

Peer Review File

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Reviewer A

Comments 1: Authors defines the radiological vessel invasion as "tumor abutment or encasement". Since these diagnostic criteria is the most important in this manuscript, author should provide the typical images and clarify the diagnostic criteria in more detail. Also, although authors showed both encasement and abutment as a combined data, it should be showed separately.

Reply 1: We have added our text, table, and figure as advised (see manuscript file, Page 11, line 209-210, table 1 & 3, Figure 1 & 2)

Changes in the text: The radiologic SVs invasion status was classified as abutment in 91 patients, and encasement in 83 patients.

Comments 2: While the 65% of patients in recurrence group were diagnosed as radiological vessel invasion, the number of patients who were diagnosed pathological invasion was only 35%. As authors mentioned, this discrepancy is often observed in clinical. However, in this trial, pathological invasion was not a predictive factor for recurrence. Therefore, authors should describe what factors radiological vessel invasion cases possibly included except pathological vessel invasion (ex. Perineural invasion).

Reply 2: We have added our text as advised (see manuscript file, Page 16-17, line 324-332).

Changes in the text: Kitamura et al. (38) suggested that radiologic and pathologic splenic artery involvement are not consistent because the periarterial plexus is thick, making it difficult for tumors to invade the arterial wall pathologically. According to our study results, although not pathologic SVs invasion, radiologic SVs invasion is a significant predictor of early systemic recurrence. Therefore, radiologic SVs invasion does not only indicate pathologic SVs invasion, but includes other factors affecting prognosis. For example, in present study, a higher perineural invasion was confirmed in patients with radiologic SVs invasion but no pathologic SVs invasion (53/64, 82.8%) than in the entire study cohorts (239/311, 76.8%).

Comments 3: Authors described "did not analyze the splenic artery and splenic vein separately since the study cohort would have been heterogeneously divided into small groups". However, unless both the pathological splenic vessel invasion and radiological splenic vessel invasion are predictive factors, it may be helpful to analyze splenic artery and splenic vein separately even if they are small groups. Please add the information in Table 1 and 3.

Reply 3: We have added our text and table as advised (see manuscript file, Page 11, line 208-209, table 1 & 3).

Changes in the text: Of 174 patients with radiologic SVs invasion, 28 had splenic artery invasion, 55 had splenic vein invasion, and 91 had both.

Comments 4: Around 30% of patients do not have the pathological data regarding vessel invasion. If they were performed distal pancreatectomy, pathological SPA/SPV invasion should be diagnosed in all cases. Authors should add the reason in the manuscript (in pathological evaluation).

Reply 4: We have added the reason that splenic vessels invasion was omitted from the pathologic reports (see manuscript file, Page 8, line 142-145).

Changes in the text: The institution of present study has been obligated to report the presence or absence of SVs invasion in pathologic reports of specimens following distal pancreatectomy since 2012. In previous reports, the presence of SVs invasion was omitted in some cases.

Comments 5: Postoperative complications such as PORF is observed more often in early recurrence group, compared with late recurrence groups. Lately, earlier adjuvant chemotherapy has been reported to be crucial in several cancers. Therefore, please check and add the duration between the surgery to adjuvant chemotherapy in Table 1 and 3. It makes the manuscript more instructive to readers.

Reply 5: We have added our table and text as advised (see manuscript file, Page 12, line 216-219, table 1 & 3)

Changes in the text: Median interval between surgery and adjuvant chemotherapy for the entire cohort was 36.0 days. There was no statistically significant difference in interval

between surgery and adjuvant chemotherapy between the groups.

Comments 6: Please share the information regarding adjuvant chemotherapy and radiotherapy.

Reply 6: We have added our text as advised (see manuscript file, Page 8-9, line 147-159)

Changes in the text: Adjuvant chemotherapy and radiotherapy was determined by the oncologists and radiotherapy-oncologists on the consultation of the pancreatic surgeons. Adjuvant chemotherapy comprising gemcitabine, conventional 5-fluorouracil (5-FU), 5-FU with leucovorin (FL) or capecitabine was administered. Conventional 5-FU chemotherapy consisted of 500 mg/m² for 5 consecutive days for 4weeks. FL chemotherapy consisted of leucovorin 25 mg/m² BSA by 2-hour intravenous infusion, followed by 5-FU 375 mg/m² by bolus intravenous infusion for 5 consecutive days for 4weeks. Gemcitabine chemotherapy consisted of six cycles of either 1000mg/m² intravenous gemcitabine administered once a week for three of every 4 weeks. Oral capecitabine chemotherapy administrated 1250 mg/m² twice daily on days 1–14 of a 21-day cycle, for eight cycles. Three-dimensional conformal radiotherapy consisted of a total dose of 45 Gy (1.8 Gy daily fraction, five fractions per week for 5 weeks), followed by an additional 9 Gy (1.8 Gy daily fraction, five fractions).

Comments minor1: Please correct the number in Figure 1. Given the Table.2, there should be 79 patients in late recurrence group.

Reply minor1: We have modified our figure as advised (see Figure 1).

Changes in the text: Late (>12months) (n=79)

Comments minor2: The title, "Left-side pancreatic ductal adenocarcinoma" should be corrected to "left-sided pancreatic..."

Reply minor2: We have modified our text as advised (see manuscript file, Page1, line 2).

Changes in the text: Impact of radiologic splenic vessel invasion in resectable left-sided pancreatic ductal adenocarcinoma: Predictor of early systemic recurrence following upfront surgery

Reviewer B

Comments 1: Abstract: In the multivariate analysis of prognostic factors, four factors (CA19-9, radiologic splenic vein invasion, positive resection margin, no adjuvant chemotherapy) were independent risk factors. Thus, In terms of biological borderline respectable status, CA19-9 should be included. It might be stated that CA19-9 and radiologic splenic vein invasion are biological borderline respectable status. Among them, however, odds ratio (95%CI) including p-value is the highest in splenic vein invasion. This should be emphasized. Therefore, Odds ration and p-value should be mentioned in the text. If so, your conclusion is reasonable.

Reply 1: We have added odds ratio and p-value in our abstract as advised (see manuscript file, Page 3, line 52-54).

Changes in the text: In multivariable analysis, preoperative CA19-9 ≥ 500 U/mL (Odd ratio [OR] 2.037, p=0.035), radiologic splenic vessels invasion (OR 5.014, p<0.001), positive radial resection margin (OR 2.638, p<0.001), and no adjuvant chemotherapy (OR 2.084, p=0.001) were predictors of an early systemic recurrence.

Comments 2: The following procedure name, “anterior or posterior radical antegrade modular pancreateosplenectomy”, so-called RAMPS anterior or posterior, should be cited by reference (Strasberg, et al).

Reply 2: We have added reference as advised (see manuscript file, Page 7, line 119, and Page 21, line 427-428).

Changes in the text: In selected cases, depending on the degree of tumor invasion, both anterior or posterior radical antegrade modular pancreateosplenectomy (16)

16. Strasberg SM, Drebin JA, Linehan D. Radical antegrade modular pancreateosplenectomy. *Surgery* 2003;133:521-7.

Comments 3: In the explanatory text regarding Table 1, for items with statistically significant differences, the word "significantly" should be added and the specific numerical values

should be stated (as is already the case). On the other hand, for items with no statistically significant differences, it is only necessary to state that there was no significant difference, and there is no need to provide specific numerical values. This is because the text is lengthy and can be understood by looking at Table 1.

In Table 3, the same things are found.

Reply 3: We have modified our text as advised (see manuscript file, Page 10-12, line 202-205, 207-210, 214-216, 231-233, 235-236, 238, and 240-243).

Changes in the text:

There were no statistically significant differences in age, sex, BMI, or Charlson-age comorbidity index between the groups. Preoperative CA19-9 (69.7 vs 29.9 U/mL, $p=0.018$) was significantly higher and the tumor size on preoperative CT (2.89 vs 2.24 cm, $p<0.001$) was significantly larger in patients with recurrence than in those without recurrence. The radiologic SVs invasion and combined adjacent organ resection were significantly more frequent (13.8 vs 2.9%, $p=0.001$) in patients with recurrence than in those without recurrence. For the pathologic results, a higher T-stage (T3-4; 28.2 vs 10.0%, $p=0.002$), higher N-stage (N1-2; 55.2 vs 27.1%, $p<0.001$), lymphovascular invasion (44.4 vs 24.3%, $p=0.002$), perineural invasion (82.2 vs 58.6%, $p<0.001$), and positive radial resection margin (25.7 vs 4.3%, $p<0.001$) were significantly more frequent in patients with recurrence than in those without a recurrence. There were no statistically significant differences in postoperative CA19-9, clinically relevant POPF or postoperative complications between the groups.

Patients' demographics were not significantly differed between the ER and LR groups in terms of age, sex, BMI, or Charlson age-comorbidity index. Preoperative CA19-9 (89.2 vs 36.3 U/mL, $p=0.016$) and CEA (2.4 vs 2.0 ng/mL, $p=0.018$) were significantly higher in the ER group than in the LR group. The tumor size on preoperative CT (3.09 vs 2.49 cm, $p=0.002$) and SUVmax on preoperative FDG-PET (5.4 vs 4.0, $p<0.001$) were significantly larger in the ER group than in the LR group. The presence of SVI on preoperative CT was significantly more common in the ER group (78.4 vs 38.0%, $p<0.001$). Combined adjacent organ resection was performed significantly more frequently in the ER group than in the LR group (13.6 vs 5.1%, $p=0.045$). In terms of the pathologic results, lymphovascular invasion (50.6 vs 31.6%, $p=0.005$) and a positive radial resection margin (29.6 vs 17.7%, $p=0.047$) were significantly more frequent in the ER group than in the LR group. There were no

statistically significant differences in postoperative CA19-9, clinically relevant POPF, or postoperative complications between the groups.

Comments 4: The text regarding Fig. 2 mentions PRS (Fig. 2B) and OS (Fig. 2A) in that order, but Fig. 2 is presented in the opposite order. It is easier to understand if they are aligned.

Reply 4: We have modified our text as advised (see manuscript file, Page 12, line 227-230).

Changes in the text: The median OS in patients with ER (16.1 months, 95% CI 14.7-17.5) was also significantly shorter than in those with LR (39.9 months, 95% CI 33.2-46.6; $p<0.001$). The median PRS in patients with ER (9.6 months, 95% CI 8.6-10.7) was significantly shorter than in those with LR (17.2 months, 95% CI 15.2-19.2; $p<0.001$) (Fig. 4).

Comments 5: According to multivariate analysis, the four factors are identified as independent significance factor for early recurrence. Among them, however, odds ratio (95%CI) including p-value is the highest in splenic vein invasion. This should be emphasized. Therefore, Odds ration and p-value should be mentioned in the text.

Reply 5: We have added odds ratio and p-value in our text as advised (manuscript file, Page 14, line 273-275).

Changes in the text: In a multivariate Cox regression model that included the significant factors identified in the univariate analyses, preoperative CA19-9 ≥ 500 U/ml (Odds ratio [OR] 2.037, $p=0.035$), radiologic SVs invasion (OR 5.014, $p<0.001$), positive radial resection margin (OR 2.638, $p<0.001$), and no adjuvant chemotherapy (OR 2.084, $p=0.001$) were significant predictors of an early systemic recurrence.