Table 4
Diagnostic sensitivity, specificity and predictive value of imaging parameters in the diagnosis of ASC.

	Sensitivity (95% CI)	Specificity (95% CI)	(Sensitivity + Specificity)/2 (95% CI)	PPV (95% CI)	NPV (95% CI)
Smooth outline (CT)	43.5% (23.2%–65.5%)	93.5% (82.1%–98.6%)	0.685 (0.575–0.794)	76.9% (46.2%–95.0%)	76.8% (63.6%–87.0%)
Cystic changes (CT)	34.8% (16.4%–57.3%)	80.4% (66.1%–90.6%)	0.576 (0.461–0.691)	47.1% (23.0%–72.2%)	71.2% (56.9%–82.9%)
Ring-enhancement	65.2% (42.7%–83.6%)	89.6% (77.3%–96.5%)	0.774 (0.665–0.883)	75.0% (50.9%–91.3%)	84.3% (71.4%–93.0%)

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

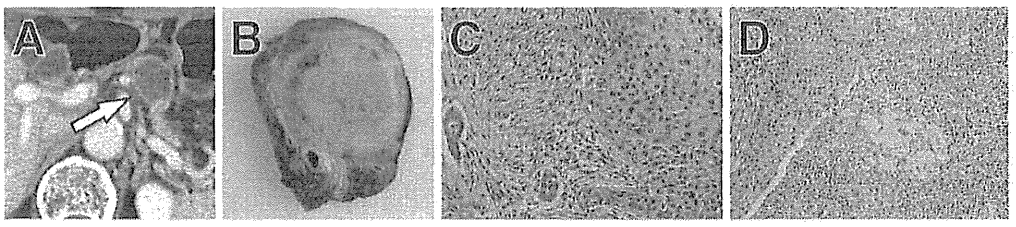

Fig. 3. Representative images of adenosquamous carcinoma (ASC) of the pancreas. (A) Contrast-enhanced CT showed a circumscribed mass in the pancreas (white arrow). The mass exhibited the ring-enhancement pattern. (B) Macroscopically, the resected tumor was soft, fleshy and circumscribed. (C) Microscopically, both glandular and squamous differentiation were present at the margins of the tumor (hematoxylin and eosin stain, original magnification ×400), and (D) extensive tumor necrosis was seen at the center of the tumor (hematoxylin and eosin stain, original magnification ×200).

pancreatic cancer. Soriano et al. reported that the accuracy of diagnosis of pancreatic tumor resectability was maximized and costs were minimized when either CT or EUS was performed initially, followed by the other test [26]. Tierney et al. suggested that although CT should be performed first, EUS should also be used because of its improved detection of vascular invasion [27].

Although EUS is a fairly sensitive modality for assessing pancreatic lesions, as previously described, a drawback of EUS is the relatively modest interobserver agreement in the interpretation of EUS findings, even by expert endosonographers. Wallace et al. reported moderate agreement (kappa = 0.45) in their examination of interobserver agreement of EUS findings for the diagnosis of chronic pancreatitis [28]. Topazian et al. reported fair to poor interobserver agreement for the interpretation of pancreatic EUS findings in familial pancreatic cancer kindreds. Furthermore, agreement was not improved by consensus [29]. On the other hand, contrast-enhanced CT is regarded as an objective imaging modality for the diagnosis of pancreatic lesions. In one study, almost perfect interobserver agreement was obtained for the assessment of CT findings in patients with pancreatic cancer (kappa >0.80) [30]. Our study, showing κ values of EUS indicating substantial agreement between the two readers (0.69), and that of CT indicating almost perfect agreement (0.90), yielded similar results to these previous studies. However, in our predictive model, the ring-enhancement pattern on contrast-enhanced CT was selected as the best predictive sign of ASC. We believe that this result might be widely acceptable.

In summary, we examined the imaging features of ASC using a matched case-control study. The present results show that presence of a ring-enhancement pattern on contrast-enhanced CT is the most useful predictive sign of ASC. In the detection and staging of pancreatic cancer, observation of a ring-enhancement pattern can indicate a poor prognosis for these patients.

Acknowledgments

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Editorial

Is endoscopic ultrasonography-guided biliary drainage really that wonderful?

RECENTLY, INTERVENTIONAL ENDOSCOPIC ultrasonography (EUS) has become remarkably popular, especially for EUS-guided biliary drainage (EUS-BD). Although several authors have reported the usefulness and safety of EUS-BD, to date, relatively few prospective studies and large-scale case reports have been conducted. Almost all papers have reported the efficacy, safety and high success rate of EUS-BD. EUS-BD enables easy access of the biliary tract, even in postoperative patients with altered anatomy or digestive tract obstruction. Whereas many authors refer to EUS-BD as a single entity, EUS-BD includes several procedures, such as EUS-guided choledochoduodenostomy (EUS-CDS), hepaticogastrostomy (EUS-HGS), EUS-rendezvous and EUS-antegrade drainage. Hence, these procedures need to be distinguished from each other to accurately evaluate them. In particular, EUS-CDS is quite different from EUS-HGS. Most papers about EUS-BD are reported from high-volume centers and by skillful endoscopists. Yet, is EUS-BD really that easy? Park *et al.* reported that the success rates of EUS-HGS and EUS-CDS were 100% (31/31) and 92% (24/26), respectively.[1] In two prospective studies, we reported a success rate of EUS-CDS of 94% (34/36).[2,3] According to these studies, EUS-BD seems to be an easy technique with a high success rate. However, contrary to these results, a Spanish national survey reported that EUS-BD, especially EUS-HGS and EUS-rendezvous, does not have such a high success rate and is sometimes technically difficult in comparison with EUS-CDS.[4] They reported success rates with EUS-HGS, EUS-CDS and EUS-rendezvous of 64.7%, 86.3% and 68.3%, respectively. However, most institutions in the Spanish survey were not such high-volume centers, with an average of <20 procedures in total. Their results seem to provide more realistic clinical data from general hospitals.

The technical difficulties with EUS-HGS include puncture of the small branch bile duct (B3) and guidewire maneuvering to the upstream part of the main bile duct. Conversely, if the bigger main bile duct is to be punctured, although maneuvering the guidewire to the hepatic hilum is easy, there is a high risk of blockage of the bile stream after insertion of the covered metal stent. When we puncture a dilated bile duct in the left hepatic lobe for EUS-HGS, we can easily puncture B2 compared with B3. However, usually B2 is punctured through the esophagus, with the consequently higher risk of mediastinitis. Hence, we should avoid puncturing B2 and instead opt for puncture of B3 via the stomach. The technical difficulties of EUS-CDS are related to dilatation of the puncture route. An electric dilator can easily resolve this problem. If the puncture site is near the hepatic hilum, we should avoid blocking the hepatic duct with a covered metal stent and instead use a plastic stent. With the rendezvous technique, guidewire maneuvering is sometimes difficult, especially while attempting to manipulate a stricture. Moreover, EUS-rendezvous is not easy to carry out and has a low success rate, particularly the transhepatic route.

The high risk of complications associated with EUS-BD is its biggest problem. Most papers have reported early complication rates of 10–30%, although late complications are rare. The rendezvous technique is not an exception. While it is commonly believed that the EUS-rendezvous technique has a low complication rate, this is, in fact, not true.[4] EUS-HGS is the most challenging of the EUS-BD procedures with a high complication rate, with one case fatality as a result of stent migration into the abdominal cavity already being reported.[5] This indicates that even if stent placement is successfully accomplished, the possibility of stent migration immediately or a few days later still remains. As there is some distance between the stomach and the liver, and these two organs are not adjacent to each other, stent migration occurs easily. Furthermore, although severe complications, such as internal stent migration, have not been published as a result of publication bias, in fact, according to medical meetings and our experience of stent migration cases, some severe complications resulting from EUS-HGS have, indeed, occurred. Bile peritonitis is also a common complication of all EUS-BD procedures. Bile peritonitis is usually, however, not severe and can be treated conservatively. Additionally, its occurrence can be minimized by using a metal stent, as in EUS-CDS.[2]

What about the clinical course following EUS-BD? We previously reported prolonged bile duct patency and a good out come with EUS-CDS.[2,3] If there is progression of duodenal obstruction, double stenting (EUS-CDS plus duodenal stent) can be done, which also has a high functional success rate. If anything, the clinical course of EUS-CDS is probably better than that of transpapillary drainage. However, the clinical course of EUS-HGS is not always good. This is

because EUS-HGS with a covered metal stent has the potential to cause segmental cholangitis and liver abscesses because of blockage of the bile stream. Indeed, we have experienced these conditions. Second, stent patency is not so long[1] and stent occlusion is sometimes frequent with EUS-HGS. If the covered metal stent of EUS-HGS is occluded by debris or bile stones, complete stone removal through the EUS-HGS is very difficult. If stone removal through the EUS-HGS is attempted, it is easy for the stones to get pushed into a bile duct branch. Hence, we sometimes have no choice but to insert an antegrade stent to push out the stones. Unlike EUS-HGS, which has the advantage of no possibility of causing pancreatitis, antegrade drainage can cause pancreatitis; hence, antegrade drainage through Vater's papilla has limited utility. Therefore, stent placement with EUS-HGS is also associated with several clinical problems.

In conclusion, EUS-BD is certainly a useful procedure, the utility of which is likely to increase with the development of newer techniques and devices. However, at present, these procedures carry the risk of major technical and clinical problems. This fact must always be kept in mind when prescribing these procedures. Further, as the occurrence of complications is closely related to the devices used, special new devices should be developed to minimize the risk of complications.

Authors declare no conflict of interests for this article.

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Can Long-Term Follow-Up Strategies Be Determined Using a Nomogram-Based Prediction Model of Malignancy Among Intraductal Papillary Mucinous Neoplasms of the Pancreas?

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Objectives: This study investigated whether a risk assessment nomogram can predict the malignant potential of intraductal papillary mucinous neoplasms (IPMNs) and provide valuable information for the follow-up and counseling strategies of such patients.

Methods: We studied 126 of 589 patients with IPMN who were followed up for at least 36 months with annual endoscopic ultrasonography. We analyzed scores derived from our nomogram, incorporating the parameters of sex, lesion type, mural nodule height, and pancreatic juice cytology determined at the initial IPMN evaluation.

Results: The rate of malignant IPMNs was 5.5% (7/126). The initial average nomogram score was 19.8 (range, 0–55), and the final follow-up average was 23.8 (range, 0–109). When a cutoff score was set at 35 points, the sensitivity, specificity, and accuracy of the nomogram to assess malignancy risk were 87.5%, 96.6%, and 96%, respectively. The area under the receiver operating characteristic curve of malignant IPMN prediction during follow-up was 0.865.

Conclusions: The ability of the nomogram to predict malignancy in patients with IPMN was validated. Our findings can suggest that a follow-up for patients at high and low risk for cancer progression could be scheduled every 3 to 6 and 12 months, respectively.

Key Words: IPMN, risk scoring model, treatment, nomogram

(*Pancreas* 2014;43: 367–372)

Ohashi et al[1] originally described intraductal papillary mucinous neoplasms (IPMNs) of the pancreas as mucin-secreting tumors in 1982. The number of individuals diagnosed with IPMN based on the 2005 International Consensus Guidelines for the Management of IPMNs[2] revised in 2012 is increasing.[3] Although IPMNs are considered malignant, clear data that can guide follow-up protocols are not available. The 2012 guidelines recommend a follow-up schedule based on cyst size, namely, annually, every 6 to 12 months, and every 3 to 6 months for cysts that are less than 10 mm, 10 to 20 mm, and more than 20 mm.[3] However, several reports have shown that cyst size alone is not a suitable morphological parameter for evaluating malignancy potential.[4–7] Moreover, a single variable such as cyst size is insufficiently reliable for planning individualized follow-up strategies. Hence, a new risk scoring model is needed to predict the likelihood of carcinoma occurrence and to establish follow-up protocols.

Nomograms are predictive mathematical models that calculate the overall probability based on several factors and are thus more accurate than other models.[8] Treatment and follow-up strategies for various neoplasms such as prostate and colorectal cancers have often been developed based on nomograms.[8–12]

Here, we validate a nomogram that we originally constructed to predict malignancy in 81 patients who had undergone an IPMN resection.[13] The nomogram predicted malignancy with an area under receiver operating characteristic curve (AUC) of 0.903 in that patient set.

In our previous study, multivariate analysis with 81 patients who had undergone IPMN resection demonstrated that pancreatic carcinoma was associated with the female sex, main pancreatic duct (MPD) IPMN, nodule size, and pancreatic juice cytology grade in patients. Thus, the present study performed a retrospective evaluation of whether a scoring system incorporating these variables was a good reflection of the risk for pancreatic carcinoma.

MATERIALS AND METHODS

Patients' Selection

A retrospective study was designed to evaluate our database registry system of endoscopic ultrasonography (EUS) procedures, which revealed 18,000 that were performed between September 1988 and April 2013 at Aichi Cancer Center Hospital (Nagoya, Japan). Of them, we identified 589 patients with IPMN. Among these 589 patients, 126 patients who fulfilled our inclusion criteria were included in the study.

Inclusion Criteria

- Patients had to be followed up for at least 3 years after diagnosis.
- Available data on sex, lesion type, mural nodule (MN) height measured by EUS, and pancreatic juice cytology findings obtained by endoscopic retrograde pancreatography (ERP).
- Patients had to be free of concomitant pancreatic ductal adenocarcinoma development.

The remaining 460 were excluded from the analysis because of the short follow up period (<3 years, n = 372), missing pancreatic juice cytology data (n = 83), or pancreatic ductal adenocarcinoma developing during the study period (n = 3). To avoid a potential for selection bias, 2 patients were also excluded because they were duplicated in our formal study of the original nomogram.

This study was approved by our institutional review board.

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TABLE 1. Clinical Characteristics of Patients

Factors	Patients (n = 126)
Male/female	70/56
Age, median (range), y	62.3 (33–77)
Period, median (range), mo	89 (36–269)
EUS times, median (range)	6.1 (2–15)
Symptomatic/asymptomatic, n (%)	14/112 (9)
MPD type-BD type ratio	6:120
Nodules, n (%)	Yes, 19 (14.%); no, 107 (89.1)
Nodule size, median (range), mm	3.5 (2–5)
Cytological classification (I/II/III/IV/V)	48/62/16/0/0

Evaluation of IPMN Size

The maximal diameter of MNs as well as the sizes of cysts and the MPD were measured by EUS along with computed to mography (CT) and/or magnetic resonance cholangiopancreatography (MRCP).

Follow-Up Protocol

This is composed of at least an annual evaluation with EUS and laboratory tests plus CT and/or MRCP examination every 12 months.

Indications for Surgery

These included MPDs 10 mm or greater, MNs 5 mm or greater, short-term disease progression with a high likelihood of malignancy, cytological detection of malignant cells in pancreatic juice, and significant symptoms such as acute pancreatitis.

Diagnosis of IPMN

Others have characterized IPMN based on the patulous appearance of the ampulla of Vater, filling defects in the pancreatic duct on ERCP, or cystic lesions connecting with the MPD, as determined by EUS, MRCP, and/or CT imaging. Lesions that predominantly involved the MPD and caused a dilatation 10 mm or greater were classified as MPD-IPMN, whereas those that mainly involved a branch pancreatic duct were classified as branch duct (BD)–IPMN.

Cytopathological Evaluation

Two experienced pathologists (Y.Y. and W.H.) reviewed all resected lesions. Based on the degree of cytoarchitectural atypia and the arrangement of the intraductal components, tumors were classified as IPMN adenoma, borderline IPMN, IPMN carcinoma in situ (noninvasive intraductal papillary mucinous carcinoma [IPMC]), or invasive IPMC in accordance with the World Health Organization classification system.[14]

Nomogram

The nomogram incorporated the following risk factors: sex, lesion type, MN height, and pancreatic juice cytology data according to the logistic regression model. Each predictor was scored between 0 and 100, and the scores were totaled. The sum of all scores was represented on a vertical axis that was used to estimate malignancy risk (Fig. 1). The ability of the nomogram to predict malignancy potential had an AUC of 0.903 in the original patient cohort.[13]

Statistical Analysis

Continuous variables are described as mean (SD), and dichotomous variables are expressed as simple proportions. The χ^2 test was used for comparative analyses. Data were statistically analyzed using the SPSS software for Windows, release 11 (SPSS Inc, Chicago, Ill). Significance was achieved when P is less than 0.05. The optimal cutoff levels for nomogram point were determined by receiver operating characteristic (ROC) curves to differentiate the low-risk group from the high-risk group of developing cancer and identify the point which showed equal sensitivity and specificity, which were also calculated.

RESULTS

Patients' Characteristics

A total of 108 patients with IPMN (male, n = 70; mean age, 62.3 years at the time of diagnosis) were followed up for a

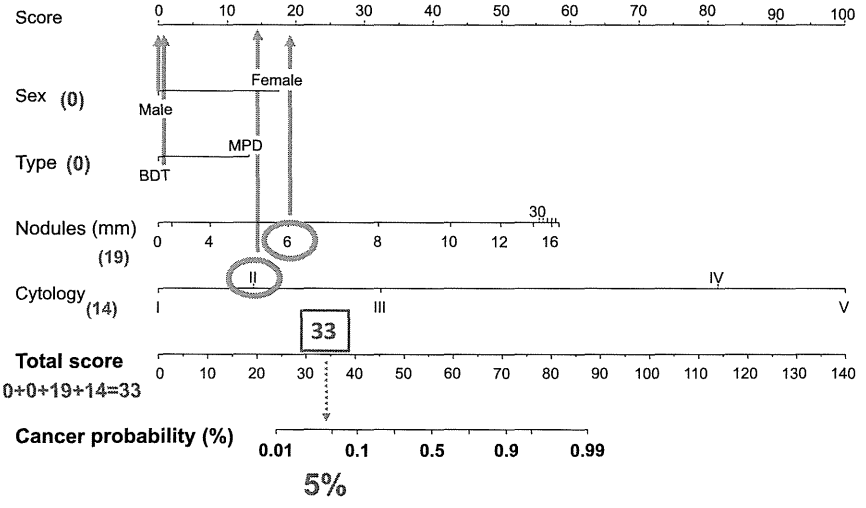

FIGURE 1. How to use the nomogram. Find the position of each variable on the corresponding axis, draw a line to the "points" axis for the number of points, add the points from all variables, and draw a line from the "total points" axis to determine cancer probability at the bottom. For example, for BD-IPMN in men, the nodule height was 6 mm, the cytological classification of the pancreatic juice was class II, men had 0 point, branch duct type was 0 point, 6-mm nodule height corresponds to 19 points, and cytological class II corresponds to 14 points. The total score was 0 + 0 + 19 + 14 = 33, where cancer probability was calculated as approximately 5%. BDT, branch duct type.

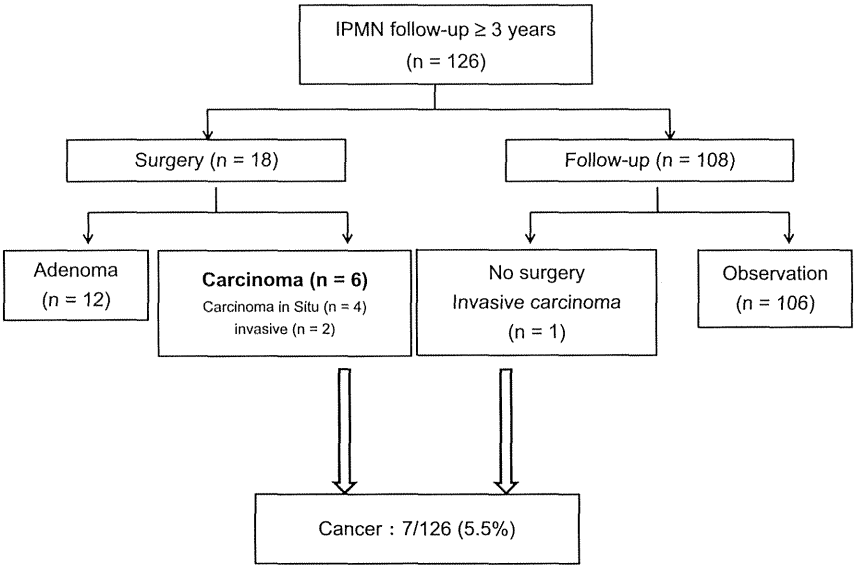

FIGURE 2. Clinical course of IPMN followed up for 3 years or more. Only 5.6% (6/108) of patients developed malignancies, assuming that the entire follow-up group had only benign lesions at the start of study.

median of 89 months (range, 36–269 months). Each patient underwent an average of 6.1 EUS procedures (range, 2–15 procedures) throughout the follow-up period. Six and 120 patients had MPD-IPMN and BD-IPMN, respectively. The median diameters of the cysts and MPDs were 18.6 mm (range, 0–60 mm) and 2.7 mm (range, 1–10 mm), respectively. Nineteen patients (14.9%) had MNs with a median size of 3.5 mm (range, 2–5 mm). Pancreatic juice cytology was classified as I, II, and III in 48, 62, and 16 patients, respectively, among whom 18 (14.2%) underwent surgery. Table 1 summarizes the clinical characteristics of the patients.

Follow-Up Results

Patients were assigned to either a group that was followed up for at least 3 years (follow-up group) or an operation group throughout the follow-up period. The follow-up group included 1 patient who developed carcinoma. This patient was managed with a best supportive care regimen because of having a poor performance status and was excluded thereafter from the analysis. The operation group (n = 18) was composed of patients who had undergone surgery to treat MPD dilation (n = 5), large MNs (n = 9), or acute pancreatitis (n = 4). Among them, 12 had adenoma and 6 had carcinoma (in situ, n = 4; minimally invasive,

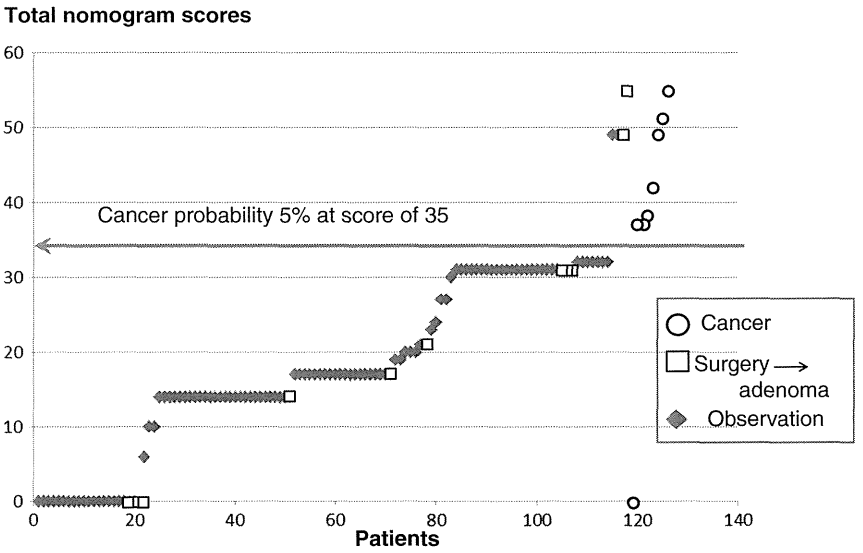

FIGURE 3. Initial nomogram total scores for all patients in order. Diamonds, squares, and circles indicate patients who were observed, underwent surgery to treat adenoma and patients with cancer respectively. A score of 35 indicates a 5% probability of developing cancer.

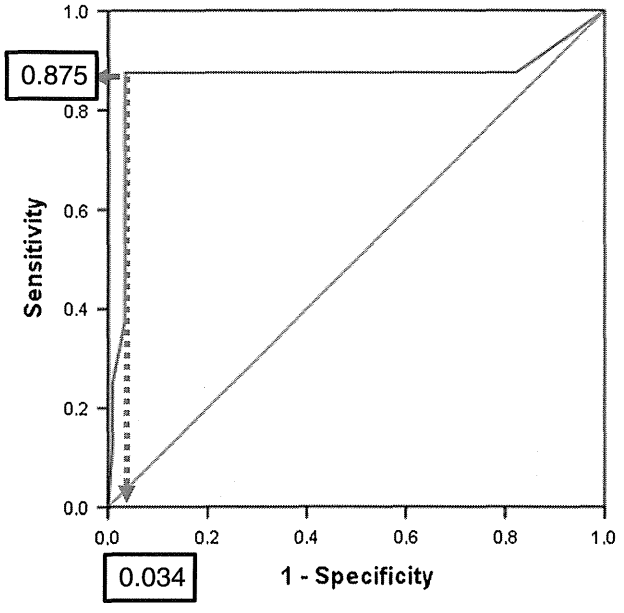

FIGURE 4. ROC analysis of prediction of IPMC during follow-up for IPMN. Area under the ROC curve, 0.865. The optimal cutoff level for nomogram point to differentiate the low-risk group from the high-risk group of developing cancercancer was 35 points. It was determined by the point, which showed equal sensitivity and specificity on the ROC curve. When a score of 35 points was taken as the cutoff, the sensitivity and specificity of the nomogram to assess malignancy risk were 87.5% and 96.6%, respectively.

n = 1; invasive, n = 1). Only 7 (5.5%) of 126 patients developed a malignant disease, assuming that the entire follow-up group had only benign lesions at the start of the study. Figure 2 summarizes these results.

Prediction of Malignant Transformation During Follow-Up

Figure 3 shows the details of all patients (including sex, lesion type, MN height, and pancreatic juice cytology) that were incorporated into our nomogram at the time of the initial presentation. The nomogram predicted IPMCs with an AUC of 0.865 (Fig. 4). The optimal cutoff point based on the ROC curve was at point 35, which was the most appropriate, and the nomogram estimated the cancer risk as 5% with a sensitivity of 87.5% (7/8), a specificity of 96.6% (114/118), a positive predictive value of 63.6% (7/11), a negative predictive value (NPV) of 99.1% (114/115), and an accuracy of 96% (Table 2). One patient with cancer who scored less than 35 points on the nomogram had carcinoma in situ without MNs.

Change of the Nomogram Point

The average score of the initial nomogram was 19.8 (range, 0–55), and the average final follow-up nomogram score was 23.8 (range, 0–109). Figure 5 shows the changing rate of the nomogram of 18 operated cases. The changing rate of 12 adenoma cases was 37.6% ± 41.2% (0%–98%), whereas the changing rate of 6 carcinoma cases were 36.2% ± 32.7% (0%–92.3%), without significant difference (P = 0.939) between the 2 groups.

DISCUSSION

Intraductal papillary mucinous neoplasms are proliferative and mucin-producing epithelial lesions that gradually progress from adenoma to carcinoma in situ and eventually to an invasive carcinoma.[1] Protocols for scheduling resection and follow-up have not been established because the progression profiles of these lesions are unclear. The 2010 consensus agreement recommended developing follow-up strategies based on cyst size,[2,3] but this recommendation remains debatable. Many studies have suggested MN height as the most suitable morphological parameter for assessing malignancy,[4,7,15] whereas others have demonstrated that a large cyst diameter is a sign of malignancy in BD-IPMN.[16–18] In contrast, Sadakari et al[19] reported that 8.2% of IPMNs progress to malignancy despite the absence of MNs. Basing management strategies on a single parameter might be inappropriate, whereas nomograms that take multiple factors into consideration should predict malignant progression more reliably and lead to the development of strategies that are more precisely tailored to the needs of individual patients.

We created a cancer prediction nomogram for patients who have undergone an IPMN resection. This nomogram based on the significant predictive factors of sex, lesion type, nodule height, and pancreatic juice cytology data provided an excellent cancer prediction capability with an AUC of 0.903.[13] Here, we validated this nomogram in a cohort of patients with IPMN who underwent follow-up during a relatively long period (≥3 years) at our institute. The outcome of this study was also excellent (positive predictive value, 63.6%; NPV, 99.1%; accuracy, 96% for development of malignancy) at a cutoff score of 35 that was equivalent to a 5% probability of developing cancer. When we define a score of 35 or higher as high risk and a score of less than 35 as low risk, the low-risk group (scores of <35) indicated an extremely low risk of developing IPMN-derived cancer during the follow-up period of 5 years (NPV, 99.1%) and the high-risk group (scores of >35) indicated a high risk of developing an IPMN-associated carcinoma, with 87.5% of patients having an IPMC at a follow-up of more than 3 years. Based on these results, we recommend a follow-up assessment every 6 months for scores of 35 or higher and annually for those with less than 35, depending on the patient's status. Patients with IPMN are at increased risk not only for cancer derived from these lesions, but also for ductal adenocarcinoma (1.9%–8.0%).[5,6,20–22] Hence, even with low-risk scores of less than 35, we recommend at least an annual follow-up. Notably, one of our patients with a score of 0 at initial testing developed carcinoma in situ without detectable MNs 6 years after the first follow-up. In the present study, ERP cytology was the only method that could detect malignancy for these cases with no MNs. It has also been reported that ERP juice cytology examination alone might be ineffective because of its low sensitivity.[23,24] Therefore, ERP cytology should be augmented with other risk assessment tools such as

TABLE 2. Diagnostic Yield of Nomogram: Benign Versus Malignant

Final Nomogram	Malignant	Benign	Total
Positive (n = 11)	7 (TP)	4 (FP)	11
Negative (n = 115)	1 (FN)	114 (TN)	115
Total	8	118	126

FN indicates false negative; FP, false positive; TN, True negative; TP, true positive.

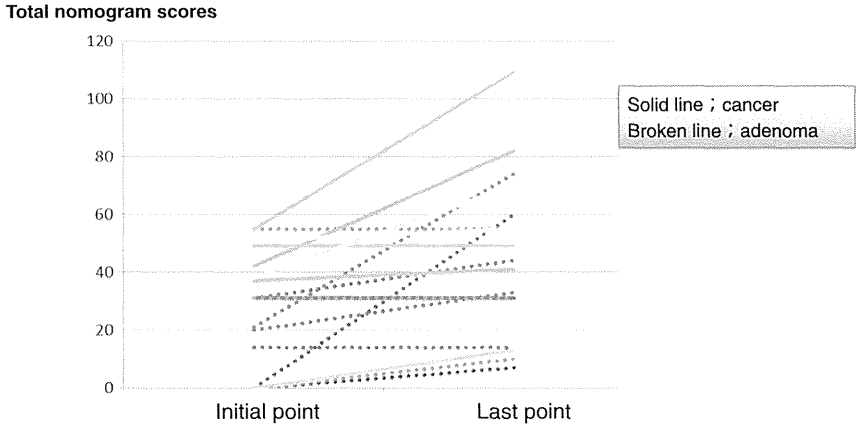

FIGURE 5. Change of the nomogram point. The changing rate of nomogram of 18 operated cases. It shows the initial nomogram point in the left, and the final follow-up nomogram point is shown in the right side. The solid line in the patients indicates cancer, a broken line indicates adenoma. The changing rate of the 12 adenoma cases was 37.6% ± 41.2% (0%–98%), whereas the changing rate of the 6 carcinoma cases were 36.2% ± 32.7% (0%–92.3%). There was no significant difference ($P = 0.939$) between the 2 groups.

nomograms to improve the probability of accurate cancer prediction and develop more appropriate management strategies. Thus, we recommend the use of both ERP cytology and our nomogram for the follow-up of IPMNs when the sizes of cysts or MPDs increase in the absence of detectable MNs.

Here, we described the ability of our nomogram to predict IPMN malignancy and showed that it can play a significant role in developing follow-up strategies. Our results indicated that an annual follow-up would be appropriate for scores of less than 35, indicating an extremely low risk of cancer developing within at least 3 years (NPV, 99.1%). Meanwhile, a 3- to 6-month close follow-up would be recommended for scores of 35 or higher, indicating a high potential for malignant transformation (87.5% from our data). The main strength of this nomogram used for follow-up is identifying patients who are at a very low risk of developing cancer and who would benefit from less frequent surveillance rather than trying to identify patients who are at intermediate or high risk of developing cancer.

Because of the retrospective nature of our study design, we plan to prospectively validate the applicability of our model to designing management strategies for IPMN lesions.

In conclusion, we can consider our nomogram as a valid model to predict malignancy in patients with IPMN and our findings can suggest that the follow-up schedule for patients at high and low risk for cancer progression should be every 3 to 6 months and 12 months, respectively.

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症例報告

エベロリムスによる間質性肺炎を惹起するも再開継続できている膵神経内分泌腫瘍の1例

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原和生　今岡大[1]　田近正洋
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山雄健次[1]

要旨：60歳代女性．膵腫大を指摘され紹介．EUS-FNAにて膵神経内分泌腫瘍（G2）と診断．門脈浸潤が著明で切除困難と判断．S-1を7カ月服用後，エベロリムスが承認されたため10mgにて開始した．4カ月目に咳嗽，発熱が出現．間質性肺炎と診断．アフィニトール®適正使用ガイドのGrade 2と判断し，休薬およびステロイド30mg/日を開始．症状は速やかに改善し，ステロイドを中止後，エベロリムスを再開し10mgを服用して治療継続中である．

索引用語：膵神経内分泌腫瘍，間質性肺炎，エベロリムス

はじめに

膵神経内分泌腫瘍（pancreatic neuroendocrine tumor；pNET）は，膵および十二指腸の構成細胞を起源とする神経内分泌腫瘍で，腫瘍から分泌されたホルモンにより臨床症状を引きおこすか否かによって，機能性，非機能性に大別される．比較的まれな腫瘍とされており，本邦における疫学調査では2005年の1年間のpNETの受療者数は約2845人，人口10万人あたりの有病患者数は約2.23人と推定されている[1,2]．また日本膵臓学会による膵癌登録報告2007では，2004年のpNETの膵腫瘍に占める割合は3.2%であるが，徐々にその患者数は増加してきている[3]．治療の基本は切除であるが，切除不能，高分化型pNETに対する化学療法としては，海外においてはStreptozocin，ドキソルビシンやインターフェロンなどが用いられてきた．しかし，本邦では保険承認を得られていないことから，通常型膵癌に準じてゲムシタビンやS-1が使用されてきたが，効果は十分なものではなかった．近年，pNETに対する分子標的薬が無作為化比較試験において有用性を示したことが報告され，2011年12月よりエベロリムスが，2012年8月よりスニチニブが適応承認された．今回，エベロリムスで間質性肺炎を惹起したがステロイド治療にて改善後再開が可能で，腫瘍縮小効果が得られているpNETの1例を経験したので，報告する．

I　症　例

症例：60歳代，女性．

主訴：腹部違和感．

既往歴：2型糖尿病．

家族歴：特記事項なし．

現病歴：2010年3月転落事故にて他院へ救急搬送された．その際施行されたCT検査で偶然，

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Table 1. 初診時検査所見

血算	
WBC	4590 /μl
RBC	382×10^4 /μl
Hb	11.9 g/dl
PLT	8.2×10^4 /μl
生化学検査	
TP	6.7 g/dl
Alb	3.9 g/dl
BUN	20 mg/dl
Cre	0.49 mg/dl
T-Bil	0.5 mg/dl
AST	18 IU/l
ALT	10 IU/l
ALP	239 IU/l
γ-GTP	13 IU/l
LDH	227 IU/l
Amylase	60 IU/l
p-Amylase	18 IU/l
Lipase	26 U/l
Na	142 mmol/l
K	3.8 mmol/l
Cl	9 mmol/l
補正 Ca	9.3 mg/l
HbA1c	9.8 %
CRP	0.07 mg/dl
IgG	1012 mg/dl
IgA	242 mg/dl
IgM	109 mg/dl
IgG4	15 mg/dl
感染症	
HBs-Ag	陰性
HCV-Ab	陰性
腫瘍マーカー	
CEA	2.7 ng/ml
CA19-9	62.3 U/ml
DUPAN-2	25 U/ml
Elastase 1	80 ng/dl
内分泌検査	
Insulin	2.4 μIU/ml
Gastrin	128 pg/ml

膵体尾部の腫大様所見および門脈閉塞，側副血行路の発達を指摘された．画像所見から自己免疫性膵炎と診断され，プレドニゾロン（Prednisolone：PSL）10mgの内服を開始した．画像上改善が得られないため，2011年2月にPSLは15mgに増量となった．しかし改善を認めず，腫瘍の可能性が疑われたため，同年3月開腹膵腫瘍生検が施行された．H.E染色で好塩基性の胞体を持った異型を有する腺房細胞の胞巣状増生を認め，一部腺管形成が見られたことから膵腺房細胞癌が疑われ，同年4月下旬当院を紹介受診した．

1．当院来院時検査成績

来院時血液検査（Table 1）：血小板減少，HbA1c上昇を認めたが，腫瘍マーカーはCA19-9が軽度高値を示す他は正常範囲であった．IgG4も正常値であった．

2．来院後経過

造影CT検査（Figure 1a）では，膵体尾部に動脈相で内部に不均一な造影効果のある腫瘍を認め，脾動脈および門脈への浸潤を認めた．超音波内視鏡検査（endoscopic ultrasound；EUS）（Figure 1b）では膵体尾部に径35mm大の内部不均一な低エコー腫瘤を認め，周囲のリンパ節と一塊となっており，門脈は腫瘍浸潤による狭小化を認め，著明な側副血行路の発達を認めた．前医のH.E染色では，腺房細胞癌の他，pNETも鑑別に挙がったため，その鑑別にchromogranin A，synaptophysinなどの免疫染色が必要であったため，主病巣から超音波内視鏡下穿刺吸引検査（EUS-FNA）を行った（Figure 1c）．細胞診では核形不整，核小体腫大，配列の乱れ，大小不同を示す高度な異型細胞が緩い結合性を示し，組織診では腫大した類円形核と淡好酸性胞体を有する異型細胞が充実性・散在性に増生していた（Figure 2a）．免疫染色でchromogranin A，synaptophysinはともに陽性であった（Figure 2b，c）．Ki67指数は3%であった．また血清インスリン，ガストリンは正常値であり（Table 1），グルカゴノーマ，VIPoma，ソマトスタチノーマを疑う臨床症状も認めなかった．以上よりpNET，cT4N1M0（ENETS），G2（WHO 2010分類），非機能性と診断した．このため，前医で自己免疫性膵炎として投与されていたステロイドは漸減後に中止した．腫瘍は門脈本幹完全閉塞，著明な側副血行路

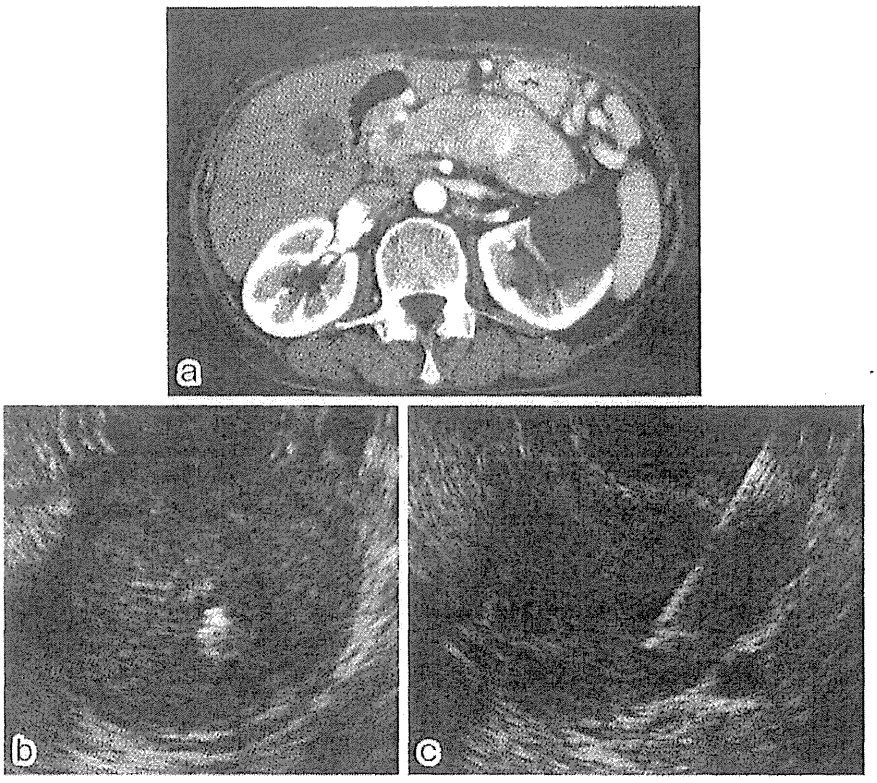

Figure 1. 初診時CT検査（a），EUS（b）およびEUS-FNA（c） a）造影CT検査．膵体尾部に，内部に不均一な造影効果のある腫瘍を認め，脾動脈および門脈への浸潤を認める．b）EUS．膵体尾部に径35mm大の内部不均一な低エコー腫瘤を認める．c）胃内より22G穿刺針にてEUS-FNAを施行した．

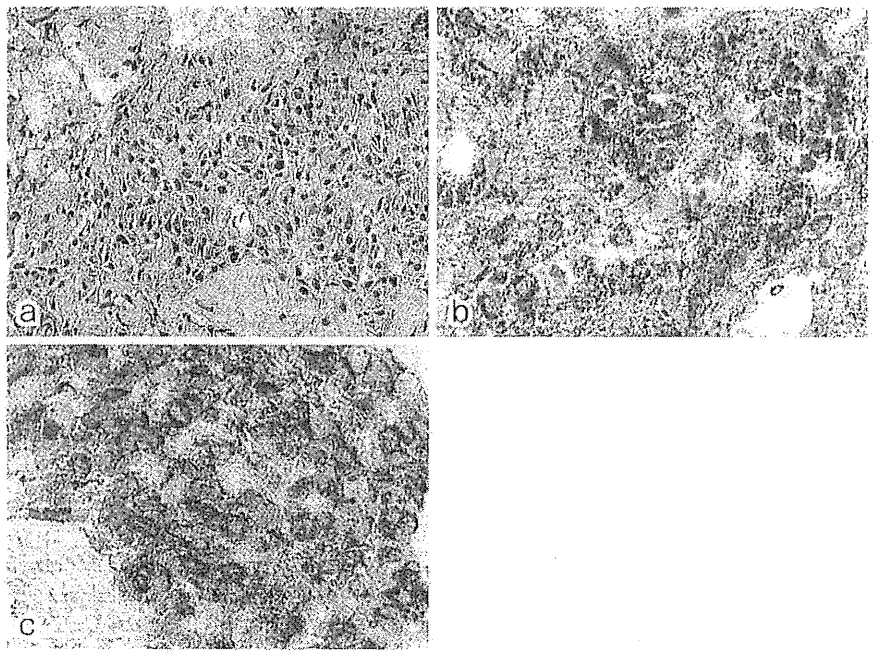

Figure 2. EUS-FNA検体の病理所見．H.E染色（a）およびchromogranin A染色（b），synaptophysin染色（c） a）H.E染色では腫大した類円形核と淡好酸性胞体を有する異型細胞が充実性・散在性に増生していた．b）Chromogranin A染色では陽性を示した．c）Synaptophysin染色では陽性を示した．

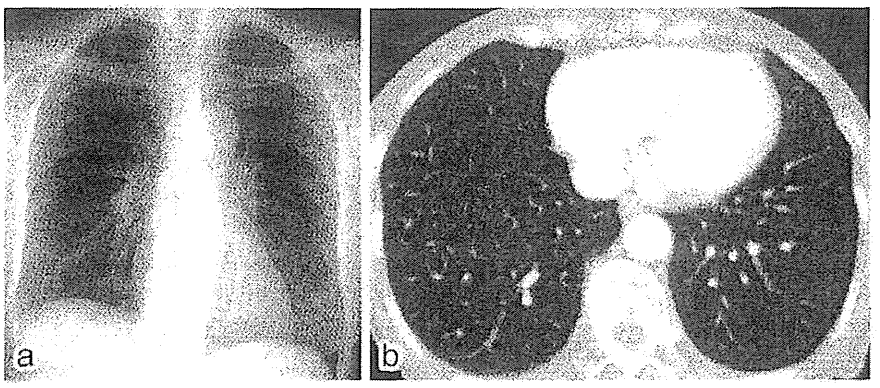

Figure 3. エベロリムス投与開始前の胸部X線写真および胸部CT検査：ともに異常を認めない．a）胸部X線写真．b）胸部CT検査．

を認めることから，局所進行ながらも切除不能と判断した．2011年6月より通常型膵癌に準じてS-1 100mgを開始した．SD（stable disease）範囲内であったが，エベロリムスがpNETに対して保険適応となったことから，2012年1月エベロリムス10mgに変更した．なお，エベロリムス投与前のHbA1cは6.7%まで低下し，血小板も11.4万と回復していた．またエベロリムス投与前の胸部X線およびCTでは異常所見は認めなかった（Figure 3a，b）．エベロリムス開始直後より口内炎（Grade 2），血小板低下（Grade 2）を認めていたが減量，休薬にて対応し，継続していた．2012年4月エベロリムス開始後16週目に咳嗽，発熱が出現したため，当科を受診され入院となった．

身体所見では体温38.2℃で，右下肺野中心に吸気時にfine crackleを認めた．動脈血ガス分析ではroom airでPH 7.43，PaO_2 79.6mmHg，$PaCO_2$ 36.5mmHg，SaO_2 95.4%と軽度の低酸素血症を認め，胸部X線（Figure 4a）では右肺底部を中心に索状・斑状影を認めた．胸部CTでは両葉に地図状の網状影を認めた（Figure 4b，c）．血液検査では，LDHは322U/l，CRPは3.9mg/dlとともに軽度上昇していた．β-Dグルカンは2.27pg/mlと正常，サイトメガロウイルス抗原および尿中レジオネラ抗原も陰性であり，喀痰培養からも細菌性肺炎を疑う所見はなかった．以上の所見からエベロリムスによる薬剤性肺障害と診断した．なおKL-6も319U/mlと上昇は認めなかった．

発熱，咳嗽を認めるもののSpO_2はroom airで95%以上が保たれており，呼吸苦や呼吸困難感の自覚症状を認めなかった．これらの所見から酸素吸入は必要なく日常生活には支障がないレベルと判断し，アフィニトール®適正使用ガイドにおけるGrade 2に相当すると考えられた．エベロリムスを中止し，PSLを30mgより開始したところ，症状および胸部X線上肺炎像の改善を認め，PSLを3日ごとに20mg，10mg，5mgと漸減し，ステロイド開始後14日目に中止した．その後も症状の再燃を認めず，エベロリムス開始後20週目（エベロリムス休薬より4週目）に胸部X線およびCT検査上の肺炎像はほぼ消失したことから（Figure 5a～c），エベロリムスの投与を5mgから再開し，開始後24週目に10mgまで増量が可能であった．治療開始18カ月後のCT検査（Figure 6）では，膵腫大は治療開始時と比較して短径では30%以上縮小を認め，PR（partial response）であり，現在も有害事象なく治療継続中である（Figure 7）．

II 考 察

Mammalian target of rapamycin（mTOR）は，細胞の成長や増殖，代謝，および血管新生に関与する細胞内シグナル伝達に関与するタンパクキナーゼのひとつである．エベロリムスはrapamycinの誘導体で，mTORを選択的に阻害する[4)～6)]．mTOR阻害薬は免疫抑制薬の作用の他，mTOR活性阻害を介する腫瘍細胞増殖抑制および血管新生阻害の2つの作用機序を持つため，固形臓器移

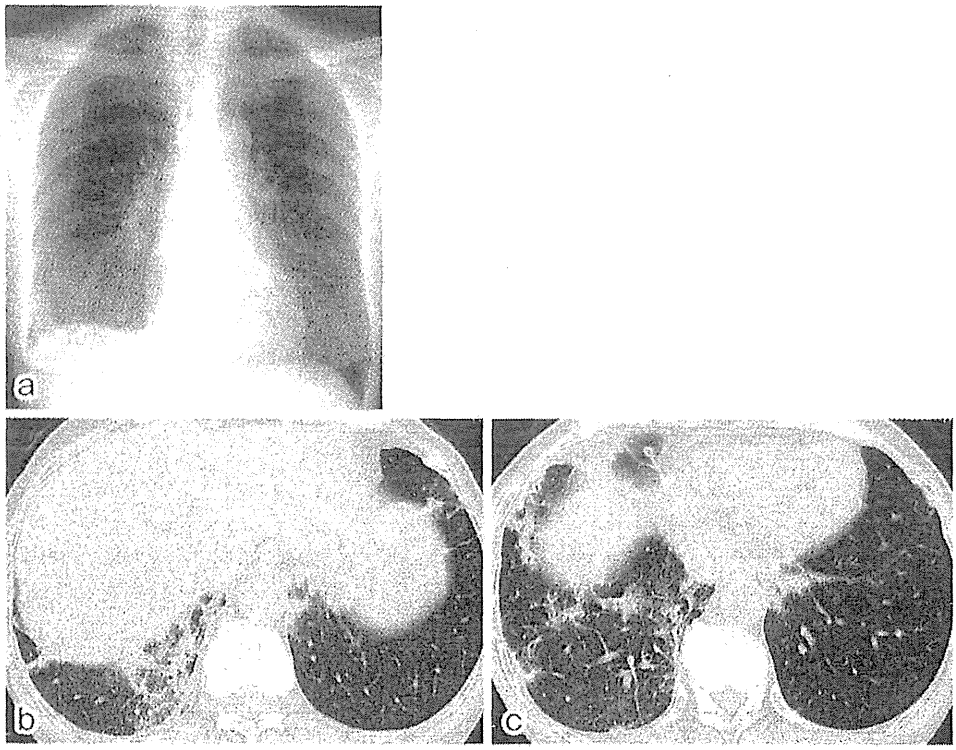

Figure 4. エベロリムス開始後16週目（エベロリムス休薬時）の間質性肺炎時の胸部X線写真および胸部CT検査 a）エベロリムス開始後16週目．右下肺野に網状影を認める．b）c）エベロリムス開始後16週目．両葉に地図状の網状影を認める．

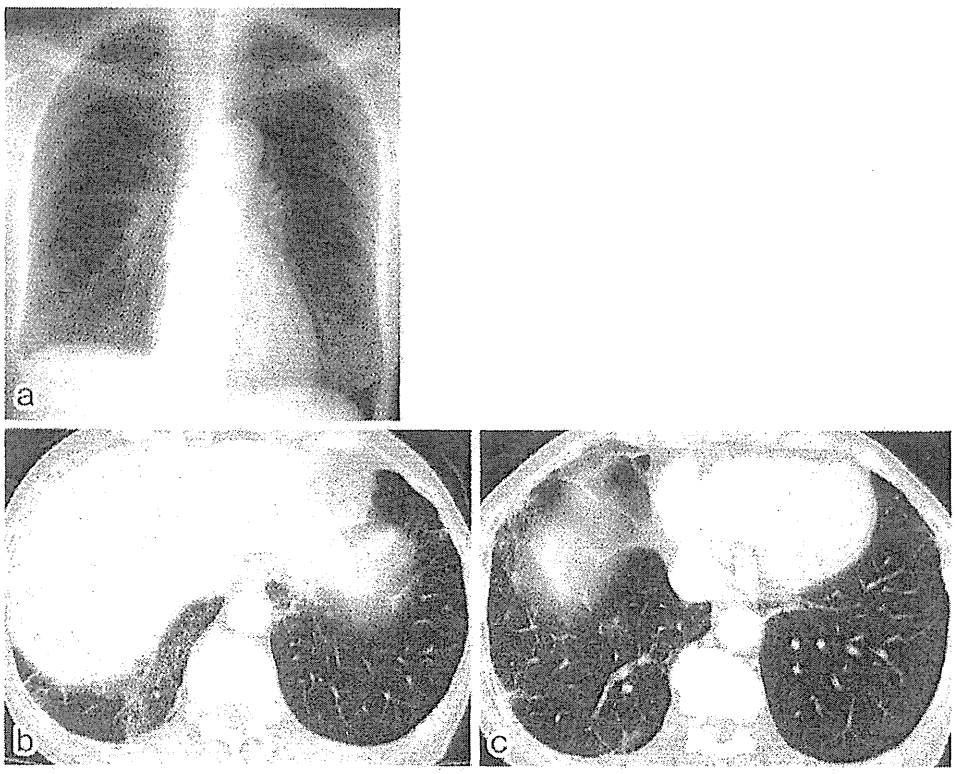

Figure 5. エベロリムス開始後20週目（エベロリムス再開時）の胸部X線写真および胸部CT検査 a）エベロリムス開始後20週目．網状影はほぼ消失している．b）c）エベロリムス開始後20週目．網状影はわずかに残るもかなり改善している．

植後の同種移植片拒絶反応予防，腎細胞癌に保険承認されて使用されてきた．他にも多くのがん腫において臨床試験が進められているが，pNETを対象とした第III相臨床試験（RADIANT-3試験）[7]では，エベロリムスはPFSの有意な延長を示した（PFSの中央値：エベロリムス群11.04カ月，プラセボ群4.60カ月，ハザード比0.35，$p<0.001$）．この結果を受け，2012年1月本邦でもpNETに対して保険承認された．

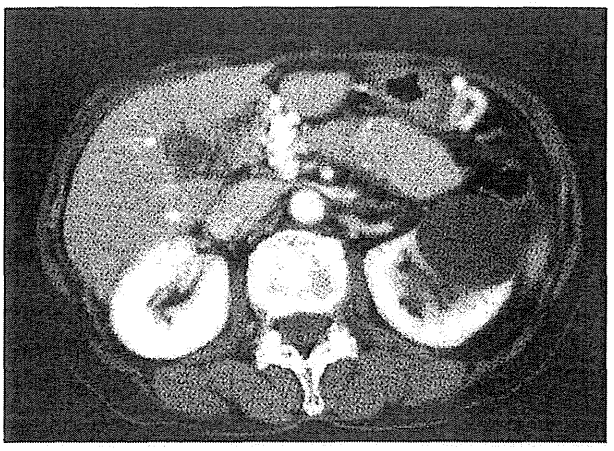

Figure 6. エベロリムス開始18カ月後CT検査：腫瘍縮小が得られている．

有害事象である間質性肺炎の頻度は，RADIANT-3試験で17%（35/204例）[7]，日本人患者における追跡調査では43%（10/23例）と高率に発現したが，Grade 3以上は比較的少なく9%（2/23例）であった[8]．他のmTOR阻害薬でも同程度の間質性肺炎の報告がされている[9]~[11]．mTOR阻害薬による間質性肺炎のCTでは，両側の非対称の斑状陰影やスリガラス陰影を認める．気管支肺胞洗浄（bronchoalveolar lavage；BAL）では，リンパ球性肺胞炎，特にCD4優位のリンパ球増加が見られ，他に肺胞出血や少量の好酸球，マスト細胞を認め，肺生検では閉塞性細気管支炎性をともなった器質化肺炎や間質のリンパ球浸潤を認めるとされる[12]~[14]．肺胞出血，およびリンパ球性間質性肺炎など，臨床病理学的パターンはさまざまである[12]~[15]．

エベロリムスは間質性肺炎を高頻度に引きおこす一方で，免疫抑制作用も有しているため，間質性肺炎と感染症（ニューモシスチス肺炎，サイトメガロウイルス肺炎）との鑑別が重要である．これらの鑑別にはβ-Dグルカン，サイトメガロウイルス抗原の測定の他，BAL液を用いてのニューモシスチス・カリニDNAや巨細胞核内封入体を

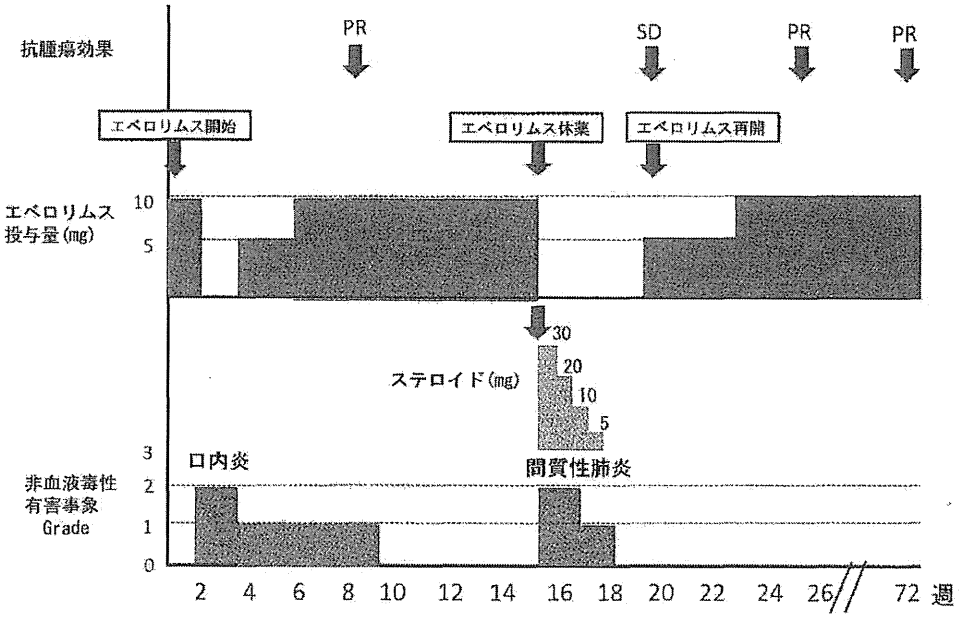

Figure 7. 臨床経過：間質性肺炎惹起後，エベロリムスの休薬およびステロイド30mg/日を開始．症状改善後，エベロリムスを再開し10mgを服用して治療継続中である．

有する細胞の検出が重要となってくる．本症例ではBALは施行していないが，臨床症状，画像所見，血液学的所見より間質性肺炎と診断した．またステロイドのみの治療で著効したことからも薬剤性間質性肺炎に矛盾しない経過であった．BALの細胞分画のみでは薬剤性間質性肺炎とニューモシスチス・カリニ肺炎との鑑別は困難であるとの報告もある[16]が，サイトメガロウイルス肺炎はきわめて予後不良であるため，これらの鑑別のためにはBALも積極的に考慮すべきであったと考える．

一般的に薬剤性肺障害の治療としては，原因薬剤の中止，副腎皮質ステロイドの投与，呼吸不全の対策，全身管理が基本である．mTOR阻害薬の間質性肺炎はステロイド治療の反応性が見られることや，無症状例や軽症例が多いことから，独自の対応が必要とされている[17][18]．しかしながら前述のようにエベロリムスによる間質性肺炎と感染症の鑑別は困難な場合もあるので，ステロイドによる治療効果が乏しい場合にはニューモシスチス・カリニ肺炎やサイトメガロウイルス肺炎などの感染症も常に念頭に置く必要があると考えられる．

アフィニトール®適正使用ガイド[17]では，無症状例では投与継続が可能であり，有症状例であってもGrade 2および3であれば，投与再開が可能とされている．本症例もGrade 2の薬剤性肺障害を認めたものの，休薬およびPSL投与により改善した．その後4週間の休薬期間の後，エベロリムスを再開することができた．S-1計5コース終了後の治療効果はSDであったが，エベロリムス投与を継続することによりPRを得られ，その後の病勢コントロールが可能であった．間質性肺炎改善後のエベロリムスの再投与に関しては，その有益性が間質性肺炎再発の危険性を上回ると判断された場合のみに適応されると考えられる．本症例も間質性肺炎発症前のpNETに対する抗腫瘍効果が得られていたこと，間質性肺炎以外の有害事象がコントロールできていることから，エベロリムスの再投与を行った．この場合，適正使用ガイドに記載のあるように1日1回5mgの半量から開始し，他の有害事象とともに間質性肺炎の再燃がないかを十分に観察しながら，問題がない場合のみ10mgに増量するなどの注意深い管理が重要であろう．

また間質性肺炎の発症時期に関しては，本症例では投与後16週目であった．RADIANT-3試験では投与期間が8～12週での発症が最も多かったが，1年を超えての発症も認め[7]，発症時期はばらつきが多く投与中は常に間質性肺炎の出現には注意する必要があると考えられた．

今回われわれが，医学中央雑誌にて1982年から2014年までの期間で，「エベロリムス」，「間質性肺炎」をキーワードとして検索（会議録および解説/特集をのぞく）したところ6例があった[19]～[24]．検索し得た限りでは間質性肺炎治癒後の再投与の報告はなかった．

近年，腫瘍分子学の恩恵によりpNETも他のがん腫と同様に分子標的薬が保険承認され，pNETの治療方針は大きく変化した．薬剤コントロールにより長期生存が期待できる腫瘍であるためそのマネージメントは非常に重要である．特にエベロリムスによる間質性肺炎は高頻度におこるものの，症例によっては再投与も可能である特殊な薬剤であり，投与にあたっては注意深い管理および対策が重要であると考えられた．

本論文内容に関連する著者の利益相反
：なし

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A patient with a pancreatic neuroendocrine tumor who developed everolimus-induced interstitial pneumonia : a case report

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A patient in her 60s was referred to our hospital with pancreatic enlargement. Laboratory data and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) revealed a nonfunctioning pancreatic neuroendocrine tumor (WHO classification 2010 G2). Resection was contraindicated because of portal vein invasion and extensive collateral vascularization. Everolimus (10mg/day) was started after seven months of treatment with S-1 (an oral formulation of tegafur with the modulators gimeracil and oteracil) following its insurance approval in Japan. Four months later, the patient developed cough and fever, and there was radiological and clinical evidence of Grade 2 everolimus-associated interstitial pneumonia (according to the Everolimus Proper-Usage Guide). Everolimus was replaced with steroid therapy (30mg/day), resulting in immediate symptomatic improvement. After conclusion of steroid therapy, everolimus was restarted. The patient has since remained on a dosage of 10mg/day of everolimus, with the tumor in a state of partial response.

Clinical Characteristics of Adenosquamous Carcinoma of the Pancreas

A Matched Case-Control Study

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Objectives: Adenosquamous carcinoma of the pancreas (ASC) is a variant of pancreatic ductal adenocarcinoma (PDAC), but the prognosis remains unclear. The purpose of this study was to clarify the prognosis of ASC using a matched case-control design.

Methods: We evaluated clinical characteristics of ASC treated between 2001 and 2011 in our institution. As controls, PDAC cases matched with ASC cases for sex, age, pretreatment Eastern Cooperative Oncology Group performance status, location, initial therapy and American Joint Committee on Cancer TNM staging for pancreatic cancer were also evaluated.

Results: Of the 914 cases of pancreatic neoplasm, 28 cases (3.06%) of ASC were identified, and 56 cases of PDAC were matched as controls. Median overall survival (OS) was significantly worse for ASC (8.38 months) than for PDAC (15.75 months; hazard ratio [HR], 1.94; 95% confidence interval, 1.07–3.51; $P = 0.026$). Of the 22 unresected cases, median OS was again significantly worse for ASC (4.67 months) than for PDAC (12.36 months; HR, 2.39; 95% confidence interval, 1.27–4.51; $P = 0.007$).

Conclusion: These results demonstrate that ASC is more aggressive than PDAC.

Key Words: adenosquamous carcinoma of the pancreas (ASC), pancreatic ductal adenocarcinoma (PDAC), endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), matched case-control study, pancreatic cancer

(*Pancreas* 2014;43: 287–290)

Pancreatic neoplasms may exhibit more than one line of cellular differentiation.[1–3] Adenosquamous carcinoma of the pancreas (ASC) is one such mixed neoplasm, exhibiting both glandular and squamous differentiation.[4–6] Herxheimer[7] reported the first case of ASC in 1907, but despite the accumulation of reports, most descriptions have been from case studies[8] and small surgical series.[9] Adenosquamous carcinoma of the pancreas has anecdotally been considered aggressive and has shown poor prognosis compared with pancreatic ductal adenocarcinoma (PDAC). However, as 2 recent population-based analyses reported,[10,11] whether ASC is actually more aggressive than PDAC remains unclear. Furthermore, many clinical trials have treated both PDAC and ASC equally. The purpose of this study was therefore to clarify the clinical features and prognosis of ASC using a matched case-control design.

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The authors declare no conflict of interest.

MATERIALS AND METHODS

We evaluated the pathological and clinical records of ASC and PDAC treated in our institution between 2001 and 2011. All cases were diagnosed based on cytological or histological confirmation from a surgical specimen or endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA). Pathological diagnosis of ASC was made based on the following criteria for surgical and EUS-FNA specimens. In the surgical specimen, the tumor exhibits both glandular and squamous differentiation, with the squamous component accounting for at least 30% of the neoplasm.[4,5] In the EUS-FNA specimen, aspirate shows both glandular and squamous differentiation characterized by an infiltrating sheetlike arrangement of polygonal cells with keratinization, confirmed by cytological or histological examination (Fig. 1).[12] To distinguish between primary ASC and metastasis from another site,[13] patients with any history of squamous cell carcinoma or other cancers were excluded from this analysis.

The procedure for EUS-FNA has been described previously.[14] After the procedure, one slide was air-dried and examined immediately with a rapid staining method (Diff-Quik stain; International Reagents, Kobe, Japan) to verify adequacy of the specimen and provide a presumptive diagnosis, if possible. Multiple passes were made in each case to provide specimens for cytological studies with Papanicolaou stain. Samples were also exposed to 10% formalin and then processed as a tissue block for histopathological evaluation using hematoxylin-eosin staining.

As controls, PDAC cases matched in a 2:1 ratio to ASC cases for pretreatment Eastern Cooperative Oncology Group performance status (0–1 or ≥2), initial therapy and tumor staging were also included in this study. Data were abstracted from medical records by 2 reviewers (T.O. and T.O.) who were blinded to case-control status. Two reviewers independently assessed these data, and disagreements were resolved by discussion with a third reviewer (K.Y.). In surgical cases, tumor staging was made based on pathological findings. In unresectable cases, staging was made based on computed tomographic results. In both situations, staging was performed in accordance with the American Joint Committee on Cancer staging system for pancreatic cancer. Tumor response and lymph node status were determined according to the Response Evaluation Criteria in Solid Tumor.[15]

Statistical Analysis

All values represent mean ± standard deviation. Bivariate analysis was performed using the Student *t* test for continuous