



Novel implications of combined arterial resection for locally advanced pancreatic cancer in the era of newer chemo-regimens



Fuminori Sonohara^a, Suguru Yamada^{a,*}, Hideki Takami^a, Masamichi Hayashi^a, Mitsuro Kanda^a, Chie Tanaka^a, Daisuke Kobayashi^a, Goro Nakayama^a, Masahiko Koike^a, Michitaka Fujiwara^a, Tsutomu Fujii^b, Yasuhiro Kodera^a

^a Department of Gastroenterological Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

^b Department of Surgery and Science, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Japan

ARTICLE INFO

Article history:

Accepted 17 May 2019

Available online 22 May 2019

Keywords:

Pancreatic cancer
Artery resection
Preoperative therapy
Prognosis

ABSTRACT

Introduction: In this study, we assessed the prognostic efficacy and feasibility of combined arterial resection (AR) for locally advanced pancreatic cancer (LAPC), and aimed to identify significant prognostic factors for patients who underwent combined AR.

Methods: Between 1981 and 2018, 733 consecutive patients who underwent pancreatic surgery for PC were identified. The 730 cases with detailed information were enrolled in the analysis.

Results: Among 730 resected PC patients, 44 (6%) underwent AR including 21 hepatic (48%), 12 celiac (27%), five splenic (12%), four superior mesenteric (9%), and two other arteries (4%). The combined AR surgery showed significantly longer operative time (median, 608 vs 451 min, $P < 0.0001$), and the incidence of intraoperative blood transfusion was significantly higher in AR than surgery without AR ($P = 0.0002$), whereas there was no significant difference in the intraoperative blood loss (970 vs 1200 mL, $P = 0.2$) and occurrence of major complications ($P = 0.5$). In prognostic analysis of AR cases, multivariate Cox proportional hazard models revealed preoperative and postoperative therapy were the independent factors for both recurrence-free survival (RFS) and overall survival (OS) (preoperative therapy: RFS, HR = 0.21, $P = 0.007$; OS, HR = 0.18, $P = 0.01$; postoperative therapy: RFS, HR = 0.31, $P = 0.003$; OS, HR = 0.19, $P = 0.002$).

Conclusion: This study showed the feasibility of combined AR for LAPC and robust association of pre- and postoperative therapy and survival after AR surgery. Preoperative therapy following combined AR surgery is potentially powerful strategy for LAPC.

© 2019 Elsevier Ltd, BASO ~ The Association for Cancer Surgery, and the European Society of Surgical Oncology. All rights reserved.

Introduction

Pancreatic cancer (PC), comprising primarily of pancreatic ductal adenocarcinoma, remains one of the most lethal

malignancies in the world, currently ranks as the third leading cause of cancer-related death and is estimated to become the second most common cause by 2030 [1]. Although surgically margin-free resection has been considered to be a significantly important prognostic factor for locally advanced pancreatic cancer (LAPC) patients without distant metastasis, the LAPC easily involves main abdominal blood vessels such as portal vein (PV), superior mesenteric vein (SMV), hepatic artery (HA), celiac artery (CA) and superior mesenteric artery (SMA). With recent reports in favour of combined PV resection for LAPC patients, skills needed for PV/SMV resection with concurrent reconstruction are currently considered essential for a pancreatic surgeon [2,3]. In contrast, value of pancreatic resection with combined arterial resection (AR) for LAPC involving main abdominal artery remains to be a matter of debate

Abbreviations: PC, pancreatic cancer; LAPC, locally advanced pancreatic cancer; PV, portal vein; SMV, superior mesenteric vein; HA, hepatic artery; CA, celiac artery; SMA, superior mesenteric artery; AR, arterial resection; UICC, Union for International Cancer Control; CDC, Clavien-Dindo Classification; RFS, recurrence-free survival; OS, overall survival; POPF, postoperative pancreatic fistula; MST, median survival time.

* Corresponding author. Department of Gastroenterological Surgery, Nagoya University Graduate School of Medicine, 65, Tsurumai-cho, Showa-ku, Nagoya, 466-8550, Japan.

E-mail address: suguru@med.nagoya-u.ac.jp (S. Yamada).

<https://doi.org/10.1016/j.ejso.2019.05.019>

0748-7983/© 2019 Elsevier Ltd, BASO ~ The Association for Cancer Surgery, and the European Society of Surgical Oncology. All rights reserved.

even though complete surgical resection achieving sufficient surgical margin is the only hope for long-term survival in patients with LAPC [4].

Recent advances in newer chemotherapeutic regimens such as FOLFIRINOX (comprising of folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin), and GnP (gemcitabine plus nab-paclitaxel) could potentially provide demonstrable efficacy as multidisciplinary treatment modalities, both in the neoadjuvant settings for resectable or borderline-resectable PC, as well as in palliative settings for patients with unresectable PC [5]. Unfortunately, there is still a clear lack of universally acceptable management for LAPC with arterial invasion and clinical features that can robustly predict patients' prognosis after surgery with combined AR. There is a growing demand to fill this gap and develop adequate therapeutic strategy that offer more individualized treatment and, consequently, improved outcome for patients with this lethal disease.

In this study, we retrospectively assessed the feasibility and prognostic efficacy of AR for consecutively resected cases of LAPC. In addition, we sought to discover meaningful prognostic factors that could be used to decide on the indication for AR surgery following administration of preoperative therapy comprising of newly developed drug combinations with or without radiotherapy.

Methods

Patients enrolled in this study

Between July 1981 and June 2018, 733 consecutive patients who underwent pancreatic surgery for PC at the Department of Gastroenterological Surgery, Nagoya University Hospital (Nagoya, Japan) were identified. Written informed consent, as required by the Institutional Review Board, was obtained from all patients to use the anonymized information.

Arterial resection for pancreatic cancer

AR in pancreatic surgery was defined as combined resection of main intraabdominal arteries such as HA, left gastric, celiac, and/or SMA, and resection of splenic artery in pancreaticoduodenectomy and resection of left gastric artery in distal pancreatectomy were also considered as resection of the main abdominal artery in this analysis.

Tumors were categorized as described by the Union for International Cancer Control (UICC) [6]. We employed the definition of the Clavien-Dindo Classification (CDC) to assess postoperative complications and grade IIIa or greater was considered as positive [7].

Perioperative therapy for pancreatic cancer

Preoperative therapy was administered to the patients diagnosed with LAPC with PV invasion or arterial invasion for several months. Patients with unresectable LAPC or unresectable PC with distant metastasis received systemic chemotherapy or chemoradiotherapy for over eight months [8]. As postoperative chemotherapy, gemcitabine and/or S-1 were administered to 464 patients (64%) without contraindication by the patient's condition or for other reasons [9–11].

Statistical analysis

All statistical analyses were performed using R version 3.4.3 (<http://www.r-project.org/>). The recurrence-free survival (RFS) was defined as the time between the resection of PC and confirmation of recurrence. Overall survival (OS) was defined as the time between

the operation and all-cause death. The level of statistical significance was set at $P < 0.05$, which was obtained using two-tailed tests.

Additional information on methods is available in **supplementary materials**.

Results

Patient characteristics and combined arterial resection in pancreatic surgery

In this study, 730 PC patients were enrolled as other three cases do not have information of AR. Patient demographic and clinical characteristics are shown in [Table 1](#). Among 730 resected PC patients, 44 patients (6%) underwent AR during surgery with co-resection of 21 hepatic (48%), 12 celiac (27%), five splenic (12%), four superior mesenteric (9%), and two other arteries (4%). Histogram of number of the patients who underwent AR based on the 10-year period is shown in [Fig. 1A](#). In the period between 2011 and 2018, much more AR surgeries were performed compared to previous decades. The number of AR cases was particularly small during the period between 2001 and 2010 ([Fig. 1A](#)). Distributions of clinicopathological features of the PC patients according to whether AR was performed are shown in [Supplementary Table S1](#). The proportion of female patient was significantly higher among patients who underwent AR ($P = 0.03$). Patients with PC of more advanced T categories and stages were associated with AR and resulted in R1 resection despite more frequent use of preoperative therapy. ($P < 0.0001$, [Supplementary Table S1](#)).

Next, we investigated the impact of AR on operative time, intraoperative blood loss (IOBL), and rate of transfusion during pancreatic surgery ([Fig. 1B–C](#)). The surgery with AR resulted in significantly longer operative time (median, 608 vs 451 min, $P < 0.0001$, [Fig. 1B](#)), reflecting the fact that 18 cases underwent concurrent arterial reconstruction by plastic and reconstructive surgeons. The information of arterial reconstruction was available only in patients who underwent surgery after 2000, among which median operative time of cases with arterial reconstruction was significantly longer than that of cases without reconstruction (median, 618 [range, 411–865] minutes; median, 480 [range, 397–622] minutes, $P = 0.02$). The incidence of intraoperative blood transfusion was significantly higher in AR cases (26/18) than cases without AR (non-AR, 212/474, $P = 0.0002$), and the IOBL was higher in AR cases although not significantly so (median, 970 [range, 9–16,526] mL; median, 1200 [range, 164–17,310] mL, $P = 0.2$). On the other hand the comparison of postoperative morbidity between the AR and non-AR patients ([Fig. 1D](#)) revealed that AR had no significant association with postoperative complications (the CDC grade \geq III, 180/506 vs 9/35, $P = 0.5$). Because postoperative pancreatic fistula (POPF) is the most common and important complication for pancreatic surgery, we compared the incidence of POPF (International Study Group of Pancreatic Fistula, grade \geq B [12]) between AR and non-AR patients and occurrence of POPF did not significantly differ between AR and non-AR (7 vs 15%, $P = 0.41$). These results indicate that AR is technically feasible and could be indicated when it is deemed necessary for R0 resection, pending long-term survival benefits.

Prognosis of pancreatic cancer patients stratified by arterial resection

The survival analysis with 730 PC patients revealed the RFS and OS of AR patients tended to be worse than those of non-AR patients though the difference was not significant (RFS: median survival time [MST], 7.4 vs 11 months, $P = 0.47$; OS: MST, 14 vs 18 months,

Table 1
Patient characteristics (n = 730).

| Characteristics | Value | MV | |
|------------------------------|-------------------------|--|---------------------------------|
| Age (years) | Median (range) | 65 (34–84) | 1 |
| Sex | Female, male | 267(37), 463(63) | |
| BMI | Median (range) | 21.2 (13.2–43.6) | 97 |
| Tumor marker | CEA (ng/mL) | 3.2 (0.4–284) | 219 |
| | CA19-9 (U/mL) | Median (range) | 215 |
| Comorbidities | Ischemic heart disease | -, + | 699(96), 31(4) |
| | DM | -, + | 541(74), 189(26) |
| | Pancreatitis | -, + | 674(92), 56(8) |
| | Hepatitis | -, + | 701(96), 29(4) |
| | Hypertension | -, + | 588(81), 142(19) |
| Main location | Head, body/tail, whole | 556(76), 161(22), 13(2) | |
| Resectability | R,BR,UR | 130(27), 311(63), 49(10) | 240 |
| Pancreatic texture | Hard, soft | 239(43), 323(57) | 168 |
| Operation | Operative time (min) | Median (range) | 63 |
| | Blood loss (mL) | Median (range) | 64 |
| | Type | PD,DP,TP,Others | 497(68), 141(19), 89(12), 30(4) |
| | PV resection | -, + | 309(42), 421(58) |
| | Arterial resection | -, + | 686(94), 44(6) |
| Perioperative transfusion | -, + | 668(92), 62(8) | |
| Peritoneal lavage cytology | -, + | 659(92), 56(8) | 15 |
| T (UICC) | 0,1,2,3,4 | 4(1), 23(3), 15(2), 656(90), 30(4) | 2 |
| N (UICC) | 0,1,2 | 265(36), 460(63), 2(0) | 3 |
| M (UICC) | 0,1 | 626(86), 102(14) | 2 |
| Stage (UICC) | 0,1,2,3,4 | 4(1), 31(4), 570(78), 21(3), 102(14) | 2 |
| Clavien-Dindo classification | 0,I,II,IIIa, IIIb,IVa,V | 424(58), 18(2), 99(14), 165(23), 12(2), 6(1), 6(1) | |
| POPF (ISGPF) | -,BL,B,C | 578(79), 53(7), 90(12), 9(1) | |
| Preoperative therapy | -, + | 633(87), 97(13) | |
| Postoperative therapy | -, + | 260(36), 464(64) | 6 |

Abbreviations: BMI, body mass index; UICC, Union for International Cancer Control; POPF, postoperative pancreatic fistula; ISGPF, International Study Group for Pancreatic Fistula; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; DM, diabetes mellitus; PV, portal vein; R, resectable; BR, borderline resectable; UR, unresectable; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy; MV, missing value.

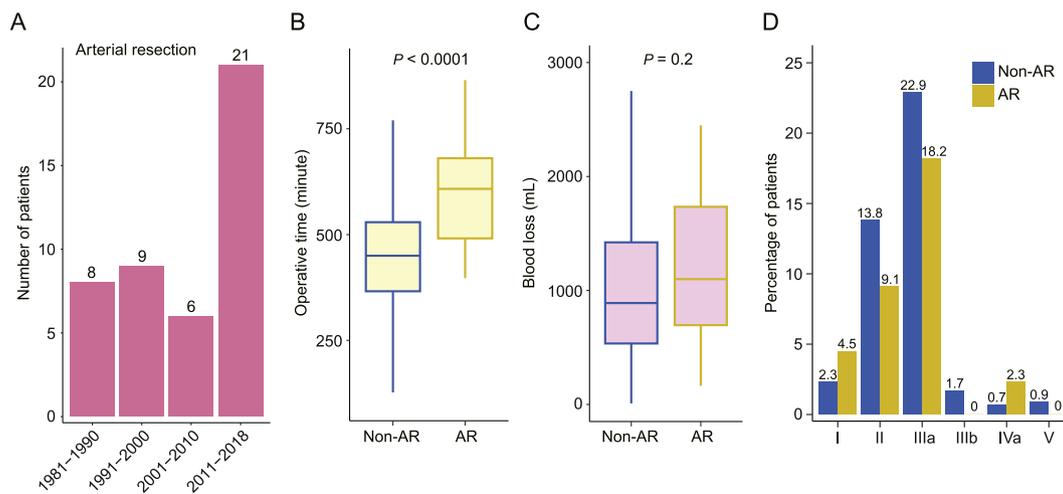


Fig. 1. Combined arterial resection (AR) in surgery for locally advanced pancreatic cancer. (A) Distribution of patients underwent arterial resection according to period of surgery. (B) Operative time according to combined AR. (C) Intraoperative blood loss according to combined AR. (D) Distribution of postoperative complications according to combined AR. Complications are classified using Clavien-Dindo Classification. Non-AR, cases without combined AR.

$P = 0.14$, [Supplementary Figs. S1A and S1B](#)). Next, we performed survival analysis with more recent PC cases (from 2010) considering the advancement of surgical technics as well as more vigorous multidisciplinary approach notably with preoperative therapies using newly developed regimens. According to this analysis, AR cases ($n = 22$) tended to benefit from better prognosis than non-AR cases ($n = 267$) although, again, the difference was not significant (RFS: MST, 19 vs 14 months, $P = 0.16$; OS: MST, over 60 vs 35 months, $P = 0.5$, [Supplementary Figs. S1C and S1D](#)). Distributions of clinicopathological features in the PC patients after 2010 are shown

in [Supplementary Table S2](#). Among AR cases from 2010, there were 19 cases (86%) who underwent preoperative therapy while 78 cases (29%) underwent preoperative therapy in non-AR cases ($P < 0.0001$). There was no significant difference in proportion of patients who received postoperative therapy between the AR and non-AR cases from 2010 ($P = 1$). These facts suggest that the improvement in prognosis among both all PC cases and cases after 2010 may be caused by the more frequent use of preoperative therapy in AR cases ([Supplementary Table S3](#)).

Prognostic factors for patients who underwent combined arterial resection

To discover prognostic factors for patients who underwent AR, we performed the prognostic analysis stratified by the clinical features with the Cox proportional hazard models (Tables 2 and 3). Those analysis identified PV resection (RFS: HR, 2.97; 95%CI, 1.03–8.55; $P = 0.04$, OS: HR, 10.0, 95%CI, 1.36–74.0, $P = 0.02$), status of remnant tumor (RFS: HR, 2.27; 95%CI, 1.10–4.70; $P = 0.03$, OS: HR, 2.71, 95%CI, 1.22–6.01, $P = 0.01$), preoperative therapy (RFS: HR, 0.20; 95%CI, 0.09–0.49; $P = 0.0004$, OS: HR, 0.15, 95%CI, 0.05–0.43, $P = 0.0004$), and postoperative therapy (RFS: HR, 0.24; 95%CI, 0.11–0.50; $P = 0.0001$, OS: HR, 0.13, 95%CI, 0.06–0.32, $P < 0.0001$) as significant factors for both RFS and OS of AR patients (Tables 2 and 3), whereas UICC Stage was a significant factor for OS (HR, 2.32, 95%CI, 1.05–5.09, $P = 0.04$, Table 3). Furthermore, multivariate analysis revealed preoperative and postoperative therapy were the independent factors significantly associated with both RFS and OS (preoperative therapy, RFS: HR, 0.21, 95%CI, 0.06–0.66, $P = 0.007$, OS: HR, 0.18, 95%CI, 0.05–0.66, $P = 0.01$; postoperative therapy, RFS: HR, 0.31, 95%CI, 0.14–0.67, $P = 0.003$, OS: HR, 0.19, 95%CI, 0.07–0.54, $P = 0.002$, Fig. 2A–B). Moreover, the prognostic analysis using Kaplan-Meier method for the prognosis of AR cases stratified by preoperative therapy indicated significant differences in both RFS and OS (RFS: MST, 5.2 vs > 60 months, $P = 0.0001$; OS: MST, 5.5 vs > 60 months, $P < 0.0001$, Fig. 2C–D).

Pathological examination of pancreatic cancer resected by combined arterial resection

Among AR cases, preoperative radiological evaluation revealed that the median rate of tumor shrinkage induced by preoperative therapies was 14% (range, -13–57%). In addition, serum CA19-9 returned to normal levels (<37 U/mL) in nine cases (47%) before surgery and the median rate of pathological tumor regression was 30% (range, 5–100%). The complete resection status of residual tumor was significantly higher in AR cases who treated by preoperative therapies (R0, 89% vs 28%, $P = 0.0002$) and our resected PC cases demonstrated cases with R0 resection can achieve

significantly better prognosis than R1 (RFS: MST, 13 vs 7.2 months, $P < 0.0001$ [log-rank], HR, 2.0, 95%CI, 1.7–2.4; OS: MST, 24 vs 11 months, $P < 0.0001$ [log-rank], HR, 2.3, 95%CI, 1.9–2.8, Supplementary Fig. S2). Despite the relatively high rate of pathological tumor resection, however, pathological evidence of arterial invasion was seen in 10 patients (53%) who underwent preoperative therapy. Among patients after 2010 ($n = 289$), 26 cases (9%) had preoperative imaging of arterial invasion. Four of those 26 cases (15%) underwent pancreatectomy without AR as they did not have the intraoperative findings of arterial invasion. In the end, three of them without AR (75%) were diagnosed as R1 by postoperative pathological examination. Consequently, combined AR was desirable for complete resection of PC suspicious for arterial invasion.

Discussion

In this study, we mainly evaluated prognostic efficacy of AR in LAPC. Because PC with invasion to the major abdominal arteries is generally considered contraindicated for surgery, we firstly evaluated safety of pancreatic surgery with combined AR performed at our department. Our findings suggested although patients who received AR suffered from significantly longer operation time there was no significant increase in the incidence of severe postoperative complications. These findings suggest that AR is feasible for well selected patients with LAPC. In addition, survival analysis revealed recent AR cases had marginally better prognosis than non-AR cases, and further analyses suggested the improvement to be a consequence of preoperative therapy with newly developed chemoregimens. To support those hypotheses, among AR cases, PC patients treated by preoperative therapy has significantly better prognosis than the patients who underwent upfront surgery, and multivariate analysis using Cox proportional hazard models discovered pre- and postoperative therapies were independent prognostic factors for both RFS and OS in LAPC with AR. Thus, for LAPC with arterial invasion, perioperative therapy followed by complete resection with AR could be a promising strategy that warrants further prospective studies.

Currently, according to current NCCN guidelines for LAPC, solid tumor contact with CA and SMA over 180° is considered the main

Table 2
Univariate analysis with cox proportional hazard model for recurrence-free survival.

| Variables | | HR | 95% CI Low | 95% CI High | P |
|------------------------------|-------------------|-------------|-------------|-------------|---------------|
| Age (years) | ≥65 vs < 65 | 1.18 | 0.57 | 2.45 | 0.66 |
| Sex | Male vs female | 0.58 | 0.28 | 1.22 | 0.15 |
| BMI | ≥22 vs < 22 | 0.79 | 0.32 | 1.92 | 0.60 |
| CEA | ≥5 vs < 5 | 0.93 | 0.26 | 3.33 | 0.91 |
| CA19-9 | ≥200 vs < 200 | 1.72 | 0.60 | 4.93 | 0.31 |
| Ischemic heart disease | (+) vs (-) | 3.11 | 0.88 | 11.02 | 0.08 |
| DM | (+) vs (-) | 0.65 | 0.26 | 1.59 | 0.34 |
| Pancreatitis | (+) vs (-) | <0.0001 | 0.00 | Inf | 1.00 |
| Hepatitis | (+) vs (-) | <0.0001 | 0.00 | Inf | 1.00 |
| Hypertension | (+) vs (-) | 0.57 | 0.20 | 1.63 | 0.29 |
| Resectability | R vs BR/UR | 0.71 | 0.16 | 3.16 | 0.65 |
| Operation | PD vs others | 0.78 | 0.38 | 1.60 | 0.50 |
| PV resection | (+) vs (-) | 2.97 | 1.03 | 8.55 | 0.04 |
| Perioperative transfusion | (+) vs (-) | 1.22 | 0.43 | 3.51 | 0.71 |
| Peritoneal lavage cytology | (+) vs (-) | 3.07 | 0.39 | 24.10 | 0.29 |
| Residual tumor | R1 vs R0 | 2.27 | 1.10 | 4.70 | 0.03 |
| Stage (UICC) | III/IV vs I/II | 1.98 | 0.96 | 4.09 | 0.06 |
| Clavien-Dindo classification | ≥3 vs < 3 | 0.40 | 0.14 | 1.14 | 0.09 |
| POPF (ISGPF) | B vs BL | 0.29 | 0.04 | 2.10 | 0.22 |
| Postoperative therapy | (+) vs (-) | 0.24 | 0.11 | 0.50 | 0.0001 |
| Preoperative therapy | (+) vs (-) | 0.20 | 0.09 | 0.49 | 0.0004 |

Abbreviations: BMI, body mass index; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; DM, diabetes mellitus; PV, portal vein; UICC, Union for International Cancer Control; POPF, postoperative pancreatic fistula; ISGPF, International Study Group for Pancreatic Fistula; R, resectable; BR, borderline resectable; UR, unresectable; PD, pancreaticoduodenectomy; HR, hazard ratio; CI, confidence interval; Inf, infinite.

Table 3
Univariate analysis with cox proportional hazard model for overall survival.

| Variables | | HR | 95% CI Low | 95% CI High | P |
|------------------------------|-----------------------|--------------|-------------|--------------|--------------------|
| Age (years) | ≥65 vs < 65 | 1.10 | 0.50 | 2.39 | 0.82 |
| Sex | Male vs female | 0.73 | 0.33 | 1.59 | 0.42 |
| BMI | ≥22 vs < 22 | 0.66 | 0.23 | 1.83 | 0.42 |
| CEA | ≥5 vs < 5 | 0.82 | 0.17 | 3.89 | 0.81 |
| CA19-9 | ≥200 vs < 200 | 0.68 | 0.18 | 2.63 | 0.57 |
| Ischemic heart disease | (+) vs (-) | 1.93 | 0.57 | 6.55 | 0.29 |
| DM | (+) vs (-) | 0.49 | 0.17 | 1.42 | 0.19 |
| Pancreatitis | (+) vs (-) | <0.0001 | 0.00 | Inf | 1.00 |
| Hepatitis | (+) vs (-) | <0.0001 | 0.00 | Inf | 1.00 |
| Hypertension | (+) vs (-) | 0.42 | 0.13 | 1.41 | 0.16 |
| Resectability | R vs BR/UR | 0.90 | 0.19 | 4.27 | 0.90 |
| Operation | PD vs others | 0.74 | 0.34 | 1.59 | 0.44 |
| PV resection | (+) vs (-) | 10.02 | 1.36 | 74.03 | 0.02 |
| Perioperative transfusion | (+) vs (-) | 1.44 | 0.49 | 4.22 | 0.51 |
| Peritoneal lavage cytology | (+) vs (-) | 3.42 | 0.43 | 27.16 | 0.24 |
| Residual tumor | R1 vs R0 | 2.71 | 1.22 | 6.01 | 0.01 |
| Stage (UICC) | III/IV vs I/II | 2.32 | 1.05 | 5.09 | 0.04 |
| Clavien-Dindo classification | ≥3 vs < 3 | 0.36 | 0.11 | 1.19 | 0.09 |
| POPF (ISGPF) | B vs BL | 0.33 | 0.04 | 2.41 | 0.27 |
| Postoperative therapy | (+) vs (-) | 0.13 | 0.06 | 0.32 | < 0.0001 |
| Preoperative therapy | (+) vs (-) | 0.15 | 0.05 | 0.43 | 0.0004 |

Abbreviations: BMI, body mass index; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; DM, diabetes mellitus; PV, portal vein; UICC, Union for International Cancer Control; POPF, postoperative pancreatic fistula; ISGPF, International Study Group for Pancreatic Fistula; R, resectable; BR, borderline resectable; UR, unresectable; PD, pancreaticoduodenectomy; HR, hazard ratio; CI, confidence interval; Inf, infinite.

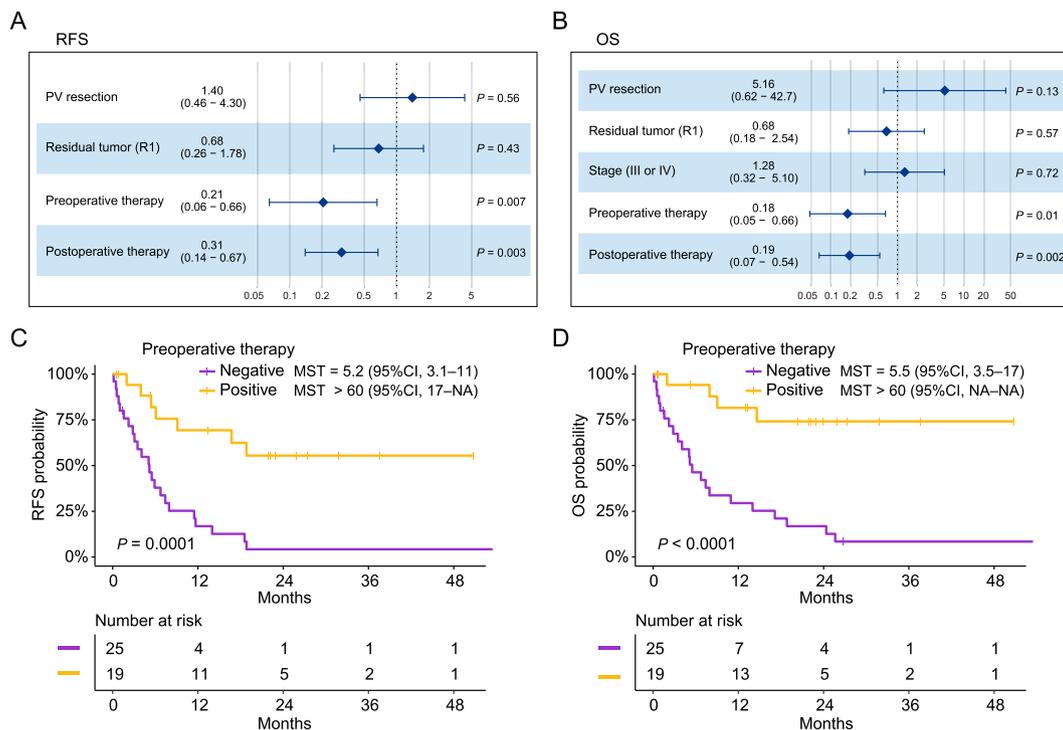


Fig. 2. Prognostic factors for the PC patients who underwent combined arterial resection (AR) in pancreatic resection. (A) Multivariate analysis of clinical features significantly associated with recurrence-free survival (RFS) of AR cases using Cox proportional hazard models. (B) Multivariate analysis of clinical features significantly associated with overall survival (OS) of AR cases using Cox proportional hazard models. (C) RFS of AR cases stratified by preoperative therapy. (D) OS of AR cases stratified by preoperative therapy.

criterion defining unresectable disease, while invasion to the common HA that allows for safe and complete resection and reconstruction is classified as borderline resectable [13]. However, the detailed definition and description for resectability of LAPC has been under frequent revision. In the past, combined AR for LAPC had not been considered acceptable, because pancreatotomy with concomitant AR for PC had been reported to be associated with increased postoperative complications with little, if any, survival benefit [14,15]. Thus, LAPC involving main abdominal arteries such

as HA, CA, and SMA used to be considered a marginal contra-indication to surgical resection [16]. Recently, several reports of a relatively small number of patients who underwent combined AR with distal pancreatectomy for pancreatic body and tail cancer, combined common hepatic arterial resection with pancreaticoduodenectomy or total pancreatectomy for pancreatic head cancer [17–20] support extended surgery for LAPC. Newest guidelines also describes the combined HA or CA resection as one of the putative options for LAPC [13]. However, combined AR is still

considered as potential risks of intra and postoperative complications, including excessive IOBL that calls for intraoperative transfusion [21]. Consequently, the place for combined AR in pancreatic surgery has not yet been fully established.

Recently, preoperative therapy has been delivered widely for both resectable and borderline resectable PC [22]. This trend is attributed largely to the current NCCN guidelines [13], and increasing body of evidence supports feasibility and efficacy of this treatment strategy [23–25]. In addition, preoperative therapy for unresectable disease has in no small measure been supported by availability of newly developed chemotherapy or concurrent chemoradiotherapy regimens [8,26–28]. Early studies on preoperative therapy for PC raised concerns over whether preoperative therapy increase postoperative complications or mortality [29,30]. In contrast, a growing number of recent studies have reported that preoperative therapy for PC is safe, with no significant increase in overall morbidity or mortality, despite evidence for more advanced disease [25,31]. In addition, several reports suggested the preoperative chemotherapy is associated with lower rate of POPF [24,32]. In terms of complications related to pancreatic surgery, POPF is worthy of additional attention because it can cause severe problems including postoperative aneurysm of the abdominal artery and hemorrhage resulting in mortality [33]. The effect of preoperative therapy to decrease the rate of POPF might be favourable for early postoperative morbidity and mortality. Although the optimal duration of preoperative therapy is unclear, the current study at least suggests that the preoperative therapy for LAPC is safe and AR is likely to be essential for achieving better prognosis.

There are several inherent limitations in this study. Firstly, this study is based on retrospective single-institutional clinical information obtained from Japan. Secondly, due to the limitation of the information availability, we were not able to perform the analysis specific to each preoperative regimen and the optimal regimens and duration of preoperative therapy prior to combined AR surgery is still unknown. Thus, confirmation of the benefit of AR for LAPC patients along with optimal preoperative treatment strategy should be made by future prospective trials.

In conclusion, this study showed the robust association of preoperative therapy for cases that underwent combined AR in pancreatic surgery for PC. Combined AR with concurrent arterial reconstruction is a potentially powerful and feasible approach for well-selected patients with LAPC involving main abdominal arteries after an appropriate preoperative therapy.

Disclosures

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejso.2019.05.019>.

References

- [1] Rahib L, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 2014;74:2913–21.
- [2] Yekebas EF, et al. En bloc vascular resection for locally advanced pancreatic malignancies infiltrating major blood vessels: perioperative outcome and long-term survival in 136 patients. *Ann Surg* 2008;247:300–9.
- [3] Ravikumar R, et al. Portal vein resection in borderline resectable pancreatic cancer: a United Kingdom multicenter study. *J Am Coll Surg* 2014;218:401–11.
- [4] Mitra A, et al. Extended pancreatectomy as defined by the ISGPS: useful in selected cases of pancreatic cancer but invaluable in other complex pancreatic tumors. *Langenbeck's Arch Surg* 2018;403:203–12.
- [5] Gourgou-Bourgade S, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. *J Clin Oncol : Off. J. Am. Soc. Clin. Oncol.* 2013;31:23–9.
- [6] Leslie H, Sobin MKG, Christian Wittekind, editors. *TNM classification of malignant tumours*, seventh ed. Wiley-Blackwell.
- [7] Clavien PA, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009;250:187–96.
- [8] Satoi S, et al. Role of adjuvant surgery for patients with initially unresectable pancreatic cancer with a long-term favorable response to non-surgical anti-cancer treatments: results of a project study for pancreatic surgery by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. *J. Hepatobiliary Pancreatol. Sci.* 2013;20:590–600.
- [9] Oettle H, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *Jama* 2013;310:1473–81.
- [10] Uesaka K, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). *Lancet* 2016;388:248–57.
- [11] Murakami Y, et al. Adjuvant gemcitabine plus S-1 chemotherapy after surgical resection for pancreatic adenocarcinoma. *Am J Surg* 2008;195:757–62.
- [12] Bassi C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years after. *Surgery* 2017;161:584–91.
- [13] Network NCC. *NCCN clinical practice guidelines in oncology (NCCN Guidelines)*. NCCN; 2017.
- [14] Mollberg N, et al. Arterial resection during pancreatectomy for pancreatic cancer: a systematic review and meta-analysis. *Ann Surg* 2011;254:882–93.
- [15] Ouaisi M, et al. Vascular resection during radical resection of pancreatic adenocarcinomas: evolution over the past 15 years. *J. Hepatobiliary Pancreatol. Sci.* 2014;21:623–38.
- [16] Tempero MA, et al. Pancreatic adenocarcinoma, version 2.2014: featured updates to the NCCN guidelines. *J Natl Compr Cancer Netw : J Natl Compr Cancer Netw* 2014;12:1083–93.
- [17] Gagandeep S, et al. Extended pancreatectomy with resection of the celiac axis: the modified Appleby operation. *Am J Surg* 2006;192:330–5.
- [18] Hartwig W, et al. Outcomes after extended pancreatectomy in patients with borderline resectable and locally advanced pancreatic cancer. *Br J Surg* 2016;103:1683–94.
- [19] Miyazaki M, et al. Combined hepatic arterial resection in pancreatic resections for locally advanced pancreatic cancer. *Langenbeck's Arch Surg* 2017;402:447–56.
- [20] Sato T, et al. Distal pancreatectomy with celiac Axis resection combined with reconstruction of the left gastric artery. *J Gastrointest Surg : Off. J. Soc. Surg. Aliment Tract* 2017;21:910–7.
- [21] Beane JD, et al. Pancreatoduodenectomy with venous or arterial resection: a NSQIP propensity score analysis. *HPB* 2017;19:254–63.
- [22] Unno M, et al. Long-term outcome following neoadjuvant therapy for resectable and borderline resectable pancreatic cancer compared to upfront surgery: a meta-analysis of comparative studies by intention-to-treat analysis. *Surg Today* 2019;49:295–9.
- [23] Cooper AB, et al. Does the use of neoadjuvant therapy for pancreatic adenocarcinoma increase postoperative morbidity and mortality rates? *J Gastrointest Surg : Off. J. Soc. Surg. Aliment Tract* 2015;19:80–6. discussion 6–7.
- [24] Denbo JW, et al. Preoperative chemoradiation for pancreatic adenocarcinoma does not increase 90-day postoperative morbidity or mortality. *J Gastrointest Surg : Off. J. Soc. Surg. Aliment Tract* 2016;20:1975–85.
- [25] Czosnyka NM, et al. Pancreatic adenocarcinoma: effects of neoadjuvant therapy on post-pancreatectomy outcomes - an American College of Surgeons National Surgical Quality Improvement Program targeted variable review. *HPB* 2017;19:927–32.
- [26] Hackert T, et al. Locally advanced pancreatic cancer: neoadjuvant therapy with folirinix results in resectability in 60% of the patients. *Ann Surg* 2016;264:457–63.
- [27] Yamada S, et al. Phase I study of chemoradiotherapy using gemcitabine plus nab-paclitaxel for unresectable locally advanced pancreatic cancer. *Cancer Chemother Pharmacol*; 2018.
- [28] Cheng Z, et al. Improving prediction of surgical resectability over current staging guidelines in patients with pancreatic cancer who receive stereotactic body radiation therapy. *Adv. Radiat. Oncol.* 2018;3:601–10.
- [29] Allendorf JD, et al. Neoadjuvant chemotherapy and radiation for patients with locally unresectable pancreatic adenocarcinoma: feasibility, efficacy, and survival. *J Gastrointest Surg : Off. J. Soc. Surg. Aliment Tract* 2008;12:91–100.
- [30] Laurence JM, et al. A systematic review and meta-analysis of survival and surgical outcomes following neoadjuvant chemoradiotherapy for pancreatic cancer. *J Gastrointest Surg : Off. J. Soc. Surg. Aliment Tract* 2011;15:2059–69.
- [31] Marchegiani G, et al. Neoadjuvant therapy versus upfront resection for pancreatic cancer: the actual spectrum and clinical burden of postoperative complications. *Ann Surg Oncol* 2018;25:626–37.
- [32] Sho M, et al. Pathological and clinical impact of neoadjuvant chemoradiotherapy using full-dose gemcitabine and concurrent radiation for resectable pancreatic cancer. *J. Hepatobiliary Pancreatol. Sci.* 2013;20:197–205.
- [33] Lee JH, et al. Clinical features and management of pseudoaneurysmal bleeding after pancreatoduodenectomy. *Am Surg* 2012;78:309–17.