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Volume of the whole pancreatic duct is useful in determining indication of surgery for intraductal papillary mucinous neoplasms of the pancreas: Analyses of 3D volumetry with MR cholangiopancreatography

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ABSTRACT

Background/Aims: To investigate the association between the volume of the pancreatic duct as measured by magnetic resonance cholangiopancreatography (MRCP) and the pathological stage of intraductal papillary mucinous neoplasm (IPMN).

Methods: MRCP images were reconstructed in three dimensions by volume rendering, and the association between the volume of the whole pancreatic duct (WPD) and pathological stage, malignancy, Ki67 labeling index and prognosis was retrospectively investigated for 70 IPMN patients.

Results: There were 47 patients with low- or intermediate-grade dysplasia, 12 with high-grade dysplasia, and 11 with invasive carcinoma derived from IPMN. The volume of the WPD was significantly greater in cases of high-grade dysplasia and invasive carcinoma. The area under the curve for the volume of the WPD for the prediction of high-grade dysplasia and invasive carcinoma was 0.810. Setting a cutoff value of 30 cm^3 predicted with 78.6% accuracy. The volume of the WPD was statistically correlated with the Ki67 labeling index (R = 0.591) and this mean proliferating. Patients for whom the volume of the WPD was ≥30 cm^3 had a significantly poorer prognosis.

Conclusions: The volume of the WPD (≥30 cm^3), as measured by 3D volumetry using MRCP, is a useful predictive factor for malignancy in IPMN.

Key words: intraductal papillary mucinous neoplasm, whole pancreatic duct, three dimensional volumetry, MR cholangiopancreatography, cellular proliferation potential

Introduction

Intraductal papillary mucinous neoplasms (IPMNs) are papilliform tumors that grow in the pancreatic duct and cause the excessive production of mucus, which results in the distention of the papilla of Vater and dilation of the main pancreatic duct and its branches[1]. IPMNs tend to exhibit low invasiveness and slow growth, with a good prognosis in the case of non-invasive carcinoma. However, invasive carcinoma is present in around 30% of patients who undergo resection, and postoperative five-year survival is reported as 27–60%[2)–7)].

IPMN was first reported as a "mucin-producing tumor" by Ohashi *et al*. in 1982[8]. International guidelines for IPMN were subsequently revised in 2012[9], and now state that cystic legion diameter ≥30 mm and main pancreatic duct diameter 5–9 mm are classified as "worrisome features," in which case

further testing rather than immediate surgery is recommended.

Since then, however, other studies have found that cystic lesion diameter ≥30 mm is actually a useful index[10], and there controversial described limitation of cystic lesion diameter and main pancreatic duct diameter.

Magnetic resonance cholangiopancreatography (MRCP) is a globally accepted, minimally invasive method of imaging the pancreaticobiliary duct system. Advances in MRI systems mean that today's 3D-MRCP provides isotropic voxel images that are almost equivalent to the high-resolution images obtained from conventional 2D-MRCP[13), 14)]. Numerous studies have addressed the evaluation of pancreatic cystic lesions on MRI[15)−17)], but none has yet reported the assessment of the volume of the pancreatic duct.

The Ki67 labeling index is used as an index of proliferating due to its association with the response to treatment and prognosis of many types of tumor[18), 19)]. A correlation between the Ki67 labeling index and pathological stage has also been reported for IPMN[20)], but no study has yet investigated the association between the Ki67 labeling index and the volume of the pancreatic duct.

In the present study, we investigated the association between IPMN, malignancy, and Ki67 labeling index, with the objective of exploring whether or not pancreatic duct volume measured by 3D volumetry using MRCP images is useful for evaluating surgical indications in patients with IPMN.

Materials and Methods

Patients

Seventy patients out of 113 who underwent IPMN resection between 2000 and 2013 for whom the digital image data required for 3D-MRCP. Surgery was also indicated for BD-IPMN patients with mural nodules, those with positive pancreatic juice cytology, and symptomatic patients even if cystic lesion diameter was < 30 mm. The surgical procedure used was pancreaticoduodenectomy[24)] in 41 cases, distal pancreatectomy with splenectomy in 20 cases, and spleen-preserving distal pancreatectomy[25)] in 9 cases. No surgically related deaths occurred during the study period. This study was approved by the Ethics Committee of our institution.

Pathological diagnosis and count for Ki67 labeling index was performed by dividing resected specimens into 5-mm slices and having hematoxylin and eosin (H&E)-stained slides examined by two or more doctors (W.K., T.W.)[20)]. Pathological stage was determined in accordance with the 2010 WHO stages[7)], and patients were classified as either low- or intermediate-grade dysplasia, high-grade dysplasia (non-invasive carcinoma), or IPMN with an associated invasive carcinoma (invasive carcinoma).

The diameters of the main pancreatic duct and cystic lesions were measured as the maximum diameters on axial images from MRI T2-weighted images. Patients were categorized as either MD (main duct)-IPMN, BD(Branch duct)-IPMN, or mixed type in accordance with the morphological classification set out in the 2012 international guidelines[9)]. In this study we prioritized objectivity, and as no objective method for evaluating mural nodules exists, we did not include them in our investigation. Patient characteristics were collected from medical records and compared by pathological stage.

Pancreatic duct volumetry

Two types of MRI scanner were used: an Achieva 1.5-T (Philips Healthcare, Amsterdam, Netherlands; n=55) and a Signa 1.5-T (GE Medical Systems, Milwaukee, WI, USA; n=15). Volumetry of the pancreatic duct was performed in Ziostation 2 (2011, Ziosoft, Inc., Redwood City, CA, USA) image analysis workstation (Fig. 1).

The signal intensity of the pancreatic duct at this boundary was around 500 in all patients, rising steeply to 1500−3000 toward the central part of the duct (Fig. 2). Varying the window level according to the signal intensity of the original MRCP images on the workstation also changed the apparent volume obtained. In this study, we therefore fixed the window level lower bound on the workstation at 500 during volumetry.

The volume of the whole pancreatic duct was obtained by extracting the volume of the biliary duct alone and subtracting it from the volume of the pancreatobiliary duct (Fig. 1A). In cases of BD-IPMN

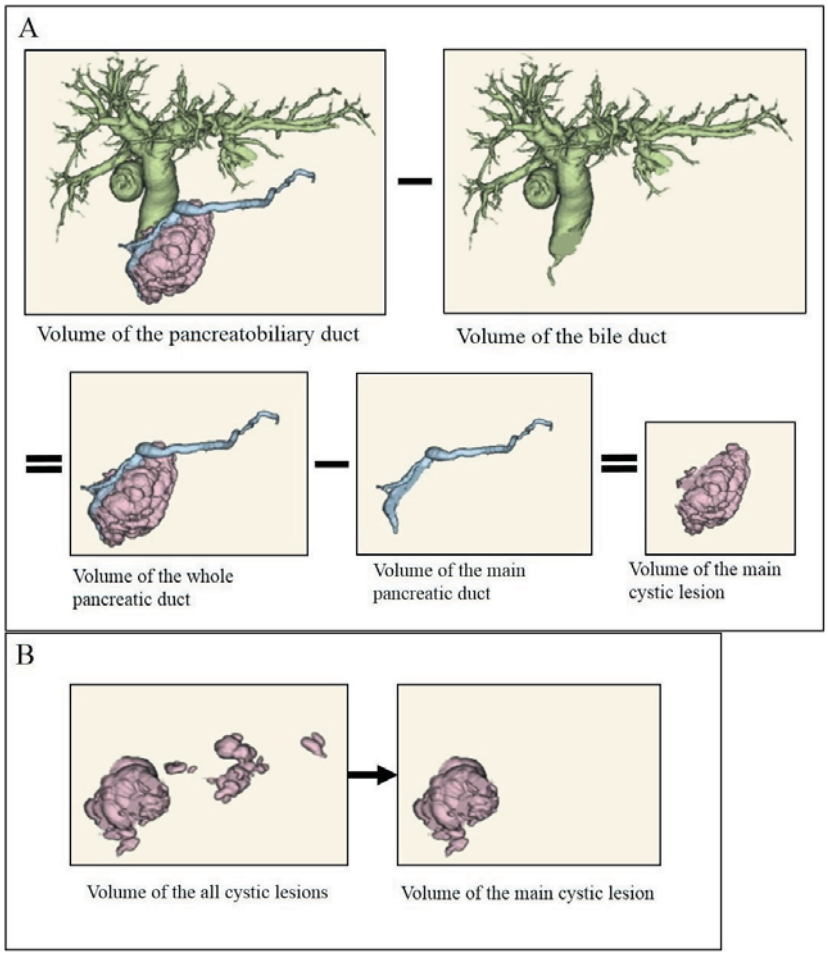

Fig. 1. Calculation method for each volume

The volume of the main pancreatic duct alone was extracted from the volume of the whole pancreatic duct. In patients with multiple cystic lesions, the volume of the main lesion with the largest volume among all the cystic lesions was calculated separately and regarded as the volume of the main cystic lesion.

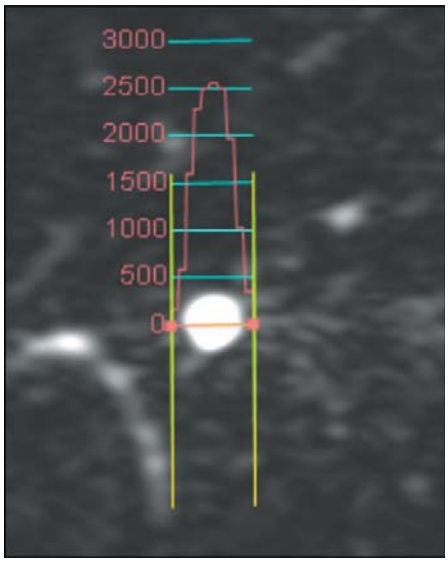

Fig. 2. Signal intensity of the pancreatic duct on an original MRCP image.

On MRCP images, the signal intensity of the boundary between the pancreatic duct and the surrounding pancreatic parenchyma was around 500, rising steeply toward the central part of the pancreatic duct.

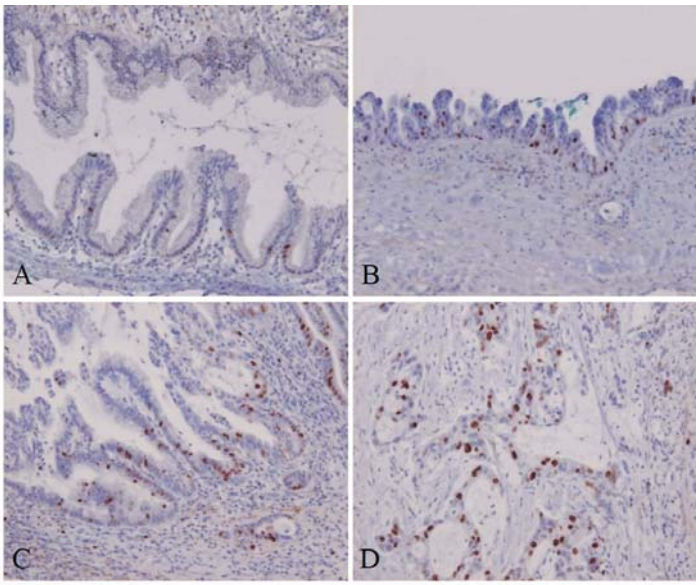

Fig. 3. Ki67 staining images for the various pathological stages.
(A) Low- or intermediate-grade dysplasia, (B) high-grade dysplasia (non-invasive carcinoma), (C) high-grade dysplasia area of invasive carcinoma, (D) invasive carcinoma area of invasive carcinoma.

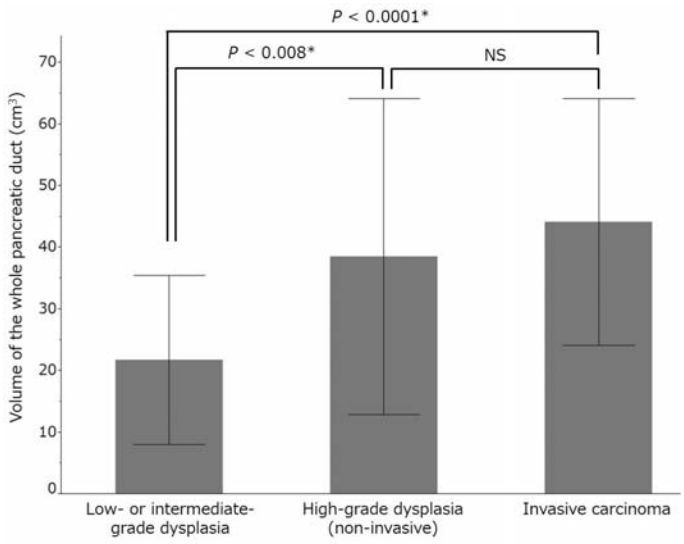

Fig. 4. Comparison of the volume of the whole pancreatic duct and pathological stage.
The mean volume of the whole pancreatic duct in cases of high-grade dysplasia (non-invasive carcinoma) and invasive carcinoma was statistically significantly greater than in cases of low- or intermediate-grade dysplasia. *, Statistically significant.

or the mixed type, the volume of the main pancreatic duct was calculated by trimming cystic lesions from the volume of the whole pancreatic duct. In patients with multiple cystic lesions, the volume of the main lesion with the largest volume among all the cystic lesions was calculated separately as the volume of the main cystic lesion (Fig. 1B).

Immunohistochemical staining

Two or three typical slices confirmed by H&E staining were selected for immunohistochemical staining. A microtome was used to prepare 4-μm-thick paraffin sections. After deparaffinization, the sections were immersed in a citric acid buffer (pH 6.0), and antigen retrieval was carried out in an

Table 1. Characteristics of 70 patients with IPMN

	Total	Low- or intermediate-grade dysplasia	High-grade dysplasia or invasive carcinoma		Invasive carcinoma	
	n = 70	n = 47	n = 23	*P value*	n = 11	*P value*
Sex				1.00		1.00
Men	48	32	16		8	
Women	22	15	7		3	
Age, years				0.03*		0.26
Mean ± S.D.	67 ± 8	66 ± 7	69 ± 10		68 ± 13	
Diabetes				1.00		1.00
Yes	18	12	6		3	
No	52	35	17		8	
Symptoms				0.003*		0.004*
Yes	24	10	14		7	
No	46	37	9		4	
Serum CEA, ng/ml				0.50		0.04*
≥ 3.4	14	8	6		5	
< 3.4	56	39	17		6	
Serum CA19-9, IU/L				0.04*		0.17
≥ 37	5	1	4		2	
< 37	65	46	19		9	
Main lesion				0.45		0.45
Head	41	26	15		7	
Body and/or tail	29	21	8		4	
Multiple lesions				0.20		0.19
Yes	26	20	6		2	
No	44	27	17		9	
Morphological classification				0.06 †		1.00 †
MD-IPMN	8	4	4	0.001 ‡ *	1	0.27 ‡
BD-IPMN	42	35	7	0.69§	5	0.64§
Mixed type	20	8	12		5	
Follow-up period, months				0.08		0.08
Mean ± S.D.	47 ± 26	51 ± 25	39 ± 27		34 ± 26	

S.D., standard deviation; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; IPMN, intraductal papillary mucinous neoplasm; MD-IPMN, main duct type IPMN; BD-IPMN, branch duct type IPMN; *, statistically significant; †, MD-IPMN vs. BD-IPMN; ‡, BD-IPMN vs. Mixed type; §, Mixed type vs MD-IPMN

autoclave (120℃, 20 min). Endogenous peroxidase removal was performed with 0.3% hydrogen peroxide (30 min), and 3% skim milk was used to eliminate nonspecific reactions (room temperature, 20 min). Monoclonal mouse anti-human Ki67 antigen (clone MIB-1; dilution 1:120) (Dako, Glostrup, Denmark) was reacted overnight at 4℃ as the primary antibody. The secondary antibody and peroxidase-labeled streptavidin (Histofine SAB-PO Multi-kit; Nichirei Biosciences Inc, Tokyo, Japan) were then added and reacted (each at room temperature for 10 min). Color development was carried out on a diaminobenzidine substrate (3 min), and finally hematoxylin was used for nuclear staining.

Calculation of Ki67 labeling index

Fig. 3 shows Ki67 staining images for each pathological stage. Three to five areas were selected within the field of view at 200× magnification, and at least 2000 cells were counted. The Ki67 labeling index was calculated as the proportion of Ki67-positive cells among the total cell count.

Statistical analysis

Values are expressed as mean ± standard deviation. Nominal variables were analyzed by using Fisher's exact test. Either Student's *t*-test or the Wilcoxon test was used to analyze nominal and continuous variables, depending on their normality. The Shapiro-Wilk test was used to test the normality of continuous

Table 2. Single logistic regression analysis of each size for the prediction of either invasive carcinoma alone or of non-invasive carcinoma and invasive carcinoma

	Low- or intermediate-grade dysplasia N=47	Non-invasive carcinoma N=12	Invasive carcinoma N=11	*P value* (*vs. invasive carcinoma*)	*P value* (*vs. high-grade dysplasia and invasive carcinoma*)
Volume of the whole pancreatic duct (cm^3)	22 ± 14	39 ± 26	44 ± 20	0.006*	<0.0001*
Volume of the main pancreatic duct (cm^3)	8 ± 6	23 ± 19	14 ± 13	0.49	0.0002*
Volume of the main cystic lesion (cm^3)	14 ± 12	21 ± 21	32 ± 20	0.008*	0.005*
Volume of all cystic lesions (cm^3)	15 ± 12	26 ± 24	32 ± 20	0.02*	0.003*
Diameter of the main pancreatic duct (mm)	4.3 ± 2.8	8.0 ± 5.1	7.0 ± 5.8	0.2	0.002*
Diameter of the main cystic lesion (mm)	28 ± 13	34 ± 15	39 ± 10	0.04*	0.02*

Data was shown as mean ± standard deviation. *: statistical significance.

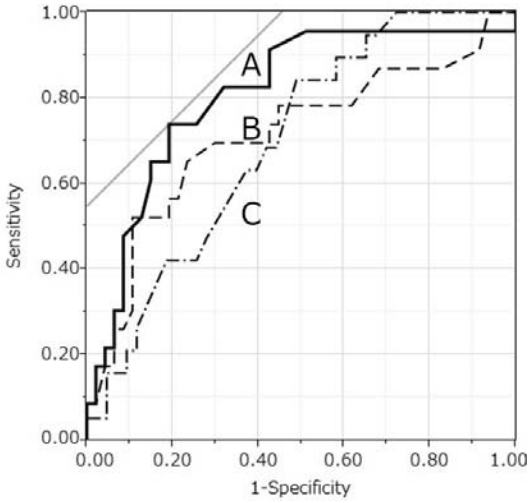

Fig. 5. Receiver operating characteristic (ROC) curves for the volume of the whole pancreatic duct (A), the main pancreatic duct diameter (B), and the main cystic lesion diameter (C). Area under the curve of A, B and C were 0.810, 0.728, 0.698.

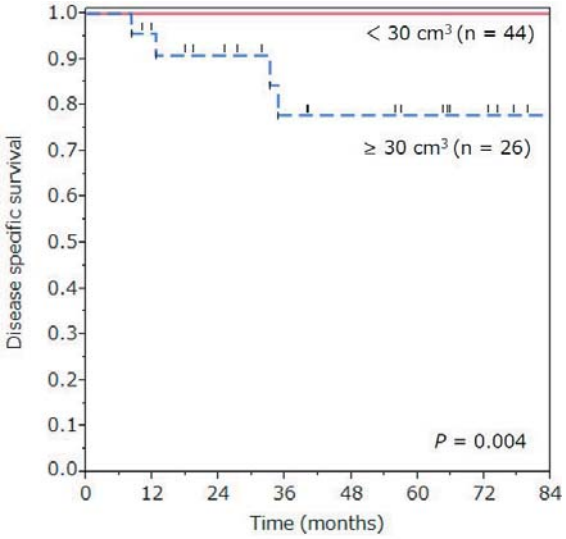

Fig. 6. Disease-specific survival curves when the cutoff value for the volume of the whole pancreatic duct was 30 cm^3.

Disease-specific survival was statistically significantly lower for patients for whom the volume of the whole pancreatic duct was ≥30 cm^3 compared with <30 cm^3 (5-year survival 77.9% vs. 100%).

variables. Single logistic regression analysis was used to search for predictive factors for either invasive carcinoma alone or high-grade dysplasia and invasive carcinoma. Their predictive power for either invasive carcinoma alone or high-grade dysplasia and invasive carcinoma was compared by producing a receiver operating characteristic (ROC) curve, calculating the area under the curve (AUC), and calculating their sensitivity, specificity, and diagnostic accuracy at the optimum cutoff value. Disease-specific survival was calculated by the Kaplan-Meier method (log-rank test). The correlation between the Ki67 labeling index and volume was analyzed by calculating Spearman's rank correlation coefficient to evaluate whether there was any correlation. The level of statistical significance was set as $P < 0.05$. JMP version 10.0.2 statistical software (SAS Institute Inc., Cary, NC, USA) was used for all statistical analysis.

Results

Patient characteristics

The mean age of the 70 subjects was 67 ± 8 years (range 39–80 years), and they comprised 48 men and

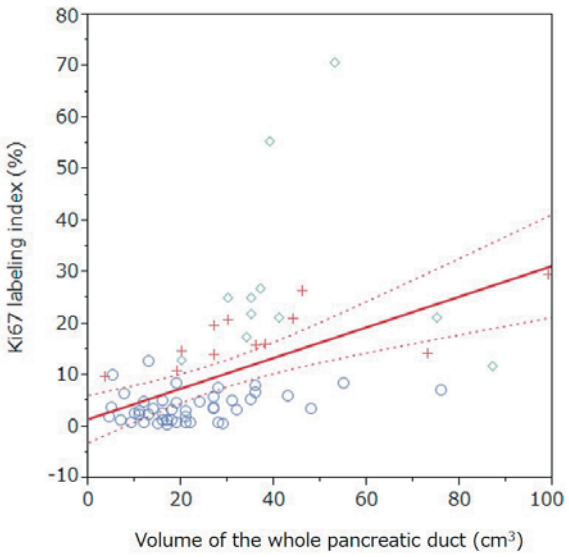

Fig. 7. Analysis of the correlation between the volume of the whole pancreatic duct and the Ki67 labeling index

The volume of the whole pancreatic duct was statistically significantly correlated with the Ki67 labeling index ($P < 0.0001$), and Spearman's rank correlation coefficient r was 0.591.

Round shape, low- or intermediate-grade dysplasia; cross shape, high-grade dysplasia; diamond shape, invasive carcinoma; solid line, regression line; dotted line, 95% confidence interval.

22 women. There were 47 patients (67.1%) with low- or intermediate-grade dysplasia, 12 (17.1%) with high-grade dysplasia (non-invasive carcinoma), and 11 (15.8%) with invasive carcinoma. Table 1 shows the patient characteristics by pathological stage.

Pancreatic duct volumetry

For all the 70 patients, the mean volume of the whole pancreatic duct was 28 ± 19 cm^3, the mean volume of the main pancreatic duct was 11 ± 12 cm^3, and the mean diameter of the main pancreatic duct was 5.4 ± 4.1 mm. In 62 of the 70 patients (excluding those with MD-IPMN), the mean volume of all cystic lesions was 20 ± 17 cm^3, the mean volume of the main cystic lesion was 18 ± 16 cm^3, and the mean diameter of all cystic lesions was 31 ± 13 mm. The mean volume of the whole pancreatic duct in cases of high-grade dysplasia (non-invasive carcinoma) and invasive carcinoma was statistically significantly greater than in cases of low- or intermediate-grade dysplasia (Fig. 4) .

Predictive power for high-grade dysplasia and invasive carcinoma

Single logistic regression analysis found that all sizes were significant predictive factors for high-grade dysplasia and invasive carcinoma (Table 2).

A comparison of the predictive power of each size for high-grade dysplasia and invasive carcinoma by means of ROC curve analysis found that the AUC was highest for the volume of the whole pancreatic duct, at 0.810 (Fig. 5), and that sensitivity was 73.9%, specificity 80.9%, and diagnostic accuracy 78.6% when the optimum cutoff value was set at 30 cm^3. The AUC for the prediction of invasive carcinoma by the volume of the whole pancreatic duct was also high, at 0.823, and setting the optimum cutoff value at the same value of 30 cm^3 predicted 10/11 cases of invasive carcinoma.

Comparison of disease-specific survival

Fig. 6 shows the disease-specific survival curves when the volume of the whole pancreatic duct was ≥ 30 cm^3 or < 30 cm^3. Disease-specific survival was significantly lower for patients for whom the volume of the whole pancreatic duct was ≥30 cm^3 compared with those for whom it was < 30 cm^3 ($P = 0.004$).

Association between the volume of the whole pancreatic duct and the Ki67 labeling index

The volume of the whole pancreatic duct was statistically correlated with the Ki67 labeling index ($R = 0.591$), which was higher at greater volumes (Fig. 7). The Ki67 labeling index was significantly higher in patients for whom the volume of the whole pancreatic duct was ≥30 cm^3 compared with those for whom it was < 30 cm^3 ($P < 0.0001$) (Fig. 8). In patients with high-grade dysplasia, the Ki67 labeling index was significantly higher in patients for whom the volume of the whole pancreatic duct was ≥30 cm^3 compared with those for whom it was < 30 cm^3.

Discussion

This is the first study to report 3D volumetry of the whole pancreatic duct, main pancreatic duct, and cystic lesions in IPMN patients by using original MRCP images. When this method was used, the volume of the whole pancreatic duct was more useful for the prediction of either high-grade dysplasia and

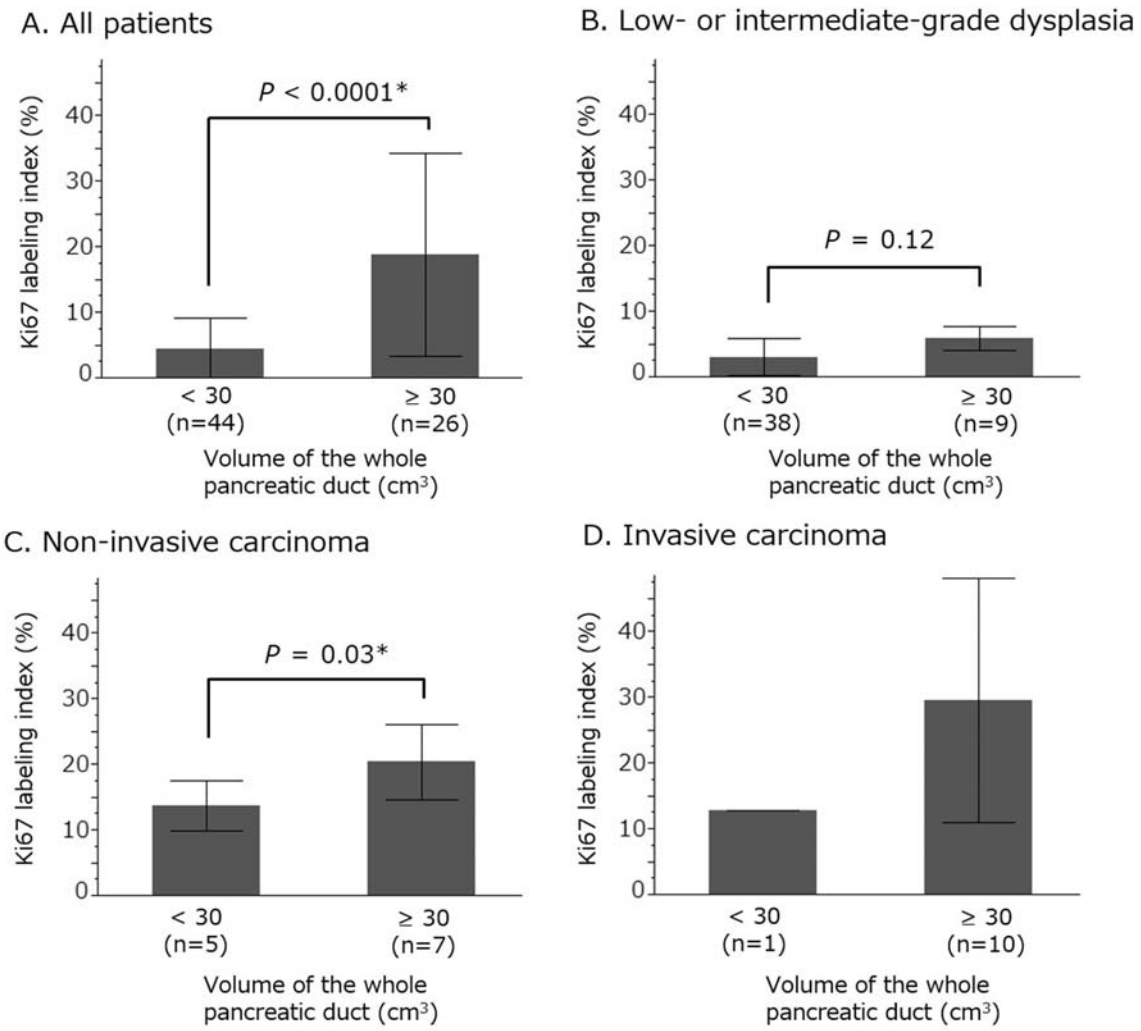

Fig. 8. Comparison of the Ki67 labeling index when the cutoff value for the volume of the whole pancreatic duct was 30 cm^3.

In only patients with high-grade dysplasia, the Ki67 labeling index was significantly higher in patients for whom the volume of the whole pancreatic duct was ≥30 cm^3 (20% ± 6%) compared with <30 cm^3 (14% ± 3%).
*, Statistically significant.

invasive carcinoma or of invasive carcinoma alone than conventional morphological indices. The volume of the whole pancreatic duct was positively correlated with the Ki67 labeling index, an indicator of cell proliferative potential, and cell proliferative potential was higher when the volume of the whole pancreatic duct was ≥30 cm^3. Patients for whom the volume of the whole pancreatic duct was ≥30 cm^3 also had statistically significantly poorer prognoses.

Our colleagues Murayama et al.[12] have previously used CT volumetry to demonstrate the theory that the pancreatic duct constitutes a single system within which mucus accumulates, and that the volume of the entire pancreatic duct provides a good reflection of the pathology of IPMN. The results of the present study, which used a different modality and subjects, also support this theory.

A recent meta-analysis of the predictive value of IPMN for malignancy found that few studies have included detailed descriptions of the method used to measure the diameters of the main pancreatic duct and cystic lesions, and stated that no specified method exists[14]. There have been four main problems with the methods of measuring the diameters of the main

pancreatic duct and cystic lesions so far reported. These are differences in modality, differences in the image cross-sections and sites used for measurement, differences in the selection of the margins to be measured, and differences in evaluation method, such as whether the maximum diameter or mean diameter is used. Due to these problems, variations occur. The volumetry used for measurements in the present study offered greater objectivity by using the same modality and stipulating the window level lower bound in advance.

Invasive IPMN has a poor prognosis, and surgical treatment should therefore be considered immediately before IPMN becomes invasive. However, no previous reports have described an index for estimating the stage immediately prior to invasion. Predictions must therefore include carcinoma in situ to enable the reliable early diagnosis of invasive carcinoma and the determination of surgical indications. In this present study of the volume of the whole pancreatic duct, we were similarly unable to reach a differential diagnosis between high-grade dysplasia and invasive carcinoma. The fact that cellular proliferative potential is higher in cases of high-grade dysplasia may indicate high malignant potential; however, this is a result that may be important when considering indications for surgical treatment.

Many previous reports have only evaluated cystic lesion diameter and main pancreatic duct diameter in isolation from each other[10), 27)]. In the present study, we also found that, by themselves, neither of these indices was sufficiently powerful as a predictive factor for malignancy. The volume of the whole pancreatic duct, which encompasses both cystic lesion diameter and main pancreatic duct diameter, may constitute an important indicator for indicating surgical treatment that resolves this problem. Additionally, MRI is recommended internationally for the evaluation of IPMN as it does not entail the problem of radiation exposure[28)]. The results of our study may therefore be regarded as significant.

The present study had a number of limitations. The first was that it was only a morphological study that did not include results from mural nodules (solid components). In this study we prioritized objectivity, and as no objective method for evaluating mural nodules exists, we did not include them in our investigation. Second, volumetry is only useful for predicting pathological malignancy, and is incapable of indicating the location of the primary lesion. In patients with predicted malignancy, other modalities must of course be used for evaluation. Third, this was a retrospective study of patients who underwent resection at a single institution, and we did not address questions of differences in MRI imaging conditions. Studies of more patients in multiple institutions are required. However, the results of the present study do suggest that the volume of the whole pancreatic duct measured by 3D volumetry using MRCP may be a more useful indicator for demonstrating the need for surgical treatment than the diameters of the main pancreatic duct or cystic lesions.

In conclusion, the volume of the whole pancreatic duct measured by 3D volumetry using MRCP in patients with IPMN is useful as a predictive factor for malignancy. The results of the present study demonstrated that patients for whom the volume of the whole pancreatic duct is $\geq$30 cm^3 had a poorer prognosis and higher cellular proliferative potential.

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