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Remnant pancreatic volume as an indicator of poor prognosis in pancreatic cancer patients after resection

Ryoichi Miyamoto [a, b, *], Yukio Oshiro [b], Naoki Sano [a], Satoshi Inagawa [a], Nobuhiro Ohkohchi [b]

[a] Department of Gastroenterological Surgery, Tsukuba Medical Center Hospital, 1-3-1 Amakubo, Tsukuba, Ibaraki, 305-8558, Japan
[b] Department of Surgery, Division of Gastroenterological and Hepatobiliary Surgery and Organ Transplantation, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki, 305-8575, Japan

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ABSTRACT

Background: Remnant pancreatic volume (RPV) is a well-known marker for short-term outcomes in pancreatic cancer patients after resection. However, in terms of the long-term outcomes, the significance of the RPV value remains unclear. Here, we address whether the RPV value is a predictor of the long-term outcomes in pancreatic cancer patients after resection by comparing various cancer-, patient-, and surgery-related prognostic factors and systemic inflammatory response markers in a retrospective cohort.

Methods: The RPV was measured on a three-dimensional (3D) image, revealing the actual pancreatic parenchymal remnant volume. Ninety-one patients who underwent pancreaticoduodenectomy were retrospectively enrolled. We divided the cohort into high- and low-RPV groups based on a cut-off value ($>31.5\ cm^3$, $n = 66$ and $\leq 31.5\ cm^3$, $n = 25$, respectively). The median survival times (MSTs) were compared between the two groups. Using multivariate analysis, the RPV and other well-known prognostic factors were independently assessed.

Results: The MSTs (days) were significantly different between the two groups (high, 823 vs. low, 482, $p = 0.001$). Multivariate analysis identified the RPV ($\leq 31.5\ cm^3$) (hazard ratio [HR], 2.015; $p = 0.011$), lymph node metastasis (HR, 8.415; $p = 0.002$), lack of adjuvant chemotherapy (HR, 5.352; $p < 0.001$), stage III/IV disease (HR, 2.352; $p = 0.029$), and pathological fibrosis (HR, 1.771; $p = 0.031$) as independent prognostic factors.

Conclusions: The present study suggests that the RPV value is also useful for predicting long-term outcomes in pancreatic cancer patients after resection.

Introduction

Pancreatic cancer is still refractory to treatment, and its prognosis is the worst among all solid tumors, with a 5-year survival rate of only 5–7% [1,2]. A variety of predictive factors have been identified and applied to determining the long-term prognosis of pancreatic cancer patients [3–12]. These predictors can be divided into cancer-related factors, such as serum carcinoembryonic antigen (CEA) level, carbohydrate antigen 19-9 (CA19-9) level, tumor size, lymph node involvement, histological differentiation types, histopathological stage, and resection margin status; patient-related factors, such as age, sex, and body mass index (BMI); surgery-related factors, such as operation times, volume of intraoperative blood loss, and intraoperative blood transfusion; and systemic inflammatory response markers, such as the serum C-reactive protein (CRP) level, lymphocyte count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and Glasgow Prognostic Score (GPS).

Recent advances in workstations for radiological diagnostic imaging have made it easier to construct three-dimensional (3D) images of vasculature and organs. In particular, 3D-measured volumetry is widely used in hepatic resection to facilitate risk prediction as early as the preoperative setting [13,14]. Recent studies suggested that a large remnant pancreatic volume (RPV), as estimated using preoperative multidetector computed tomography

* Corresponding author. Department of Gastroenterological Surgery, Tsukuba Medical Center Hospital, 1-3-1 Amakubo, Tsukuba, Ibaraki, 305-8558, Japan.
E-mail address: goodfirst883@gmail.com (R. Miyamoto).

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(MDCT) images, significantly and independently affected the short-term outcomes, including the risk of postoperative pancreatic fistula (POPF) in pancreatic cancer patients after resection [15–17]. However, with regard to the long-term outcomes, the significance of the RPV remains unclear.

We performed 3D surgical simulations of pancreatic surgeries, including the measurement of the pancreatic volume [18,19]. In this study, we addressed whether the RPV is a predictor of long-term outcomes in pancreatic cancer patients by comparing various cancer-, patient-, and surgery-related prognostic factors and systemic inflammatory response markers in a retrospective cohort. To the best of our knowledge, this is the first report to indicate a correlation between the RPV and the long-term postoperative prognosis of patients with resected pancreatic cancer.

Materials and methods

Patients

We retrospectively evaluated 101 consecutive pancreatic cancer patients who underwent pylorus-resecting pancreaticoduodenectomy (PD) at the Tsukuba Medical Center Hospital, Tsukuba, Japan, between January 2007 and December 2017. First, we excluded 10 patients, including 5 with intraductal papillary mucinous carcinoma, 1 with preoperative adjuvant treatment, 2 with synchronous distant metastasis, and 2 who underwent surgeries that were more extensive than the standard PD procedure, including simultaneous resection of the transverse colon. The final cohort included 91 patients with pancreatic ductal adenocarcinoma who underwent PD. The ethics committee of the Tsukuba Medical Center Hospital approved this study (#2018-010). According to the RPV cut-off value, the cohort was divided into the following two groups: a high-RPV group and a low-RPV group. The demographic and histopathological characteristics were compared between the two groups.

Measurement of the RPV

We used the SYNAPSE VINCENT® medical imaging system (Fujifilm Medical Co., Ltd., Tokyo, Japan) to construct 3D images by integrating MDCT and MRCP images. This software offers a standardized analysis of liver anatomy and a volumetric risk analysis based on two-dimensional MDCT images [13,14]. In previous studies, we developed 3D reconstructions by integrating MDCT and MRCP images to produce accurate preoperative anatomic images and extended this system to pancreatic surgery [18,19]. The 3D-measured RPV was calculated from MDCT scans taken within 1 month after operation. Serial transverse enhanced MDCT scan images were obtained at 1.0- or 2.0-mm intervals. Each slice of the remnant pancreas parenchyma was traced, and the corresponding RPV was calculated as the sum of the pancreatic tissue areas (Fig. 1A and B). The volumetric analysis was conducted by two senior physicians who were blinded to the outcomes.

Pancreatic cancer survival analysis according to the RPV

We first examined the extent to which the RPV affected the overall survival of pancreatic cancer patients. The cut-off value for the RPV was defined according to the receiver operating characteristic (ROC) curve analysis. The cut-off value is typically determined using ROC curves, which visually represent the sensitivity (i.e., probability of correctly identifying an event, e.g., death) and the specificity (i.e., probability of correctly identifying a nonevent) of various cut-off values.

Pancreatic cancer survival analysis according to various prognostic factors

In addition to the RPV, we also analyzed the relationship between the overall survival of pancreatic cancer patients and prognostic factors at different treatment phases, including cancer-related factors, patient-related factors, surgery-related factors, and systemic inflammatory response markers. Cut-off values for each continuous variable were defined according to the ROC curve analysis.

Cancer-related prognostic factors: We focused on cancer-related biomarkers, including serum CEA and CA19-9. The pathological diagnoses and classifications were based on the Union for International Cancer Control TNM classification of malignant tumors, 7th edition. The histopathological factors analyzed in this study included histological grade (well, moderately, or poorly differentiated), tumor size (T classification), lymph node metastasis, vascular invasion, perineural invasion, and surgical margins. The patients were classified into groups based on TNM stage and tumor size as follows: stage I/II (n = 64) or stage III/IV (n = 27) and T1/T2 (n = 63) or T3/T4 (n = 28).

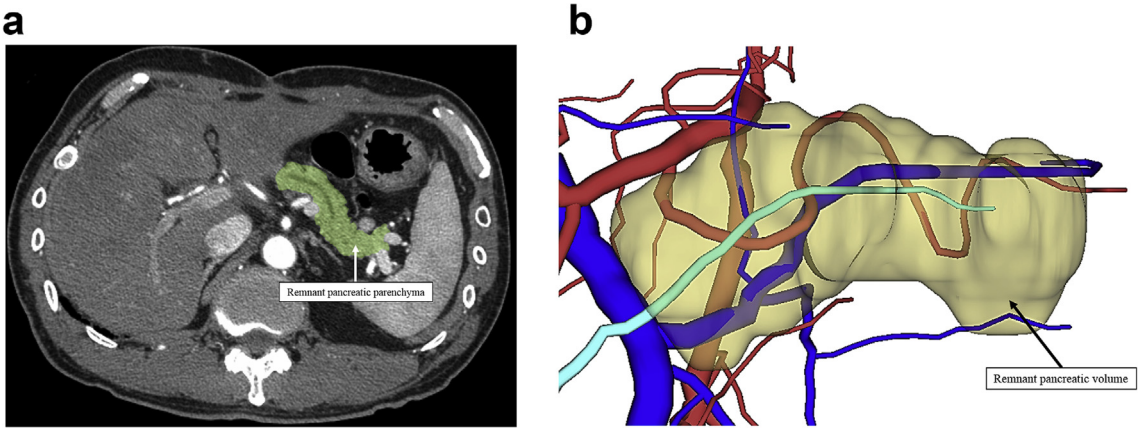

Fig. 1. A An integrated multi-detector computed tomography (MDCT) image obtained after the operation is shown. The outlined area indicates the remnant pancreatic parenchyma. Each slice of the remnant pancreatic parenchyma was traced, and the corresponding remnant pancreatic volume was calculated as the sum of the pancreatic tissue areas. **B** A three-dimensional (3D) image of the remnant pancreatic volume obtained by MDCT images from same patient is shown. This image represents a 3D view from the front of the patient. Ivory represents the remnant pancreatic volume; red represents the arteries; blue represents the veins, including the portal vein; and turquoise represents the main pancreatic duct.

Patient-related prognostic factors: We compared the age, sex ratio, BMI, ASA score, PS, and preoperative symptoms as individual patient-related factors. We also focused on pancreatic texture. The pancreatic texture was judged by surgeons and later just confirmed by the pathologic status as reference findings. Furthermore, we analyzed survival based on whether patients were administered adjuvant chemotherapy (n = 82), including gemcitabine (n = 40) and S-1 (n = 42), or not (n = 9). S-1 is an oral fluoropyrimidine derivative that combines tegafur with 2 modulators of 5-fluorouracil metabolism, 5-choloro-2,4-dihydroxypyridine and potassium oxonate [20,21].

Surgery-related prognostic factors: We focused on perioperative outcomes, including operating time, intraoperative blood loss, intraoperative blood transfusion, and portal vein resection. We also focused on pancreatic fistula, which was defined in accordance with the International Study Group on Pancreatic Fistula guidelines [22].

Systemic inflammatory response markers: Platelet count, neutrophil count, lymphocyte count, NLR, PLR, serum CRP level and GPS were also analyzed as variables associated with inflammatory responses.

Surgical procedures

First, we excluded 2 patients who underwent pancreatic surgical procedures that were more extensive than the standard PD procedure, including simultaneous resection of the transverse colon. Ninety-one patients underwent pylorus-resecting PD and modified Child's reconstruction [23,24]. In terms of the pancreatic dissection line, we routinely dissected the pancreatic tissue at the left edge of the portal vein. For the pancreaticojejunostomy procedure, we used the Kakita method [25]. From April 2015 onward, we used the Blumgart method to perform pancreaticojejunostomy [26]. For pancreaticojejunal anastomotic stents, we used internal or external stents depending on the size of the main pancreatic duct. Two drainage tubes were placed superiorly and inferiorly to the anastomotic site between the pancreas and the jejunum. All surgical procedures were performed under the supervision of one or two senior surgeons.

Statistical analyses

Correlations with patient background data were analyzed using the χ^2 test or Fisher's exact test, as appropriate. Patient survival was calculated using the Kaplan–Meier method. Differences between the survival curves were evaluated using the log-rank test.

In addition to the RPV ($\leq$31.5 cm^3), the following clinical prognostic factors were evaluated using the Kaplan–Meier method: high CEA level, stage III/IV disease and lymph node metastasis for cancer-related prognostic factors; age (>71), BMI (>21.8 kg/m^2), pathological fibrosis, and lack of adjuvant chemotherapy for patient-related prognostic factors; intraoperative blood transfusion and portal vein resection for surgery-related prognostic factors; and GPS (score of 2) for systemic inflammatory response markers. Using the multivariate Cox proportional hazards model, we compared the predictive value of these factors for patient prognosis.

Statistical analyses were performed using a statistical analysis software package (SPSS Statistics, version 21; IBM, Armonk, NY, USA), and p values < 0.05 were considered significant.

Results

Patient characteristics

In the present cohort, we observed a normal distribution of RPVs. The mean RPV (±standard deviation) was 29.8 ± 15.3 cm^3 (range, 11.3–51.5 cm^3). The cut-off value was 31.5 cm^3 for the RPV (sensitivity and specificity: 84.7% and 72.7%, respectively). The area under the concentration-time curve (AUC) was 0.817. We divided the cohort into high- and low-RPV groups based on the cut-off value (>31.5 cm^3, n = 66 and $\leq$31.5 cm^3, n = 25, respectively). The characteristics of the patients in the low- and high-RPV groups are presented in Table 1. Between the low- and high-RPV groups, significant differences were observed in TNM stage (p < 0.001), lymph node metastasis (p = 0.011), portal vein resection (p = 0.031), pancreatic texture (p < 0.001), and main pancreatic duct diameter (p < 0.001).

Survival analysis of various prognostic factors for pancreatic cancer

The survival analyses using cut-off values for prognostic factors at different phases are shown in the Supplemental Table.

Survival analysis according to the RPV: The median survival time (MST) for all 91 patients was 683 days. The 25 patients in the low-RPV group had a worse MST (MST, 482 days) than the 66 patients in the high-RPV group (MST, 823 days; p = 0.001; Fig. 2).

The survival analyses based on cancer-related prognostic factors, i.e., serum CEA level (high, 558 days vs. low, 789 days, p = 0.0038), TNM stage (I/II, 813 days vs. III/IV, 452 days, p = 0.013) and lymph node metastasis (+, 411 days vs. −, 1235 days, p < 0.001), revealed significant differences with respect to prognosis.

The survival analyses based on patient-related prognostic factors, i.e., age (high, 558 days vs. low, 959 days, p = 0.021) and BMI (high, 615 days vs. low, 904 days, p = 0.036), pathological fibrosis (yes, 532 days vs. no, 945 days, p = 0.011) and adjuvant chemotherapy (yes, 1052 days vs. no, 435 days, p < 0.001), revealed significant differences with respect to prognosis.

The survival analyses based on surgery-related prognostic factors, i.e., intraoperative blood transfusion (yes, 462 days vs. no, 828 days, $p = 0.014$) and portal vein resection (yes, 578 days vs. no, 815 days, $p = 0.024$), revealed significant differences with respect to prognosis.

The survival analysis based on systemic inflammatory response markers, i.e., GPS (score of 2, 414 days vs. score of 1 or 0, 818 or 985 days, p < 0.001), revealed a significant difference with respect to prognosis.

Multivariate analysis (Table 2)

In addition to a low RPV (hazard ratio [HR], 2.015; p = 0.011), multivariate analysis revealed that stage III/IV disease (HR, 2.352; p = 0.029), lymph node metastasis (HR, 8.415; p = 0.002), lack of adjuvant chemotherapy (HR, 5.352; p < 0.001) and pathological fibrosis (HR, 1.771; p = 0.031) were strong predictive factors for poor survival.

Discussion

In the present study, we found that postoperative 3D-measured RPV was a prognostic factor for pancreatic cancer patients, in addition to stage III/IV disease, lymph node metastasis, lack of adjuvant chemotherapy, and pathological fibrosis. Therefore, we believe that the RPV has an additional useful predictive value for long-term outcomes in pancreatic cancer patients after PD.

Questions regarding the mechanisms by which low RPV values potentially contribute to pancreatic cancer progression remain unanswered. One potential hypothesis is that in patients with low RPVs, atrophic changes in the remnant pancreatic texture are often attributed to obstructive pancreatitis induced by advanced

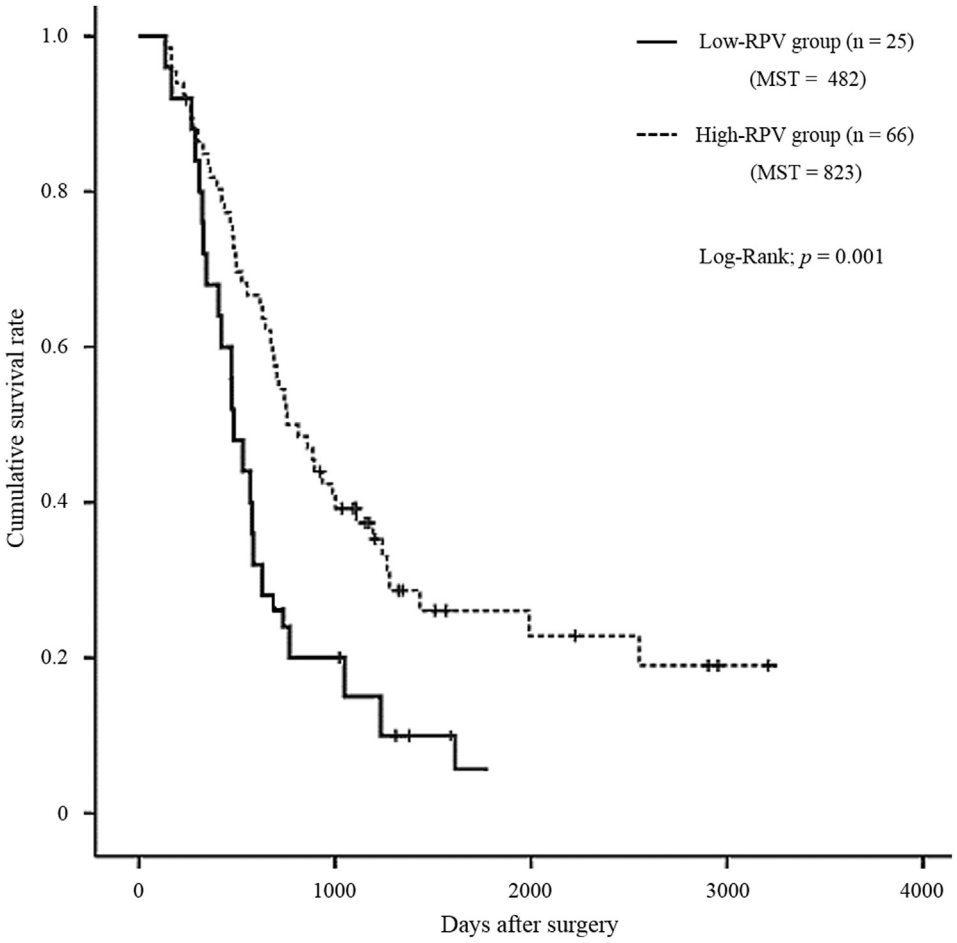

Fig. 2. Kaplan–Meier survival curves of pancreatic cancer patients after surgical resection. A significant difference was observed between the two groups stratified by RPV. MST, median survival time (days); RPV, remnant pancreatic volume.

pancreatic head cancer. Therefore, we assume that the severity of pancreatic atrophy could represent the progression of pancreatic cancer. However, the relationship between pancreatic atrophy and advanced disease remains controversial. A previous study reported that the severity of pancreatic atrophy was positively associated with pancreatic cancer progression [27]. Other previous studies reported the onset of fibrosis near tumors accompanied by pancreatic atrophy, even in cases of pancreatic intraepithelial neoplasia (Pan-IN) and intraepithelial carcinomas [28–30]. Indeed, in the present study, we found significant differences in pancreas texture between the two groups, with pathological fibrosis ($p < 0.001$) and advanced disease ($p < 0.001$) in the low-RPV group (Table 1). Furthermore, our multivariate analysis indicated that stage III/IV disease and hard pancreas texture were identified as prognostic parameters.

Another possible explanation is that the involvement of pancreatic stellate cells (PSCs) has been reported as being part of the pathogenesis of pancreatic fibrosis [31,32]. The structure of the cancerous microenvironment induced by the interaction between PSCs and pancreatic cancer cells is believed to correlate with the aggressiveness of the pancreatic cancer, and more aggressive pancreatic cancer has been reported to be associated with a poorer prognosis [32].

Our multivariate analysis indicated that lymph node metastasis was the strongest prognostic factor (HR, 8.415; Table 2). Second, a lack of adjuvant chemotherapy was also identified as a prognostic parameter (HR, 5.352; Table 2). Third, the results indicated that stage III/IV disease was a prognostic parameter (HR, 2.352; Table 2). These prognostic factors are well known and are widely used as prognostic risk factors for pancreatic cancer patients. In terms of the RPV, our multivariate analysis also indicated that a low RPV ($\leq$31.5 cm^3) was also a prognostic marker. Because the RPV is objectively measured by postoperative 3D images, we conclude that, in addition to other well-known risk factors, the RPV is another useful prognostic marker. In terms of relationship between the effects of the RPV and adjuvant chemotherapy, significant differences were not observed in terms of the conduct of adjuvant chemotherapy between the low- and high-RPV groups (Table 1). Therefore, we assumed that both the RPV and adjuvant chemotherapy would affect the long-term prognosis of the patients.

In terms of preoperative 3D-measured RPV, a positive correlation between RPVs and short-term outcomes, including the presence of POPF, has been thoroughly discussed [15–17]. Frozanpor et al. and Kirihara et al. reported that RPVs calculated using preoperative MDCT images were useful predictors of POPF [16,17]. However, the potential correlation between preoperative 3D-measured RPV and the long-term outcomes of pancreatic cancer patients remains unclear. In a previous study, we showed that preoperative 3D imaging is useful for understanding and sharing anatomic information in pancreatic surgery [18,19]. Our multivariate analysis indicated that lymph node metastasis, lack of adjuvant chemotherapy, stage III/IV disease, and pathological fibrosis were independent prognostic factors. However, these prognostic factors were identified during the postoperative period.

Table 1
Patient characteristics.

Factor	Low-RPV group (n = 25)	High-RPV group (n = 66)	p value
Age	71 (39–97)	72 (31–94)	0.310
Sex ratio (male: female)	15: 10	45: 21	0.142
BMI (kg/m^2)	21.0 ± 3.56	23.5 ± 2.91	0.063
ASA score (1–4)	1 (1–3)	1 (1–3)	0.442
PS (0–4)	0 (0–2)	1 (0–3)	0.085
Preoperative symptoms	18 (72%)	51 (77%)	0.087
CEA (mg/dL)	7.85 ± 8.67	8.9 ± 6.32	0.155
CA19-9 (mg/dL)	101 ± 494	91.6 ± 291	0.482
Adjuvant chemotherapy			
Yes	22 (88%)	60 (91%)	0.153
No	3 (12%)	6 (9.0%)	
Histological differentiation type			
Well	2 (8.0%)	7 (11%)	0.411
Moderately	21 (84%)	55 (83%)	
Poorly	2 (8.0%)	4 (6.1%)	
Stage (UICC 7th)			
IA	1 (4.0%)	2 (3.0%)	<0.001*
IB	3 (12%)	5 (7.5%)	
IIA	2 (8.0%)	8 (12%)	
IIB	6 (24%)	37 (56%)	
III	12 (48%)	11 (17%)	
IV	1 (4.0%)	3 (4.5%)	
Tumor size			
T1	3 (12%)	7 (11%)	0.331
T2	15 (60%)	38 (57%)	
T3	4 (16%)	13 (19%)	
T4	3 (12%)	8 (12%)	
Lymph node metastasis			
Positive	22 (88%)	43 (65%)	0.011*
Negative	3 (12%)	23 (35%)	
Vascular invasion			
Positive	23 (92%)	56 (84%)	0.115
Negative	2 (8.0%)	10 (16%)	
Perineural invasion			
Positive	23 (92%)	59 (89%)	0.311
Negative	2 (8.0%)	7 (11%)	
Surgical margin			
Positive	4 (16%)	15 (23%)	0.159
Negative	21 (84%)	51 (77%)	
Portal vein resection	5 (20%)	8 (12%)	0.031*
Pancreas texture (hard: soft)	23: 2	55: 11	<0.001*
Main pancreatic duct diameter (mm)	6.3 ± 4.5	2.5 ± 1.5	<0.001*

RPV, remnant pancreatic volume; BMI, body mass index; ASA, American Society of Anesthesiologists; PS, performance status; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; Well, well differentiated adenocarcinoma; Moderately, moderately differentiated adenocarcinoma; Poorly, poorly differentiated adenocarcinoma; UICC, Union for International Cancer Control.
*: $p < 0.05$.

Table 2
Multivariate analyses of prognostic factors.

Parameter	Hazard ratio	95% CI	*p* Value
Low RPV (≤31.5 cm^3)	2.015	0.272–3.619	0.011*
High CEA level	0.738	0.356–1.444	0.307
Stage III/IV	2.352	0.601–3.685	0.029*
Lymph node metastasis	8.415	0.728–10.58	0.002*
Age (>71)	1.501	0.724–3.394	0.084
BMI (>21.8 kg/m^2)	0.513	0.201–2.226	0.249
lack of adjuvant chemotherapy	5.352	0.949–9.279	<0.001*
Pathological fibrosis	1.771	0.356–2.444	0.031*
Intraoperative blood transfusion	0.799	0.421–1.562	0.151
Portal vein resection	0.972	0.340–2.778	0.958
GPS score 2	1.133	0.740–2.236	0.256

CI, confidence interval; RPV, remnant pancreatic volume; CEA, carcinoembryonic antigen; BMI, body mass index; GPS, Glasgow Prognostic Score.
*: $p < 0.05$.

If the postoperative RPV is precisely simulated by preoperative 3D images, we propose that, compared with other well-known postoperative prognostic factors, preoperative 3D-measured RPV is more useful for determining a prognosis. During the standard PD procedure, we routinely dissected the pancreatic tissue at the left edge of the portal vein. Therefore, unless surgery was performed for advanced stage disease, the 3D-measured RPV could be preoperatively calculated using the pancreatic resection line at left edge of the portal vein. We propose that patients with low RPVs should be recognized as being at high risk for a poor prognosis. The early identification of patients with poor prognoses can increase the accuracy of the perioperative benefit/risk assessment and the information given to patients. We suggest that these patients should be more carefully monitored for the recurrence of pancreatic cancer during the postoperative follow-up period. Therefore, we would like to further extend our research, focusing on preoperative measurement of the RPV.

In conclusion, we found that postoperative 3D-measured RPV was a prognostic factor for pancreatic cancer patients. Therefore, we believe that the RPV has additional useful value for predicting long-term outcomes in pancreatic cancer patients after PD. The present study had limitations, including being a retrospective single-center study with a relatively small patient cohort. These results require confirmation by additional multicenter large-scale studies and prospective randomized controlled studies.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2019.05.464.

Disclosure

The authors declare no conflict of interest or source of funding.

References

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. Ca - Cancer J Clin 2011;61:69–90.
[2] Warshaw AL, Fernandez-del Castillo C. Pancreatic carcinoma. N Engl J Med 1992;326:455–65.
[3] Distler M, Pilarsky E, Kersting S, Grützmann R. Preoperative CEA and CA 19-9 are prognostic markers for survival after curative resection for ductal adenocarcinoma of the pancreas - a retrospective tumor marker prognostic study. Int J Surg 2013;11:1067–72.
[4] Sierzega M, Popiela T, Kulig J, Nowak K. The ratio of metastatic/resected lymph nodes is an independent prognostic factor in patients with node-positive pancreatic head cancer. Pancreas 2006;33:240–5.
[5] Luo J, Margolis KL, Adami HO, LaCroix A, Ye W. Obesity and risk of pancreatic cancer among postmenopausal women: the women's health initiative (United States). Br J Canc 2008;99:527–31.
[6] Kanda M, Fujii T, Kodera Y, Nagai S, Takeda S, Nakao A. Nutritional predictors of postoperative outcome in pancreatic cancer. Br J Surg 2011;98:268–74.
[7] Nagai S, Fujii T, Kodera Y, Kanda M, Sahin TT, Kanzaki A, et al. Impact of operative blood loss on survival in invasive ductal adenocarcinoma of the pancreas. Pancreas 2011;40:3–9.
[8] Benson D, Barnett Jr CC. Perioperative blood transfusions promote pancreas cancer progression. J Surg Res 2011;166:275–9.
[9] Jamieson NB, Glen P, McMillan DC, McKay CJ, Foulis AK, Carter R, et al. Systemic inflammatory response predicts outcome in patients undergoing resection for ductal adenocarcinoma head of pancreas. Br J Canc 2005;92:21–3.
[10] Fogar P, Sperti C, Basso D, Sanzari MC, Greco E, Davoli C, et al. Decreased total lymphocyte counts in pancreatic cancer: an index of adverse outcome. Pancreas 2006;32:22–8.
[11] Bhatti I, Peacock O, Lloyd G, Larvin M, Hall RI. Preoperative hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: neutrophil-lymphocyte versus platelet-lymphocyte ratio. Am J Surg 2010;200:197–203.
[12] Miyamoto R, Oda T, Hashimoto S, Kurokawa T, Kohno K, Akashi Y, et al. Platelet × CRP multiplier value as an indicator of poor prognosis in patients with resectable pancreatic cancer. Pancreas 2017;46:35–41.
[13] Nakayama K, Oshiro Y, Miyamoto R, Kohno K, Fukunaga K, Ohkohchi N. The effect of three-dimensional preoperative simulation on liver surgery. World J Surg 2017;41:1840–7.
[14] Takahashi K, Sasaki R, Kondo T, Oda T, Murata S, Ohkohchi N. Preoperative 3D volumetric analysis for liver congestion applied in a patient with hilar cholangiocarcinoma. Langenbeck's Arch Surg 2010;395:761–5.
[15] Kanda M, Fujii T, Suenaga M, Takami H, Hattori M, Inokawa Y, et al. Estimated pancreatic parenchymal remnant volume Accurately predicts clinically relevant pancreatic fistula after pancreatoduodenectomy. Surgery 2014;156:601–10.
[16] Frozanpor F, Loizou L, Ansorge C, Lundell L, Albiin N, Segersvärd R. Correlation between preoperative imaging and intraoperative risk assessment in the prediction of postoperative pancreatic fistula following pancreatoduodenectomy. World J Surg 2014;38:2422–9.
[17] Kirihara Y, Takahashi N, Hashimoto Y, Sclabas GM, Khan S, Moriya T, et al. Prediction of pancreatic anastomotic failure after pancreatoduodenectomy: the use of preoperative, quantitative computed tomography to measure remnant pancreatic volume and body composition. Ann Surg 2013;257:512–9.
[18] Miyamoto R, Oshiro Y, Nakayama K, Kohno K, Hashimoto S, Fukunaga K, et al. Three-dimensional simulation of pancreatic surgery showing the size and location of the main pancreatic duct. Surg Today 2017;47:357–64.
[19] Miyamoto R, Oshiro Y, Nakayama K, Ohkohchi N. Impact of three-dimensional surgical simulation on pancreatic surgery. Gastrointest Tumors 2018;4:84–9.
[20] Sudo K, Nakamura K, Yamaguchi T. S-1 in the treatment of pancreatic cancer. World J Gastroenterol 2014;20:15110–8.
[21] Maeda A, Boku N, Fukutomi A, Kondo S, Kinoshita T, Nagino M, et al. Randomized phase III trial of adjuvant chemotherapy with gemcitabine versus S-1 in patients with resected pancreatic cancer: Japan adjuvant study group of pancreatic cancer (JASPAC-01). Jpn J Clin Oncol 2008;38:227–9.
[22] Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138:8–13.
[23] Matsumoto I, Shinzeki M, Asari S, Goto T, Shirakawa S, Ajiki T, et al. A prospective randomized comparison between pylorus- and subtotal stomach-preserving pancreatoduodenectomy on postoperative delayed gastric emptying occurrence and long-term nutritional status. J Surg Oncol 2014;109:690–6.
[24] Hayashibe A, Kameyama M, Shinbo M, Makimoto S. The surgical procedure and clinical results of subtotal stomach preserving pancreaticoduodenectomy (SSPPD) in comparison with pylorus preserving pancreaticoduodenectomy (PPPD). J Surg Oncol 2007;95:106.
[25] Kakita A, Takahashi T, Yoshida M, Furuta K. A simpler and more reliable technique of pancreatojejunal anastomosis. Surg Today 1996;26:532–5.
[26] Oda T, Hashimoto S, Miyamoto R, Shimomura O, Fukunaga K, Kohno K, et al. The tight adaptation at pancreatic anastomosis without parenchymal laceration: an institutional experience in introducing and modifying the new procedure. World J Surg 2015;39:2014–22.
[27] Fukumoto T, Watanabe T, Hirai I, Kimura W. Pancreatic volume is one of the independent prognostic factors for resectable pancreatic ductal adenocarcinomas. J Hepatobiliary Pancreat Sci 2016;23:472–9.
[28] Hruban RH, Maitra A, Goggins M. Update on pancreatic intraepithelial neoplasia. Int J Clin Exp Pathol 2008;1:306–16.
[29] Strategies CantoMI. For screening for pancreatic adenocarcinoma in high-risk patients. Semin Oncol 2007;34:295–302.
[30] Meckler KA, Brentnall TA, Haggitt RC, Crispin D, Byrd DR, Kimmey MB, et al. Familial fibrocystic pancreatic atrophy with endocrine cell hyperplasia and pancreatic carcinoma. Am J Surg Pathol 2001;25:1047–53.
[31] Schneider E, Schmid-Kasas A, Zhao J, Weidenbach H, Schmid RM, Menke A, et al. Identification of mediators stimulating proliferation and matrix synthesis of rat pancreatic stellate cells. Am J Physiol Cell Physiol 2001;281:C532–43.
[32] Ikenaga N, Ohuchida K, Mizumoto K, Cui L, Kayashima T, Morimatsu K, et al. CD10+ pancreatic stellate cells enhance the progression of pancreatic cancer. Gastroenterology 2010;139:1041–51.