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ORIGINAL ARTICLE – PANCREATIC TUMORS

Vascularity and Tumor Size are Significant Predictors for Recurrence after Resection of a Pancreatic Neuroendocrine Tumor

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ABSTRACT

Background. It is difficult to identify patients at high risk of recurrence after pancreatectomy for pancreatic neuroendocrine tumor (PNET) using only the grading classification, especially the G2 category, which includes both benign and low- and high-grade malignant tumors.

Methods. Forty-one patients with PNET who underwent pancreatectomy were enrolled in this study. We defined the computed tomography (CT) ratio as the CT value of the tumor divided by that of non-tumorous pancreatic parenchyma using the late arterial phase dynamic CT. The optimal cut-off values for CT ratio and tumor size were determined using *p*-values that were calculated using the log-rank test.

Results. The optimal cut-off values of CT ratio and tumor size for dividing patients into groups according to the greatest difference in disease-free survival (DFS) were 0.85 ($p < 0.001$) and 3.0 cm ($p < 0.001$), respectively. In analysis using Spearman's correlation coefficient, CT ratio ($p = 0.007$) and tumor size ($p = 0.003$) were individually associated with the Ki-67 proliferative index. Cox proportional hazard analysis identified that a CT ratio <0.85 ($n = 10$, $p = 0.006$) and tumor size ≥3.0 cm ($n = 13$, $p = 0.023$) were independent prognostic factors associated with DFS. All patients in the CT ratio ≥0.85 and tumor size <3.0 cm group ($n = 23$, including seven patients with G2 disease) did not develop recurrence after surgery. On the other hand, 5-year DFS in the CT ratio <0.85 and tumor size ≥3.0 cm group ($n = 5$, including three patients with G2 disease) was zero.

Conclusions. PNETs with a CT ratio <0.85 and tumor size ≥3.0 cm should be considered as having a high risk of recurrence after pancreatectomy.

Pancreatic neuroendocrine tumors (PNETs) are rare neuroendocrine tumors that account for 1–5% of all pancreatic tumors; however, their incidence is increasing.[1–4] Most PNETs are generally regarded to be slow-growing tumors, whereas some occasionally develop aggressive invasion or metastases. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) can provide a preoperative histological diagnosis of tumor malignancy, however it is difficult to precisely identify tumor malignancy by EUS-FNA alone because it examines only a small part of the entire tumor.[5] The concordance rate of the 2010 WHO classification between EUS-FNA and surgical specimens was reported to be 57.1% in tumors >20 mm in size.[5] Moreover, the new G2 category of the 2010 WHO classification has been reported to be too general because it includes both benign and low- and high-grade malignant tumors, and it is difficult to identify patients at high risk of recurrence after pancreatectomy, especially in patients with broad G2 category.[6]

Various pathological parameters have been previously reported to be associated with the prognosis of patients with PNET, including tumor grade, Ki-67 proliferative index, presence of necrosis, and tumor size;[7–14] however, only tumor size is easily assessable before surgery. On the other hand, recent studies have evaluated the relationship between the imaging characteristics of PNET and the

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aggressiveness of the tumor,[15–18] and hypovascular PNET is now recognized as an important condition with a poor prognosis.[15,19–21] Some authors have discussed the vasculature of PNETs; however, the terms 'hypervascular PNET' and 'hypovascular PNET' have not yet been clearly defined, with most studies using ambiguous definitions of the vascularity of PNET compared with the non-cancerous areas of the pancreas.[15,19–21]

In this study, we first determined the optimal cut-off value of the tumor size and vascularity of PNETs according to the difference in disease-free survival (DFS). In addition, we investigated the risk factors that might contribute to recurrence after pancreatectomy for PNET and identified patients at high risk of recurrence, especially in the broad G2 category.

PATIENTS AND METHODS

Study Population

From December 2002 to December 2013, 41 patients underwent pancreatectomy for PNET at the Division of Hepato-Biliary-Pancreatic Surgery, Shizuoka Cancer Center, Shizuoka, Japan. All resected specimens were reviewed in this study. Of 41 patients with PNET, 36 had non-functional PNET and five had functional PNET, including one patient with insulinoma, two patients with gastrinoma, and two patients with glucagonoma. Two patients had Von Hippel–Lindau disease. The tumors were classified as NET grade 1 (G1, n = 21), NET grade 2 (G2, n = 17), or neuroendocrine carcinoma grade 3 (G3, n = 1) according to the 2010 WHO classification guidelines.[22] Two patients with mixed adenoneuroendocrine carcinoma (MANEC) were also included in this study.

Imaging Studies and Categorization

Computed tomography (CT) scans were performed using a quadruple phase, 64-row multidetector scanner (Aquiline; Toshiba Medical Systems Co., Ltd, Tokyo, Japan). The scanning parameters were as follows: 1 mm slice thickness; data reconstructed at 1 mm intervals (0.5 mm overlap); rotation time 0.5 sec; tube voltage 135 kV (peak) and tube current 350–400 mA. Images were obtained after intravenous administration of 150 ml of 350 mgI/ml non-ionic contrast medium using a calibrated power injector (Auto Enhance A- 50; Nemoto Kyorindo, Tokyo, Japan) at a rate of 4 ml/s. The early and late arterial phases, portal phase, and delayed phase were started at 20, 35, 60 and 120 s, respectively, after injection. All multidetector computed tomography images were evaluated by two independent reviewers (SU and TA) who did not have access to the original interpretations or outcomes. The reviewers evaluated the specimens using the late arterial phase enhanced image, which started 35 s after injection. The degree of the enhancement was evaluated using the mean CT value of the regions of interest (ROIs), which was drawn as the largest cross-section area of the tumor and the non-tumorous pancreatic parenchyma (Fig. 1a). The CT value of pancreatic parenchyma was measured in two ROIs at different locations. We avoided measuring regions including the main pancreatic duct, blood vessels, or artifacts, and considered the mean value of two ROIs at different sectors in the pancreas as the mean CT value of the non-tumorous pancreatic parenchyma. We defined CT ratio as the CT value of the tumor divided by that of the non-tumorous pancreatic parenchyma, and we also evaluated the vascularity of PNET using the CT ratio.

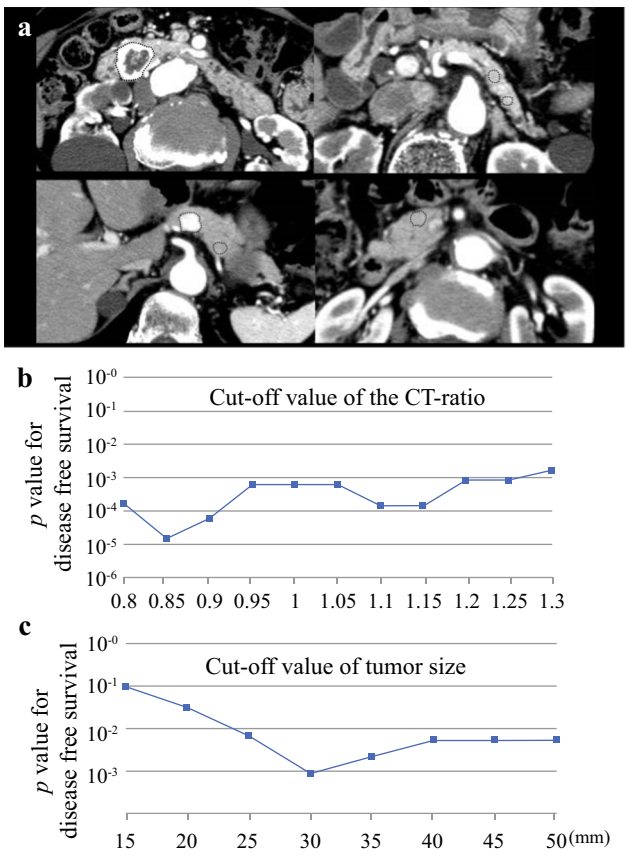

FIG. 1 **a** CT images of pancreatic neuroendocrine tumors. Black line CT values (Hounsfield units) of the ROIs of the tumor and background pancreatic parenchyma. The optimal cut-off value of the CT ratio to divide patients into two groups according to the greatest difference in **b** disease-free survival and **c** tumor size was 0.85 (p = 0.00012) and 30 mm (p = 0.0021), respectively, when using the minimum p-value approach. *CT* computed tomography, *ROIs* regions of interest

Surgical Strategy and Surgical Procedures for Pancreatic Neuroendocrine Tumors (PNETs)

The standard surgical procedure was either pancreaticoduodenectomy or distal pancreatectomy with regional lymph node dissection. For small tumors, parenchyma-preserving procedures were considered. For resectable synchronous liver metastases, simultaneous hepatic resection was performed. As a result, 13 patients underwent pancreaticoduodenectomy, 15 patients underwent distal pancreatectomy, 1 patient underwent distal pancreatectomy with celiac axis resection, 8 patients underwent middle pancreatectomy, 2 patients underwent total pancreatectomy, and 2 patients underwent partial resection. Combined hepatectomy was performed in 4 patients with liver metastasis of PNET. In all patients, tumor size was measured using the resected specimen. No patients received preoperative chemotherapy; however, 2 patients received adjuvant chemotherapy with MANEC (gemcitabine, $n = 1$; and S1, $n = 1$).

Follow-Up and Definition of Recurrence

All patients were followed in the outpatient clinic where abdominal ultrasound and a CT scan were performed every 3–6 months after surgery. Events affecting survival were death and recurrence, including local recurrence and distant metastasis. Recurrence was defined based on radiological or biopsy-proven evidence.

Statistical Analysis

Survival was estimated using the Kaplan–Meier method, and differences in survival were examined using the log-rank test. The minimum p-value was defined as the optimal cut-off value. Patients were classified into two groups based on the cut-off value set for every 0.05 increase in the CT ratio, or 5 mm increase in tumor size. We examined the best cut-off values for CT ratio and tumor size based on the minimum p-value calculated using the log-rank test.[23] A Cox proportional hazards model was used in the analysis of clinicopathological categorical variables influencing overall survival (OS). The Pearson's Chi-square test and Fisher's exact test were used for nominal variables, and continuous data were compared using the Mann–Whitney U test. Additionally, Spearman's correlation coefficient was used to determine the associations among CT ratio, tumor size, and Ki-67 proliferative index. All statistical analyses were performed using the Software Package for Social Sciences (SPSS) version 19 for Windows 1 (IBM Corporation, Armonk, NY, USA). A p-value < 0.05 was considered to be significant.

RESULTS

Optimal Cut-off Value of the Computed Tomography Ratio and Tumor Size According to Differences in the Prognosis

The cumulative 5-year DFS and OS rates were 81.2 and 94.9%, respectively, while the mean (± standard deviation [SD]) CT values of the tumor and pancreatic parenchyma were 165.9 ± 80.1 and 128.8 ± 25.6 Hounsfield units, respectively. The mean (± SD) CT ratio was 1.32 ± 0.60, and the mean (± SD) CT ratio of each grade was as follows: G1, 1.32 ± 0.53; G2, 1.41 ± 0.67; G3, 0.83; MANEC, 0.57 ± 0.04. Although the CT ratio of the G3 tumor or MANEC (CT ratio: 0.67 ± 0.15) was significantly lower compared with G1 or G2 tumors (CT ratio: 1.36 ± 0.59, $p = 0.038$), there were no significant differences in CT ratio between G1 and G2 tumors ($p = 0.542$). The optimal cut-off value of CT ratio and tumor size for dividing patients into two groups according to the greatest difference in DFS was 0.85 ($p = 0.000015$) (Figs. 1b, 2a) and 30 mm ($p = 0.00088$) (Figs. 1c, 2b), respectively, when using the minimum p-value approach.

Analysis of the Prognostic Factors in PNET After Curative Resection

Table 1 shows the results of univariate and multivariate analyses of prognostic factors associated with DFS. A Cox proportional hazard analysis of all 41 patients identified a CT ratio <0.85 ($p = 0.006$) and tumor size ≥30 mm ($p = 0.023$) to be independent prognostic factors associated with DFS.

Comparison of Disease-Free Survival according to CT Ratio and Tumor Size (Fig. 2c)

None of the patients in the CT ratio ≥0.85 and tumor size <3.0 cm group ($n = 23$) developed recurrence after surgery. The DFS of patients in the CT ratio ≥0.85 and tumor size <3.0 cm group was better than the other three groups. In contrast, the 5-year DFS in the CT ratio <0.85 and tumor size ≥3.0 cm group was 0%. The DFS of patients in the CT ratio <0.85 and tumor size ≥3.0 cm group was significantly worse compared with the other three groups.

Rate of Recurrence According to Grade Classification (Fig. 2d)

All patients with G3 tumor or MANEC developed recurrence after pancreatectomy. In contrast, none of the patients with G1 tumor developed recurrence after

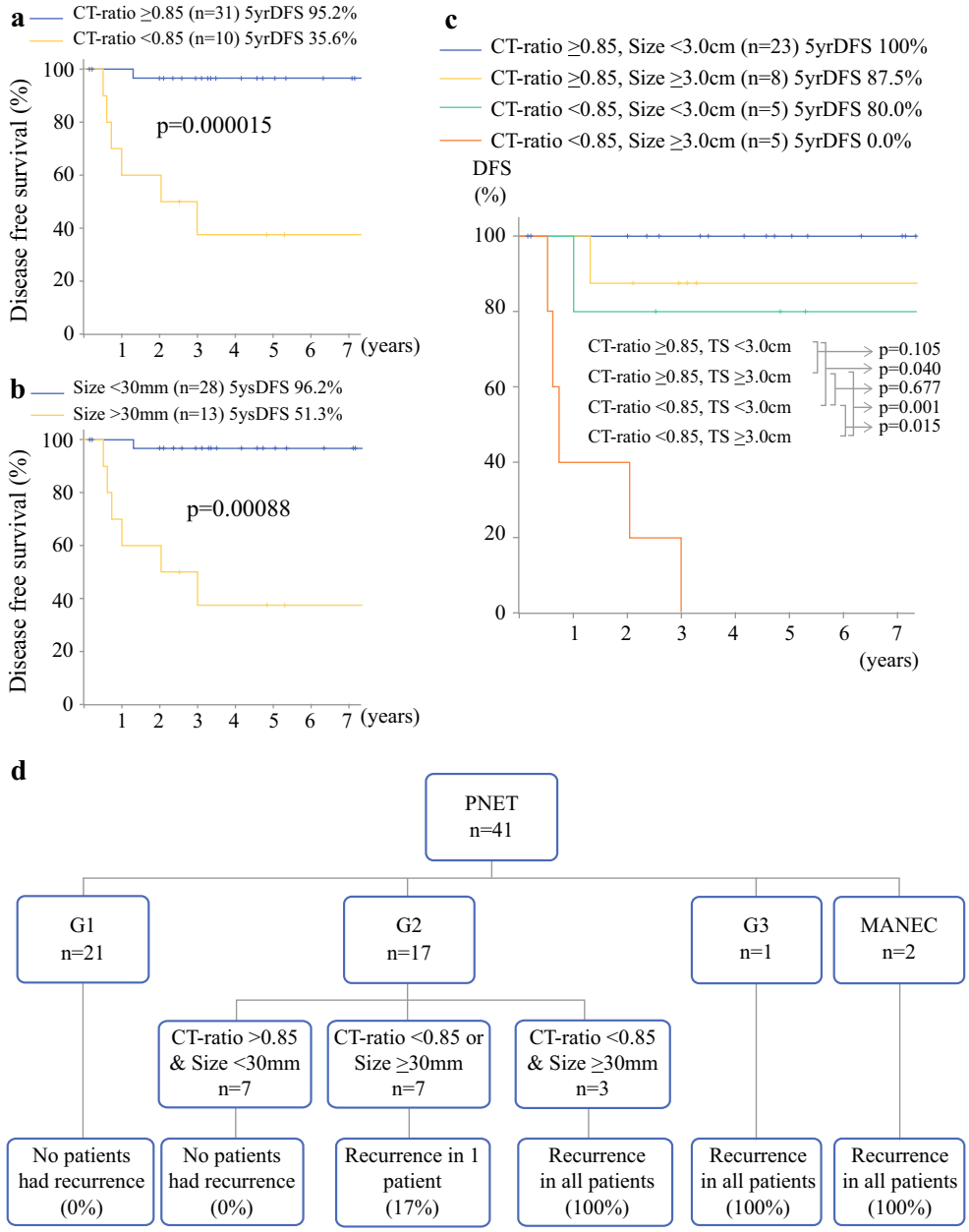

FIG. 2 **a** Comparison of the disease-free survival curves between the CT ratio ≥0.85 and <0.85 groups. **b** Comparison of the disease-free survival curves between the tumor size <3.0 cm and ≥3.0 cm groups. **c** Comparison of disease-free survival according to the CT ratio value and tumor size. **d** Rate of recurrence according to grade classification. *CT* computed tomography, *5 year DFS* cumulative 5-year disease-free survival, *PNET* pancreatic neuroendocrine tumor, *MANEC* mixed adenoneuroendocrine carcinoma

pancreatectomy. In the G2 category, all patients with a CT ratio <0.85 and tumor size ≥3.0 cm (n = 3) developed recurrence, while none of the patients with a CT ratio ≥0.85 and tumor size <3.0 cm (n = 7) developed recurrence. One (17%) patient with a CT ratio <0.85 or tumor size ≥3.0 cm developed recurrence.

One of the two patients with MANEC was subsequently treated with S1 after recurrence, and one patient with G3 underwent hepatectomy and received various chemotherapies after liver metastatic recurrence. One of four patients with G2 underwent three hepatectomies after developing multiple liver metastatic recurrences. Furthermore, one of four patients with G2 received radiation therapy after the occurrence of bone metastasis, and two of four patients with G2 received streptozocin and everolimus after developing multiple liver metastases, respectively.

TABLE 1 Results of the univariate and multivariate analyses of the prognostic factors associated with disease-free survival in patients who underwent pancreatectomy for pancreatic neuroendocrine tumor

	No.	5-year DFS (%)	Univariate analysis *p*-value	Multivariate analysis	
				HR (95% CI)	*p*-Value
Age, years					
<70	24	81.1	0.854		
≥70	17	81.3			
Sex					
Male	25	76.3	0.478		
Female	16	87.5			
CT ratio					
<0.85	10	37.5	<0.001	20.177 (2.391–170.357)	0.006
≥0.85	31	96.6		1	
Tumor size (mm)					
<30	28	96.2	0.002	1	0.023
≥30	13	51.3		11.9.6 (1.413–100.336)	
Lymph node metastasis					
Absent	32	85.9	0.148		
Present	9	66.7			
Liver metastasis					
Absent	37	91.4	<0.001		
Present	4	0.0			
Tumor number					
Single	32	79.6	0.661		
Multiple	9	87.5			
Histological grade					
G1	21	100	0.003		
G2 or G3	20	61.2			
Lymphatic invasion					
Absent	33	89.7	0.003		
Present	8	50.0			
Venous invasion					
Absent	32	92.6	<0.001		
Present	9	44.4			
Neural invasion					
Absent	33	89.7	0.003		
Present	8	50.0			

5-year DFS cumulative 5-year disease-free survival, *HR* hazard ratio, *CT* computed tomography

Analysis of the Association Among CT Ratio, Tumor Size, and Ki-67 Proliferative Index Using Spearman's Correlation Coefficient

In an analysis of the association among CT ratio, tumor size, and Ki-67 proliferative index using Spearman's correlation coefficient, significant correlations were found between CT ratio and Ki-67 ($p = 0.007$) (Fig. 3a), as well as between tumor size and Ki-67 ($p = 0.003$) (Fig. 3b); however, no significant correlation was found between CT ratio and tumor size ($p = 0.152$).

Comparison of the Histopathological Features Between the CT Ratio <0.85 Group and the CT Ratio ≥0.85 Group (Table 2)

The frequency of lymph node metastasis ($p = 0.479$) or multiple tumors ($p = 0.234$) was comparable between both groups; however, the frequency of liver metastasis ($p = 0.013$), microscopic venous invasion ($p = 0.001$), lymphatic invasion ($p = 0.005$), or neural invasion ($p = 0.005$) in the CT ratio <0.85 group was significantly higher than in the CT ratio ≥0.85 group.

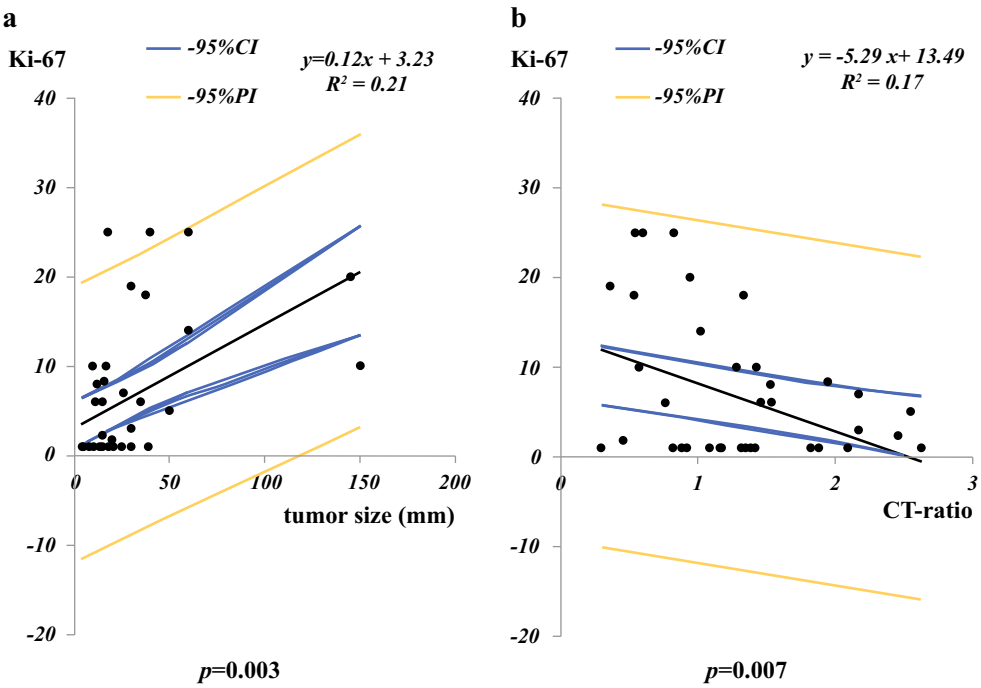

FIG. 3 Correlation analysis between the Ki-67 proliferative index and **a** tumor size and **b** CT ratio, using Spearman's correlation coefficient. *CT* computed tomograph *CI* confidence interval, *PI* prediction interval

DISCUSSION

In this study, none of the patients in the CT ratio ≥0.85 and tumor size <3.0 cm group (n = 23) developed recurrence after surgery. In contrast, patients in the CT ratio <0.85 and tumor size ≥3.0 cm group had a poor prognosis, with a 5-year DFS rate of 0%. PNETs with a CT ratio <0.85 and tumor size ≥3.0 cm should be considered to have high risk of recurrence after pancreatectomy. Furthermore, we were able to identify patients at high risk of recurrence in the new G2 category established in the 2010 WHO classification, which includes both benign and low- and high-grade malignant tumors.[6] Preoperative identification of patients at high risk of recurrence using various imaging modalities may be useful in estimating tumor aggressiveness and treatment decision making, including the extent of lymph node dissection before surgery. Recent advances in chemotherapy have improved the survival of patients with PNET.[24,25] Chemotherapy and new biological treatments may be considered as the adjuvant setting in these patients at high risk of recurrence.

Recently, the vascularity of PNET has been reported to be a significant prognostic factor;[15,19–21] however, we could not find any previous studies that classified patients into hypervascular and hypovascular PNET groups, according to assessment of the optimal cut-off value, to provide the largest difference in prognosis between the two groups.[15,18–28] A cut-off value of 1.0 for the CT ratio is readily available and is visually the most useful cut-off point; however, it is not a scientific cut-off point because a CT ratio of 1.0 is used to compare the CT value of a tumor with that of pancreatic parenchyma. In the present study, we analyzed the cut-off values of the CT ratio according to the minimum p-value approach, and found that the optimal cut-off value was 0.85 according to DFS after pancreatectomy for PNET. This value was then used to separate 10 patients (24%) from 41 patients with PNET. These results suggested that the cut-off value of 0.85 for CT ratio, which best reflects DFS after surgery, is clinically the most important cut-off value of vascularity for patients who undergo pancreatectomy for PNET.

In this study, tumor vascularity demonstrated a significant correlation with the Ki-67 index, the frequency of lymphatic invasion, venous invasion, or neural involvement, and the frequency of liver metastasis. Similar to our results, several groups reported that hypoenhancement on CT is statistically correlated with poor differentiation, necrosis rates, or G3 histological grade of PNET.[15,18,26] PNETs tend to be homogeneous in the early stages of a small tumor, while large, advanced PNETs often develop heterogeneous changes with cystic degeneration, calcification, or fibrotic changes.[29] In particular, the presence of lymphatic invasion with lymphangiogenesis has been reported in several cancers associated with intratumoral hypoxic changes, which induce a scar-like area within tumors consisting of fibroblasts and collagen fibers.[27,30–32] These fibrotic changes in the PNET, which has been reported in several cancers associated with poor prognosis,[30–32] may be related to the hypovascularity of PNETs in CT images.

TABLE 2 Comparison of the histopathological and immunohistochemical features between the CT ratio < 0.85 ($n = 10$) and ≥0.85 groups ($n = 31$)

	CT ratio <0.85 group ($n = 10$) (%)	CT ratio ≥0.85 group ($n = 31$) (%)	*p*-Value
Sex			
Male	5 (50)	11 (35)	0.540
Female	5 (50)	20 (65)	
Age, years	60.2 ± 17.4	64.8 ± 12.0	0.540
Grade			
G1	3 (30)	18 (58)	0.123
G2 or G3	7 (70)	13 (42)	
Lymph node metastasis			
Absent	7 (70)	25 (81)	0.479
Present	3 (30)	6 (19)	
Liver metastasis			
Absent	7 (70)	30 (97)	0.013
Present	3 (30)	1 (3)	
Tumor number			
Single	9 (90)	23 (74)	0.234
Multiple	1 (10)	8 (26)	
Lymphatic invasion			
Absent	5 (50)	28 (90)	0.005
Present	5 (50)	3 (10)	
Venous invasion			
Absent	4 (40)	28 (90)	0.001
Present	6 (60)	3 (10)	
Neural invasion			
Absent	5 (50)	28 (90)	0.005
Present	5 (50)	3 (10)	

CT computed tomography

In our study, tumor size was significantly related to the Ki-67 index and DFS. Several groups have reported that survival was significantly higher in patients with tumors <3 cm because the risk of malignancy increases with increasing tumor size.[33–35] Similar to our results, Kim et al.[26] compared G3 and G1/2 tumors and reported that a cut-off value of 3 cm showed the greatest sensitivity and specificity in differentiating G3 from G1/2 tumors. These results suggest that a PNET diameter of 3 cm may be a clinically important cut-off value of the tumor size that best reflects recurrence or tumor grade after surgery. On the other hand, even for tumors <3.0 cm in diameter, PNETs with a CT ratio <0.85 sometimes develop recurrence after surgery, similar to hypervascular PNETs with tumor size ≥3.0 cm. While tumor size is an important determining factor of T stage in PNET, a certain level of biological characteristics of PNET may already be present in the early stage of a small PNET, which may be represented by tumor vascularity.

There are some limitations associated with the present study. Specifically, this study was retrospective in nature and was a single-center experience. Moreover, the tumor size used in this study was determined based on the size of the resected specimen, which might have been slightly different from the radiologic tumor size. Further prospective studies are required to precisely evaluate the optimal cut-off value of CT ratio and tumor size.

CONCLUSIONS

The cut-off value of 0.85 for the CT ratio, which best reflects DFS after surgery, is a clinically important cut-off value of vascularity for patients who undergo pancreatectomy for PNET. The risk of recurrence should be estimated using not only tumor size but also tumor vascularity. In particular, PNETs with a CT ratio <0.85 and tumor size ≥3.0 cm should be considered to have a high risk of recurrence after pancreatectomy.

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