy (n=1), total pancreatectomy (n=1), or wedge resection (n=1). Other treatment options were performed, such as concurrent neoadjuvant chemoradiotherapy (n=3), palliative chemotherapy (n=6), transarterial chemoembolization (n=2), transarterial chemoinfusion (n=1), or somatostatin analog (n=3).

IV. DISCUSSION

Although 64.3% of gastroentero-pancreatic endocrine tumors present metastasis at diagnosis, the 5-year survival is up to 77.5%.[10] For pancreatic sites, a poor differentiation and distant extra-hepatic metastasis have been reported as major negative prognostic factors.[10] Han et al. reported that large PNETs, regardless of their functional status, were more likely to be associated with malignancy and a predictor of worse survival.[7] Paik et al. demonstrated that resection of primary tumors in patients with PNET was associated with improved survival regardless of tumor stage.[8] Kang et al. reported that non-functioning tumors were more likely to show recurrence.[9] In our report, patients with liver metastasis or without resection of primary tumors had shorter overall survival. Patients with bile duct or pancreatic duct invasion or tumors located in the body or tail of the pancreas were more likely to show shorter PFS. We assume that tumors located at the body or tail of the pancreas are less likely to present symptoms, so that tumors are found at advanced stages and are more likely to show disease progression. But, in our datas, there was no definite difference about tumor stages between two group (ENETS stage III, IV : 40% (head) vs. 41.7% (non-head)).

As for diagnostic tools of PNETs, Chromogranin A appears to be the most useful serum marker for diagnosis, staging and monitoring.[11] Chromogranin A is gaining acceptance as a serum marker for neuroendocrine tumors.[12] In our report, almost all patients were diagnosed by positive chromogranin A staining, but serum tests for chromogranin A was not performed. EUS is of high value for localizing primary lesions, and EUS-guided FNA can accurately diagnose and predict prognoses based on cytopathologic examination with immunocytochemistry. Somatostatin receptor scintigraphy (SRS) is a very sensitive procedure for diagnosing gastrinomas but not insulinomas. Computed tomography (CT), ultrasonography (US) and magnetic resonance imaging (MRI) are primarily useful for visualizing metastasis which predict prognoses.[13] Cholangiography can be useful for evaluating bile duct

invasion. Cholangiography was performed and was helpful in recognizing bile or pancreatic duct invasion, which was confirmed as a significant prognostic factor in our study. EUS-guided FNA were performed, but not helpful in predicting prognoses, because most of patientsô datas did not include Ki-67 index and mitotic rate. Further evaluation, such as mitoses measurement, Ki-67 labeling, will be needed for predicting more reliable prognoses.

Previous classification systems discriminated between low-grade and high-grade malignant NETs but did not allow further prognostic differentiation. In contrast, new TNM classification is able to differentiate significantly between different tumor stages and cellular proliferation rates according to Ki-67 labeling.[14] Also, according to size, mitoses, invasiveness, and Ki-67 labeling, recent WHO classification classifies PNETs into grades 1 (neuroendocrine neoplasm, low grade), 2 (neuroendocrine neoplasm, intermediate grade), 3 (neuroendocrine carcinoma) in an attempt to predict natural history from pathology reports.[4] In 2006, Rindi et al introduced a four stage TNM classification for PNETs, which has subsequently been adopted by the ENETS.[15] In 2010, the new AJCC TNM staging for PNETs distinguishes between localized tumors (stage I), locally advanced resectable tumors (stage II), locally advanced unresectable tumors (stage III), and distantly metastasized tumors (stage IV).[16] In our study, we could classify PNETs by AJCC TNM stageing, but, could not classify PNETs based on histologic factors due to insufficient data. From now on, PNETs have to be diagnosed based on both AJCC TMN staging and hitologic findings (tumor differentiation, Ki-67 index, mitotic rate) through detailed date collection.

In contrast to our study, some articles reported that a small and pathologically benign nature did not predict a good prognosis in PNETs, so, curative resection should be considered initially, even in cases of incidental PNETs.[8] Even though a patient with PNET has metastatic lesions, resection of primary tumors should be considered for reasonable operative candidates.[17] In particular, resection of primary PNETs should be given to patients with treatable hepatic metastasis.

Aggressive surgical resection for select individuals with PNETs can be performed safely and may improve both symptomatic disease and overall survival. Prognostic indices such as tumor differentiation and the ability to achieve R0/R1 resection have been prognostic factors in PNETs and should be considered when planning aggressive surgical management.[18] Surgical strategy for PNET depends on the size and location of the tumor and the risk of malignancy. The proper surgical method is important to prevent postoperative complications and recurrence. Radical resection including primary and metastatic lesion may improve survival of malignant PNETs.[19] Only patients without distant metastasis underwent surgical resection in our study. Through analyzing prognostic factors, aggressive surgical resection can be considered even in cases of distant metastasis.

Transarterial chemoembolization (TACE), peptide receptor radionuclide therapy (PRRT), systemic chemotherapy, and radiotherapy can be other treatment options. PRRT uses somatostatin analogs to convey radioactivity within the tumor itself, through somatostatin receptors. New biological agents and somatostatin tagged radionuclides are also under investigation,[20] as antiproliferative agents capable of stabilizing tumor growth in patients with metastatic PNETs.[21] Advances in therapy and cooperative multicenter studies are needed to improve diagnosis, treatment and survival of patients with PNETs.[22] Various treatment options except surgery were tried in our study. Concurrent chemoradiotherapy was performed preoperatively in patients with lymph node metastasis or vascular invasion. Palliative chemotherapy (Etoposide, cisplatin) was performed in patients with distant metastasis. Transarterial chemoembolization was performed in patients with liver metastasis where surgical resection was not feasible. Somatostatin analogs were tried in patients with carcinoid syndromes such as flushing, diarrhea, and abdominal pain.

Prognostic factors were reported inconclusively through previous reports. We analyzed prognostic factors for predicting survival and disease progression, in order to predict preoperative prognostic factors and postoperative results. From our report, resection of primary tumors can improve survival, and pancreatic or bile duct

invasion, tumor location (body or tail of pancreas) were poor prognostic factors for disease progression. Our study has some new points. We followed up patients long term period at single center, also, found pancreatic or bile duct invasion as a prognostic factor. But, our study has some limitations, including very wide confidence interval due to small number of patients.

In conclusion, patients with bile duct or pancreatic duct invasion or tumors located at non-head portions of the pancreas or without resection of primary tumor should be monitored carefully. But, because PNETs is a rare subgroup of tumor, we need more time and enough datas.

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ABSTRACT(IN KOREAN)

췌장 신경내분비 종양의 예후인자 및 특징에 대한 고찰 : 단일 기관 경험

<지도교수 송 시 영>

연세대학교 대학원 의학과

오 탁 근

배경 : 췌장 신경내분비 종양은 빈도가 드문 종양으로 생존 및 예후 와 관련된 예측인자가 잘 알려지지 않았다. 본 연구에서는 췌장 신경내분비 종양의 생존 및 질병 진행에 대한 예측인자에 대해 분석해보고자 한다.
방법 : 본 연구에서는 2005년 11월부터 2010년 3월까지 신촌 세브란스 병원에서 췌장 신경내분비 종양으로 진단된 37명의 환자들을 대상으로 후향적 분석을 진행하였다. 카플란-메이어 통계법을 사용하여 생존율 및 질병진행에 대한 예후인자를 분석하였다.
결과 : 대상군의 평균 나이는 50.0±15.0 세였으며, 8명 (21.6%)의 환자가 기능성 종양, 29명 (78.4%)의 환자가 비기능성 종양이였다. 전체 생존기간과 관련된 예후인자의 일변량 분석을 통해, 간전이 (p=0.002), 원발종양의 미절제 (p=0.002) 가 짧은 전체 생존기간의 예측인자를 나타내는 경향을 보였다. 질병 진행과 관련된 예후인자의 일변량 분석을 통해서는 담관 또는 췌관침윤 (p=0.031), 20mm 이상의 원발 종양크기 (p=0.036), 간전이 (p=0.020), 원격전이 (p=0.005), 림프절 전이 (p=0.009), 원발종양의 미절제 (p=0.020) 가 짧은 무진행 생존기간의 예측인자를 나타내는 경향을 보였다. 질병 진행과 관련된 예후인자의 다변량 분석을 통해서는 담관 또는 췌관침윤 [p=0.010, hazard ratio (HR) = 95.046], 종양의 위치 (췌장의 체부 또는 미부) (p=0.036, HR=7.381) 가 짧은 무진행 생존기간의 독립적인 예측인자로 확인되었다.
결론 : 간전이가 있거나 원발종양의 절제를 하지 않은 환자에서 좀 더 짧은 전체 생존기간을 나타내었다. 담관 또는 췌관 침윤 또는 췌장의 체부 또는 미부에 종양이 존재하는 환자의 경우 좀 더 짧은 무진행 생존기간을 나타내었다.

핵심되는 말 : 췌장 신경내분비 종양, 예후인자, 간전이, 담관침윤, 췌관침윤, 종양의 위치