detection of PR/CR and surgical resection was 127 days (8–1335). Forty-six of 52 patients with available value of any tumor marker showed a decrease in the level of tumor marker before surgical resection, and only four patients had an increase, relative to the pre-initial treatment level.

The control group included 43 patients judged to have unresectable disease on laparotomy (18 locally unresectable, 13 peritoneal dissemination, 10 liver metastasis, and 2 distant lymph node metastasis), and 58 patients who did not undergo surgical resection because of either unchanged unresectability, a poor performance status, and/or the patients' or surgeons' wishes. Thirty-seven of 58 patients had SD on RECIST, and 21 patients had PR (8 distant organ metastases and 13 locally advanced tumors; Table 1).

There were significant differences in the age, presence of peritoneal metastasis, tumor size, concomitant use of radiotherapy, and frequency of PR/CR between the adjuvant surgery and control groups ($p < 0.05$).

## Surgical background and post-operative complications in the adjuvant surgery group

The median time from initial therapy to surgical resection was 274 days (182–1418). Concomitant resections of other organs were performed in 40 patients (69 %; Table 2). As shown in Table 2, 23 patients underwent portal vein resection. The superior mesenteric artery, celiac axis and common hepatic artery were concomitantly resected in 1, 10, and 2 patients, respectively. There were 11 adrenal resections, 5 liver resections, 2 liver biopsies, and 2 colon resections. Post-operative mortality and morbidity are summarized in Table 3. There was no incidence of aspiration pneumonia, myocardial infarction, cerebral infarction, or pulmonary thrombosis.

## Pathological findings in the adjuvant surgery group

Five of the 13 patients with liver metastases underwent surgical resection for metastatic lesions and two patients underwent liver biopsies. No liver tumors were found during surgery in the residual 6 patients with liver metastases. One patient had peritoneal metastasis diagnosed on computed tomography scan which was not found during surgical resection of the primary tumor. A pathological evaluation was done in 55 patients according to the Evans classification, and showed Grade I ($n = 17$), IIa (16), IIb (10), III (5), and IV (7). Pathological CR was found in 7 patients who had 5 locally advanced tumors, 1 para-aortic lymph node metastasis, and 1 liver metastasis. The 17 patients with distant organ metastases underwent R0 ($n = 12$), R1 ($n = 4$), and R2 ($n = 1$) resection, and 41 patients with locally advanced tumor had R0 ($n = 36$) and R1 ($n = 5$).

**Table 3** Post-operative mortality and morbidity

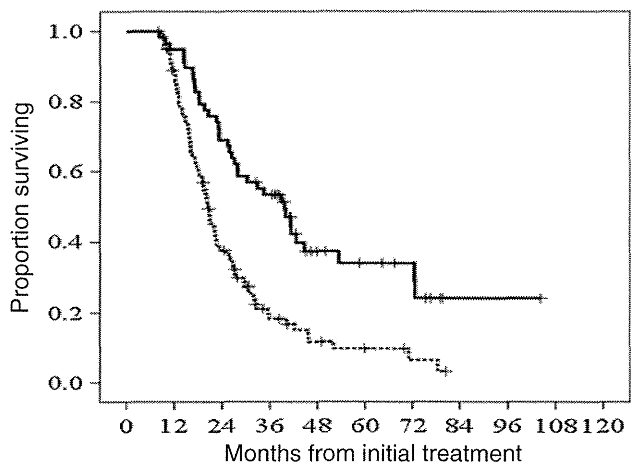
| | |
|---|---|
| In-hospital mortality: 1/58 (1.7 %) | |
| Morbidity | |
| Post-operative pancreatic fistula: 10 (17 %) | |
| Delayed gastric emptying: 4 (7 %) | |
| Post-pancreatectomy hemorrhage: 2 (3 %) | |
| Intra-abdominal abscess or infection: 12 (21 %) | |
| Wound dehiscence: 9 (16 %) | |
| Bile leakage: 2 (3 %) | |
| Deep vein thrombosis: 2 (3 %) | |
| Superior mesenteric artery thrombosis: 1 (2 %) | |

## Survival analysis in the adjuvant surgery and control groups

The median observation period was 51 months (20–122) in the control group. The overall survival rates at 1, 3, and 5 years in the control group were 88, 18, and 10 %, respectively, and the median survival time was 20.8 months. The median observation and post-operative observation periods in the adjuvant surgery group were 54 months (26–125) and 41 months (18–117), respectively. The overall survival rates at 1, 3, and 5 years were 95, 53, and 34 %, respectively, and the median survival time was 39.7 months. The overall survival rates after surgical resection at 1, 3, and 5 years were 76, 33, and 29 %, respectively, and the median survival time was 25 months. Figure 1 demonstrates that the survival curve in the adjuvant surgery group was significantly better than that in the control group ($p < 0.0001$). Five-year survival was observed in 9 patients in the adjuvant surgery group, and 4 patients in the control group. A multivariate analysis showed only a longer period of initial treatments to be a significant independent factor associated with survival in the adjuvant surgery group (Table 4). The disease-free survival rates at 1, 3, and 5 years were 54, 30, and 30 %, respectively. The primary site of recurrence was detected in a distant organ ($n = 21$; liver 11, lung 4, peritoneum 6, and liver and peritoneum 1) and in the loco-regional area ($n = 15$). One patient had an unknown site of recurrence. Twenty-one patients did not have any recurrence of disease. There was no significant difference in the primary site of recurrence and disease-free survival curve associated with the reason for unresectability.

## Univariate and multivariate Cox proportion-hazard model analyses for overall survival in all patients

Table 5 shows metastatic disease, an increase in tumor marker, dose of gemcitabine <28 g, and stable disease on RECIST each increased the risk of death relative to those without the respective risk characteristics (hazard ratio range 1.209–1.800, all $p < 0.05$). Data were further stratified by known clinical predictors of survival, and adjuvant surgery was protective and statistically significant among each risk group. A multivariate analysis using clinical predictors obtained by univariate analysis showed that the adjuvant surgery group, a decrease of tumor markers during non-surgical anti-cancer treatments, dose of gemcitabine (≤28 g), and RECIST evaluation (PR/CR) were significant favorable factors for survival (Table 6).




| | 1y | 2y | 3y | 4y | 5y | death |
|---|---|---|---|---|---|---|
| Adjuvant surgery (n=58) | | | | | | |
| OS (%) | 95 | 69 | 53 | 37 | 34 | 37/58 |
| Patient at risk | 55 | 40 | 30 | 12 | 8 | |
| Control (n=101) | | | | | | |
| OS | 88 | 38 | 18 | 12 | 10 | 83/101 |
| Patient at risk | 85 | 35 | 13 | 7 | 4 | |

**Fig. 1** Comparison of the overall survival curves between the adjuvant surgery (*solid line*) and control groups (*broken line*). The overall survival rates at 1, 3, and 5 years were 95, 53, and 34 % in the adjuvant surgery group, and 88, 18, and 10 % in the control group, respectively, and the median survival time was 39.7 months in the adjuvant surgery group and 20.8 months in the control group. The survival curve in the adjuvant surgery group was significantly better than that in the control group ($p < 0.0001$)

Cox proportion-hazard model analysis stratified over the propensity score

Propensity scores were calculated using multivariate logistic regression with calculation of the conditional probabilities for the adjuvant surgery group to adjust for the significant differences in the clinical backgrounds between two groups. A Cox proportional-hazard model analysis stratified over the propensity score was performed to account for the non-randomized provision of adjuvant surgery. Table 7 demonstrates that the adjuvant surgery group was a significant independent prognostic variable with an adjusted hazard ratio (95 % confidence interval) of 0.569 (0.36–0.89).

Optimal timing of adjuvant surgery in this study

Figure 2a shows that the longer the duration of the initial treatment prior to surgical resection, the longer the survival time. Figure 2b shows comparisons of the survival curves of adjuvant surgery according to the time from the initial treatment to surgical resection; group A, over 365 days after the initial treatment ($n = 12$); group B, between 241 and 365 days ($n = 26$); group C, between 180 and 240 days after initial treatment ($n = 20$); control group (group D, $n = 101$). Although there was no difference in the survival curves between groups C and D ($p = 0.795$), significant differences were found in the survival curve between groups B and C or D ($p < 0.0001$), and between groups A and B, C, or D ($p < 0.005$). The overall survival rate in group A + B was statistically better than in group C ($p < 0.0001$). There was no difference in the primary site of recurrence (60 % distant organ metastasis and 40 % loco-regional recurrence) between groups A + B and C.

## Discussion

A multicenter survey organized by JSHBPS collected 159 initially unresectable pancreatic cancer patients with

**Table 4** Univariate and multivariate analyses for overall survival in the adjuvant surgery group

| Parameter | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | Hazard ratio (95 % CI) | $p$ value | Hazard ratio (95 % CI) | $p$ value |
| <240 days vs. ≥ 240 days until operation | 0.237 (0.118–0.473) | <0.0001 | 0.332 (0.150–0.734) | 0.006 |
| Negative vs. positive LN metastasis | 0.487 (0.243–0.947) | 0.042 | 0.547 (0.264–1.132) | 0.104 |
| Dose of gemcitabine (≤28 g vs. >28 g) | 0.399 (0.202–0.785) | 0.008 | 0.603 (0.275–1.321) | 0.206 |

*CI* confidence interval, *LN* lymph node

**Table 5** Univariate Cox proportional-hazard analysis for overall survival: association between overall survival and patient, tumor, and treatment characteristics

| Variable | No. (%) Ad vs. CTR | MST (months) Ad vs. CTR | 2-year OS (%) Ad vs. CTR | 5-year OS (%) Ad vs. CTR | Estimate | SE | *P* | Hazard ratio (95 % CI) |
|---|---|---|---|---|---|---|---|---|
| Group | 58 vs. 101 | 39.7 vs. 20.8 | 69 vs. 38 | 34 vs. 10 | −0.862 | 0.202 | <0.0001 | 0.422 (0.284–0.627) |
| Sex | | | | | −0.165 | 0.289 | 0.385 | 0.848 (0.585–1.230) |
| Male | 37 vs. 59 | 34 vs. 20 | 76 vs. 36 | 56 vs. 9 | | | | |
| Female | 21 vs. 42 | 72 vs. 21 | 65 vs. 39 | 20 vs. 10 | | | | |
| Age | | | | | 0.010 | 0.010 | 0.321 | 1.010 (0.990–1.030) |
| <65 years | 38 vs. 51 | 40 vs. 21 | 69 vs. 40 | 34 vs. 12 | | | | |
| ≥65 years | 20 vs. 50 | 34 vs. 20 | 70 vs. 36 | 36 vs. 14 | | | | |
| Reason for UN | | | | | 0.379 | 0.186 | 0.041 | 1.461 (1.016–2.102) |
| Met | 17 vs. 45 | 39 vs. 19 | 77 vs. 33 | 30 vs. 6 | | | | |
| LA | 41 vs. 56 | 41 vs. 22 | 66 vs. 41 | 40 vs. 13 | | | | |
| Peritoneal met | | | | | 0.256 | 0.131 | 0.052 | 1.291 (0.998–1.671) |
| Presence | 1 vs. 17 | 15 vs. 20 | 0 vs. 35 | 0 vs. 12 | | | | |
| None | 57 vs. 84 | 40 vs. 21 | 70 vs. 38 | 35 vs. 9 | | | | |
| Tumor size | | | | | 0.210 | 0.183 | 0.253 | 1.233 (0.861–1.766) |
| <34 mm | 37 vs. 44 | 40 vs. 20 | 62 vs. 37 | 28 vs. 16 | | | | |
| ≥34 mm | 21 vs. 57 | 41 vs. 21 | 81 vs. 38 | 45 vs. 5 | | | | |
| Tumor location | | | | | 0.224 | 0.184 | 0.224 | 1.250 (0.872–1.793) |
| Ph | 31 vs. 50 | 41 vs. 21 | 74 vs. 45 | 34 vs. 10 | | | | |
| Pbt | 27 vs. 51 | 28 vs. 20 | 63 vs. 30 | 33 vs. 10 | | | | |
| Tumor marker | | | | | 0.868 | 0.395 | 0.028 | 2.382 (1.098–5.165) |
| Decrease or no tumor marker | 54 vs. 97 | 40 vs. 21 | 72 vs. 39 | 35 vs. 13 | | | | |
| Increase | 4 vs. 4 | 18 vs. 13 | 25 vs. 0 | 0 vs. 0 | | | | |
| Chemotherapy | | | | | 0.152 | 0.305 | 0.618 | 1.165 (0.64–2.119) |
| GEM base | 53 vs. 89 | 39 vs. 20 | 66 vs. 39 | 33 vs. 8 | | | | |
| Others | 5 vs. 12 | 43 vs. 16 | 80 vs. 30 | 40 vs. 20 | | | | |
| Dose of GEM | | | | | 0.588 | 0.185 | 0.001 | 1.800 (1.253–2.586) |
| <28 g | 29 vs. 51 | 28 vs. 18 | 55 vs. 20 | 18 vs. 9 | | | | |
| ≥28 g | 29 vs. 50 | 53 vs. 26 | 83 vs. 54 | 48 vs. 7 | | | | |
| Dose of S-1 | | | | | 0.131 | 0.184 | 0.476 | 1.140 (0.796–1.633) |
| <5600 mg | 32 vs. 49 | 28 vs. 22 | 59 vs. 45 | 39 vs. 13 | | | | |
| ≥5600 mg | 26 vs. 52 | 40 vs. 20 | 81 vs 31 | 34 vs. 7 | | | | |
| Radiotherapy | | | | | 0.280 | 0.210 | 0.184 | 1.323 (0.876–1.998) |
| None | 32 vs. 82 | 41 vs. 20 | 78 vs. 40 | 31 vs. 4 | | | | |
| Done | 26 vs. 19 | 27 vs. 21 | 58 vs. 29 | 37 vs. 23 | | | | |
| TNM | | | | | −0.548 | 0.285 | 0.055 | 0.578 (0.331–1.012) |
| II | 10 vs. 14 | 53 vs. 27 | 80 vs. 55 | 40 vs. 25 | | | | |
| III/IV | 48 vs. 87 | 39 vs. 20 | 67 vs. 32 | 35 vs. 7 | | | | |
| RECIST | | | | | 0.668 | 0.186 | <0.0001 | 1.950 (1.355–2.806) |
| SD | 12 vs. 61 | 20 vs. 20 | 42 vs. 33 | 25 vs. 4 | | | | |
| CR/PR | 46 vs. 40 | 41 vs. 22 | 76 vs. 44 | 36 vs. 17 | | | | |

*MST* median survival time, *OS* overall survival rate, *SE* standard error, *CI* confidence interval, *Ad* adjuvant surgery group, *CTR* control group, *Surg* surgery, *UN* unresectability, *met* metastasis, *Ph* pancreas head, *Pbt* pancreas body and tail, *CA19-9* carbohydrate antigen 19-9, *GEM* gemcitabine, *RECIST* Response Evaluation Criteria In Solid Tumors, *CR* complete response, *PR* partial response, *SD* stable disease

**Table 6** Multivariate Cox proportional-hazard analysis for overall survival

| Variable | Estimate | SE | *P* | Hazard ratio (95 % CI) |
|---|---|---|---|---|
| Adjuvant surgery vs. control | −0.757 | 0.233 | 0.001 | 0.469 (0.297–0.741) |
| Dose of gemcitabine (≤28 g vs. >28 g) | −0.598 | 0.190 | 0.002 | 0.550 (0.379–0.798) |
| Tumor marker (decrease or no tumor marker vs. increase) | 0.944 | 0.420 | 0.025 | 2.570 (1.128–5.855) |
| RECIST (SD vs. CR/PR) | 0.484 | 0.199 | 0.015 | 1.623 (1.099–2.395) |
| Tumor size (<34 mm vs. ≥34 mm) | 0.034 | 0.195 | 0.862 | 1.035 (0.706–1.517) |
| Reason for unresectability (met vs. locally advanced) | 0.332 | 0.223 | 0.136 | 1.394 (0.901–2.158) |
| TNM (III/IV vs. II) | −0.396 | 0.302 | 0.189 | 0.673 (0.372–1.216) |
| Peritoneal metastasis or not | −0.047 | 0.309 | 0.880 | 0.954 (0.521–1.749) |

*RECIST* Response Evaluation Criteria In Solid Tumors, *CI* confidence interval, *CR* complete response, *PR* partial response, *SD* stable disease, *met* distant organ metastasis

**Table 7** Propensity-score adjusted stratified multivariate Cox proportional-hazard analysis

| Variable | Estimate | SE | *P* | Hazard ratio (95 % CI) |
|---|---|---|---|---|
| Ad surg vs. control | −0.563 | 0.229 | 0.01 | 0.569 (0.36–0.89) |
| Propensity score | | | | |
| 2nd 25 % vs. Lowest 25 % | −0.159 | 0.249 | 0.52 | 0.853 (0.52–1.39) |
| 3rd 25 % vs. Lowest 25 % | −0.933 | 0.291 | <0.01 | 0.393 (0.22–0.70) |
| Highest 25 % vs. Lowest 25 % | −0.727 | 0.293 | 0.01 | 0.483 (0.27–0.86) |

*CI* confidence interval, *Ad surg* adjuvant surgery

favorable response to non-surgical anti-cancer treatments over 6 months after the initial treatment between 2001 and 2009. Fifty-eight patients underwent "adjuvant surgery", and the residual 101 patients who did not undergo adjuvant surgery served as a control group. The first clinical question of this survey was whether the addition of adjuvant surgery is safe treatment. The surgical mortality and morbidity in this study were 1.7 and 47 %, respectively, which was similar to the previous reports in initially resectable pancreatic cancer patients [17, 18], in spite of a more extensive/aggressive surgical approach (69 % of combined organ or vascular resection rate in this study). The second clinical question of this survey was whether additional adjuvant surgery is an effective treatment. Surprisingly, the overall survival rates at 1, 3, and 5 years from the initial treatment were 95, 53, and 34 %, respectively, in this highly selected group of patients, under a median observation period of 54 months (26–125), which was significantly better than those (88, 18, and 10 %) in the control group. The unadjusted and propensity-score adjusted stratified multivariate analyses showed adjuvant surgery to be a significant independent factor for overall survival. Furthermore, favorable survival rates were observed among all risk-stratified subgroups with the addition of adjuvant surgery.

Appropriate surgical management for the patients with initially unresectable pancreatic cancer is less clear. There are some reports from several groups on the use of chemo(radio)therapy to downstage unresectable pancreatic cancer to resectable disease [19–23]. They reported that the median survival time after surgery in these patients with unresectable tumor at presentation is 23.6 months [11, 19–24]. These results appear to be at least comparable to those reported with surgery alone or surgery plus postoperative adjuvant treatment in resectable patients [12]. The Memorial Sloan–Kettering Cancer Center (MSKCC) group reported that 36 patients who were able to undergo surgical resection following treatment of initial stage III pancreatic cancer experienced survival similar to those who were initially resectable as a matched control [24]. The current study found that the longer the median time from the initial therapy to surgical resection, the longer the median postoperative follow-up, and the higher the frequency of concomitant vascular resection, relative to the results from the MSKCC group. A major difference from the previous reports in this study is the investigation of the clinical safety and efficacy of adjuvant surgery in this highly selected group of patients in comparison to patients who did not undergo adjuvant surgery.

This study definitively selected patients at the initial detection of progressive disease during multimodal treatment over 6 months, and at the detection of occult distant organ metastasis during surgical exploration. Moreover, any patients with a poor functional status were also excluded in the process of non-surgical anticancer treatments. Therefore, 58 patients in the adjuvant surgery group were regard as "super-responders" to non-surgical anticancer treatments. This retrospective patient selection is one of the limitations of this study. The other limitation is

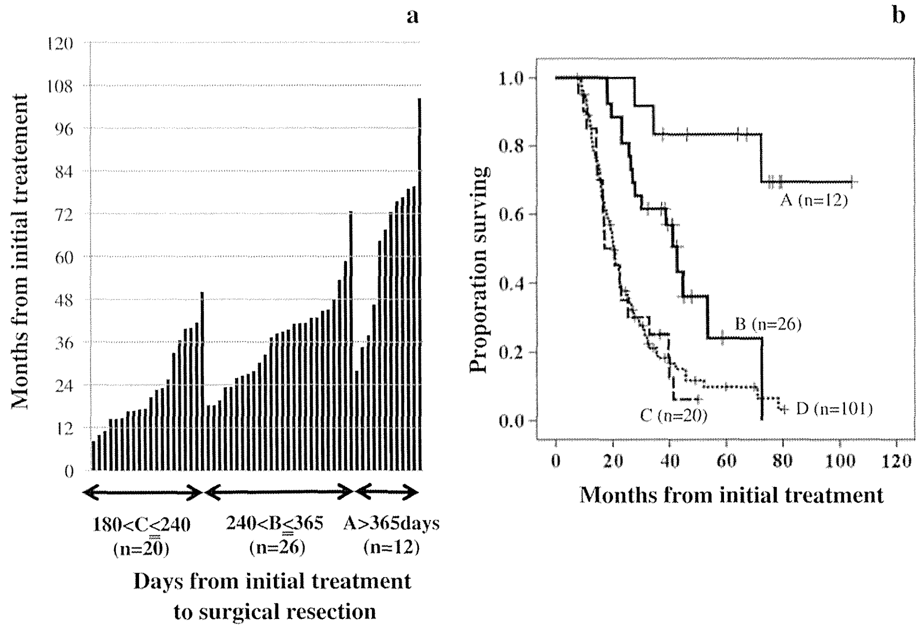



**Fig. 2** Survival time and curves according to time from initial treatment to surgical resection. **a** Survival time in each patient. Group A, 12 patients who underwent adjuvant surgery more than 365 days after initial treatment; Group B, 26 patients who underwent adjuvant surgery between 241 and 365 days; Group C, 20 patients who underwent adjuvant surgery between 180 and 240 days. **b** Comparisons of the survival curves of adjuvant surgery more than 365 days after the initial treatment [$n = 12$, group A, median survival time (MST) not reached], between 241 and 365 days ($n = 26$, group B, MST 43 months), between 180 and 240 days after initial treatment ($n = 20$, group C, MST 17 months), and the control group ($n = 101$, group D, MST 20 months). Although there was no difference in the survival curves between groups C and D ($p = 0.795$), significant differences were found in the survival curve between groups B and C or D ($p < 0.0001$), and between groups A and B, C, or D ($p < 0.005$). The overall survival rate in group A + B was significantly better than in group C ($p < 0.0001$). The dose of gemcitabine and S-1, and the tumor diameter, in group A + B were significantly greater than those in group C ($p < 0.05$) but there were no significant differences in other clinical parameters

that the criteria used to select patients who were eligible for surgical exploration during non-surgical anticancer treatments differed among institutions. The 58 patients in the adjuvant surgery group were collected from 39 hospitals over 8 years, and thus the average number was 1.2 cases per hospital. Moreover, it should be noted that a significantly higher rate of peritoneal metastasis was found in the control group.

Donahue et al. [25] reported that patients with initially unresectable pancreaticobiliary malignant tumors should be selected for surgery on the basis of lack of disease progression, good functional status, and a decrease in the CA19-9 level rather than of evidence that vessel involvement has disappeared on computed tomography or magnetic resonance imaging. The third clinical question is the optimal time for adjuvant surgery in this patient population. When should the shrunken tumor be removed in the process of maintaining chemotherapy and/or radiation therapy? The sub-group analysis according to the time from the initial treatment to surgical resection showed significant favorable differences in the overall survival rates in patients who were able to undergo adjuvant surgery more than 240 days after initial treatment. Therefore, the recommended optimal time for adjuvant surgery is at least 240 days after the initial treatment. A longer duration of non-surgical anti-cancer treatment may be associated with better patient selection, greater doses of chemotherapy, a higher rate of PR/CR, and lower levels of tumor markers, thus resulting in a better prognosis of patients, since a certain period of observation time allows for the identification of progressive disease or poor surgical candidates. The primary findings of this study indicate the importance of finding the appropriate non-surgical anticancer treatments for effective tumor downsizing over at least 240 days after the initial treatment.

The adjuvant surgery group underwent major pancreatic resection with concomitant other organ and/or vascular resection in 69 % of patients. It is technically possible to perform extensive resections with vein and/or arterial reconstruction, but concomitant arterial resection remains controversial because it is associated with a high morbidity [26–28]. Laurence et al. [28] reported that an increased risk of perioperative death appears to be associated with resection performed in patients with initially designated unresectable tumors prior to neoadjuvant chemoradiation therapy. Nakao et al. [29] reported that pancreatectomy with portal vein resection can be performed safely, and long-term survival is observed in selected patients. The current study found no significant difference in overall survival or morbidity and mortality between those receiving concomitant resection or not. Therefore, the results from this study demonstrated that concomitant resections of other organs and vessels were safely performed with special caution.

In conclusion, adjuvant surgery for initially unresectable pancreatic cancer patients with a long-term favorable response to non-surgical anticancer treatments is considered to be a safe and effective treatment. The overall survival rate from the initial treatment was extremely high, especially in patients who received non-surgical anti-cancer treatment for more than 240 days. Adjuvant surgery can occupy an important position in multimodal therapy for patients with initially unresectable pancreatic cancer.

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**Conflicts of interest** The authors have no commercial affiliations that might pose any conflicts of interest in connection with this study.

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# Stump closure of a thick pancreas using stapler closure increases pancreatic fistula after distal pancreatectomy

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**KEYWORDS:**
Distal pancreatectomy;
Stapler closure;
Pancreatic fistula

**Abstract**

**BACKGROUND:** The appropriate surgical stump closure after distal pancreatectomy (DP) is still controversial. This study investigated the benefits and risks of stapler closure during DP.

**METHODS:** The risk factors of pancreatic fistulas were investigated in 122 DPs among 3 types of stump closure: hand-sewn suture (n = 32), bipolar scissors (n = 45), and stapler closure (n = 45).

**RESULTS:** There was no significant difference in the incidence of pancreatic fistula between the 3 types of stump closure (hand-sewn suture [44%] vs bipolar scissors [37.7%] vs stapler closure [35.5%]). By using receiver operating characteristics curves, 12 mm was the best cutoff value of the thickness of the pancreas for pancreatic fistulas after DP using stapler closure. Three factors (ie, male sex, body mass index >25 kg/m$^2$, and stapler closure) were independent risk factors of pancreatic fistulas after DP with a pancreas thicker than 12 mm.

**CONCLUSIONS:** A pancreas thicker than 12 mm significantly increased the incidence of pancreatic fistulas after DP using stapler closure.



The incidence of pancreatic fistulas after distal pancreatectomy (DP) remains high (16% to 35%) although mortality has been decreased to less than 5% by recent advances in surgical techniques and perioperative management.[1–6] Although a thick pancreas is one of the risk factors of pancreatic fistula,[7,8] no previous reports described whether the thickness of the pancreas influences the incidence of pancreatic fistulas among different stump closure techniques. This study compared the incidence of pancreatic fistulas among 3 types of stump closure: hand-sewn suture, bipolar scissors, and stapler closure.

Pancreatic fistula is the most serious complication after DP and is associated with a higher incidence of other severe complications, such as intra-abdominal abscess or intra-abdominal bleeding.[9–11] Therefore, various methods and techniques for stump closure of the remnant pancreas including hand-sewn closure,[12–14] stapler closure,[15–18] ultrasonic dissection,[19] bipolar scissors,[20] seromuscular patch,[21] pancreatoenteric anastomosis,[13,22] and absorbable mesh[23] have been reported to reduce pancreatic fistula after DP. Stapler closure and hand-sewn closure are standard techniques for pancreatic stump closure. A multicenter randomized Efficacy of stapler versus hand-sewn closure after distal pancreatectomy (DISPACT) trial proposed that stapler closure did not significantly reduce the incidence of pancreatic fistulas after DP compared with hand-sewn closure[24] although several studies reported that stapler closure contributed to

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reducing pancreatic fistulas after DP.[15–18] However, there were no reports to clarify the benefit and risk of stapler closure after DP, and a thick pancreas may not be not suitable for pancreatic stump closure using stapler closure after DP.

This study prospectively performed 3 stump closure techniques during DP (ie, hand-sewn suture, bipolar scissors, and stapler closure) to reduce pancreatic fistulas. Moreover, the study investigated the benefit and risk of stapler closure during DP by assessing the association between the thickness at the resection site of the pancreas and the 3 stump closure techniques.

## Methods

### Patients

One hundred twenty-two patients underwent DP at Wakayama Medical University Hospital, Wakayama, Japan, from January 2000 to January 2011. The patients were prospectively assigned to 3 groups by the type of stump closure: hand-sewn suture of surgical stump closure in 32 patients between January 2000 and December 2005, bipolar scissors (Ethicon Endo-Surgery, Cincinnati, OH) in 45 patients between January 2006 and August 2008, and stapler closure (Echelon 60 with a gold cartridge [compressible thickness to 1.8 mm], Ethicon Endo-Surgery) in 45 patients between September 2008 and January 2011.

Patient characteristics among the 3 groups were reviewed for age, sex, history of diabetes mellitus, body mass index (BMI), histologic diagnosis (malignant or benign), operative time, intraoperative bleeding, red blood cell transfusion, pancreatic texture (soft or hard), type of stump closure (hand-sewn suture, bipolar scissors, a stapling device), combined portal vein resection, operative procedure (DP or distal pancreatectomy with en bloc celiac axis resection), contiguous organs resection, and pancreatic thickness, which was estimated and measured by preoperative computed tomographic (CT) examination.

### The resection site of the pancreas

The resection site of the pancreas was recorded by the distance from the left edge of the portal vein. The thickness of the resection site of the pancreas was estimated and measured by preoperative CT imaging based on the distance from the left portal vein edge measured intraoperatively. A 16 multidetector row CT scanner (Toshiba Aqullion Multi-Slice CT; Toshiba Medical Systems Co Ltd, Tokyo, Japan) was used to obtain CT images. CT images were reconstructed at 1-mm thickness.

### Type of stump closure and postoperative management

Only 5 of 122 patients with DP underwent laparoscopic DP, and all the others underwent open DP concerning operative procedures.

Hand-sewn suture group. The pancreas was transected with a knife after the identification of the main pancreatic duct, and the main pancreatic duct was ligated with a 3-0 silk suture. The surgical stump of the remnant pancreas was closed by vertical mattress sutures using 4-0 polypropylene.

Bipolar scissors group. The pancreas was transected using bipolar scissors (Ethicon Endo-Surgery). The small pancreatic ducts and vessels as well as the main pancreatic duct were adequately exposed during the transection of the pancreas and ligated with a 3-0 silk suture and divided. The surgical stump of the remnant pancreas was left without parenchymal suturing.

Stapler closure group. The pancreas was transected using Echelon 60 with a gold cartridge (compressible thickness to 1.8 mm). Echelon 60 with a gold cartridge provides precise and uniform wide compression throughout the entire 60-mm length with compressible thickness to 1.8 mm, which can attach 2 triple-staggered rows of titanium staples. The closure jaw was clamped carefully and slowly, taking 10 minutes at a fixed speed. The stapler was not released immediately after firing, and the jaws of the stapler were held shut for 1 minute.

One 10-mm silicon drain (BLAKE drain, Ethicon Endo-Surgery) was placed near the stump of the remnant pancreas. The drain was to be removed on postoperative day 4 to prevent an intra-abdominal abscess when the drainage fluid was clear and pancreatic fistula and bacterial contamination were absent.[25] The amylase of serum and drainage fluid was measured on postoperative days 1, 3, and 4. No patient received radiotherapy preoperatively or postoperatively. All patients received prophylactic antibiotics only intraoperatively or for 1 or 2 days postoperatively. Prophylactic octerotide was not administered to prevent pancreatic fistula.

### Postoperative complications

The diagnosis of pancreatic fistula was determined by the International Study Group on Pancreatic Fistula (ISGPF) guidelines.[26] Pancreatic fistula was classified into 3 categories (grade A, B, or C) by the ISGPF. Delayed gastric emptying (DGE) was defined according to a consensus definition and clinical grading of postoperative DGE proposed by the International Study Group of Pancreatic Surgery.[27] DGE was then classified into 3 categories (grade A, B, or C) using the International Study Group of Pancreatic Surgery clinical criteria based on the clinical course and postoperative management. Other postoperative complications were graded according to the Clavien classification.[28] Complications in this study were defined as a condition that was more than grade II according to the Clavien classification. Mortality was defined as death within 30 days after surgery.

## Statistical analysis

Data were expressed as means ± standard deviation. Patient characteristics and perioperative and postoperative factors among 3 groups were compared using the chi-square test, the Fisher exact test, and the Mann-Whitney $U$ test. Variables with $P < .100$ were entered into a logistic regression model to determine independent risk factors of postoperative complications. The independent risk factors of the variables were expressed as odds ratios with their 95% confidence intervals. The optimal cutoff levels of the thickness of the pancreas and the drain amylase level on postoperative day 1 for differentiation between the no pancreatic fistula group and the pancreatic fistula group were determined by constructing receiver operating characteristic curves, which were generated by calculating the sensitivities and specificities of the thickness of the pancreas and the drain amylase level on postoperative day 1 at several predetermined cutoff points. Line graphs were used for graphic visualization (SPSS Inc., Chicago, IL). Statistical significance was defined as $P < .05$. The protocol and study design of DP using 3 types of stump closure (hand-sewn closure, bipolar scissors, or stapler closure) were conducted according to the guidelines of the Ethical Committee of Wakayama Medical University Hospital.

## Results

### Patient characteristics

One hundred twenty-two patients with DP were divided into 3 groups according to the type of pancreatic stump closure: 32 patients with hand-sewn closure, 45 patients with bipolar scissors, and 45 patients with stapler closure. The indications for DP in the 122 patients were 72 patients with pancreatic adenocarcinomas, 14 with intraductal papillary neoplasms, 11 with tumor-forming pancreatitis, 8 with pancreatic endocrine neoplasms, 9 with mucinous cyst neoplasms, 4 with serous cyst adenomas, and 4 with other diseases.

Table 1 shows the characteristics of the enrolled patients according to the types of stump closure. There were no significant differences concerning the patient characteristics among the 3 groups. There were no significant differences between the 3 groups concerning the pancreatic texture, lymph node dissection, portal vein resection, operative procedure, or contiguous organ resection. However, there were significant differences in the operative time (268 ± 94 min vs 221 ± 83 min vs 216 ± 81 min, $P = .019$), median intraoperative bleeding (825 mL vs 460 mL vs 280 mL, $P = .009$), and red blood cell transfusion in patients (37.5% vs 8.9% vs 4.4%, $P < .001$) in the hand-sewn suture, bipolar scissors, and stapler closure groups, respectively.

### Postoperative complications after DP

Table 2 shows the results of postoperative complications and mortality. The overall rate of pancreatic fistulas

**Table 1** Characteristics of the enrolled patients (N = 122) according to the type of stump closure

| | Hand-sewn closure (n = 32) | Bipolar scissors (n = 45) | Stapler closure (n = 45) | *P* Value |
|---|---|---|---|---|
| Preoperative status | | | | |
| Age | 62 ± 14 | 65 ± 11 | 63 ± 16 | .640 |
| Sex (male/female) | 15/17 | 24/21 | 26/19 | .640 |
| Diabetes (yes/no) | 7/25 | 18/27 | 15/30 | .247 |
| BMI (kg/m$^2$) | 21.1 ± 3.3 | 22.9 ± 3.5 | 22.1 ± 2.7 | .670 |
| Benign tumors/malignant tumors | 12/20 | 16/29 | 13/32 | .690 |
| Pancreatic adenocarcinoma (%) | 17 (53) | 26 (58) | 29 (64) | |
| Intraductal papillary neoplasms (%) | 5 (16) | 5 (11) | 4 (9) | |
| Tumor-forming pancreatitis (%) | 4 (13) | 5 (11) | 2 (4) | |
| Endocrine tumor (%) | 1 (3) | 3 (7) | 4 (9) | |
| Mucinous cyst neopalsms (%) | 4 (13) | 1 (2) | 4 (9) | |
| Serous cyst adenoma (%) | 0 (0) | 4 (9) | 0 (0) | |
| Other diseases (%) | 1 (3) | 1 (2) | 2 (4) | |
| Intraoperative findings | | | | |
| Operative time (min) | 268 ± 94 | 221 ± 83 | 216 ± 81 | .019 |
| Intraoperative bleeding (mL) | | | | |
| Median (range) | 825 (60–4,680) | 460 (0–3,690) | 280 (20–2,525) | .009 |
| RBC transfusion (yes/no) | 12/20 | 4/41 | 2/43 | <.001 |
| Pancreatic texture (soft/hard) | 24/8 | 36/9 | 35/10 | .873 |
| Lymph node dissection (D1/D2) | 10/22 | 14/31 | 32/13 | .690 |
| Operative procedure (DP-CAR/DP) | 3/29 | 1/44 | 1/44 | .313 |
| Celiac artery resection (yes/no) | 2/30 | 10/35 | 7/38 | .238 |
| Contiguous organ resection (yes/no) | 5/27 | 2/43 | 5/40 | .251 |
| Thickness of pancreas (mm) | 12 ± 2.8 | 13 ± 4.1 | 12 ± 3.2 | .116 |

Contiguous organ refers to the stomach and transverse colon.
BMI = body mass index; DP = distal pancreatectomy; DP-CAR = distal pancreatectomy with en bloc celiac axis resection; RBC = red blood cell.

**Table 2** Comparison of postoperative complications according to the type of stump closure

| | Hand-sewn closure (n = 32) | Bipolar scissors (n = 45) | Stapler closure (n = 45) | *P* Value |
|---|---|---|---|---|
| Pancreatic fistula (%)* | 14 (44) | 17 (37.7) | 16 (35.5) | .761 |
| Grade A | 8 | 9 | 11 | |
| Grade B | 4 | 8 | 5 | |
| Grade C | 2 | 0 | 0 | |
| Clinical pancratic fistula (grade B + C) (%) | 6 (18.7) | 8 (17.7) | 5 (11.1) | .579 |
| Intra-abdominal abscess (%) | 6 (18.7) | 7 (15.5) | 4 (8.9) | .280 |
| Intra-abdominal hemorrhage (%) | 2 (4.4) | 1 (2.2) | 0 (0) | .216 |
| Delayed gastric emptying (%)† | 2 (4.4) | 1 (2.2) | 1 (2.2) | .232 |
| Grade A | 0 | 1 | 1 | |
| Grade B | 2 | 0 | 0 | |
| Grade C | 0 | 0 | 0 | |
| Reoperation | 0 | 0 | 0 | — |
| Mortality | 0 | 0 | 0 | — |

DGE = delayed gastric emptying.
*Pancreatic fistula is identified based on ISGPF.
†Delayed gastric emptying is identified based on International Study Group of Pancratic Surgery.

was 36.9% (45/122 enrolled patients). There were no significant differences in the incidence of pancreatic fistulas between the 3 groups (hand-sewn suture group [38%] vs bipolar scissors group [37.7%] vs stapler closure group [35.5%], $P = .327$). There were no significant differences between the 3 groups in the incidence of clinical pancreatic fistulas (ISGPF grade B/C) (hand-sewn suture group [18.7%] vs bipolar scissors group [17.7%] vs stapler closure group [11.1%], $P = .579$). The incidence of other complications was also similar among the 3 groups. No patients had reoperation or mortality.

### The association between the thickness of the pancreas and the type of stump closure in patients with pancreatic fistulas

Table 3 shows the association between the thickness of the pancreas and the type of stump closure in patients with pancreatic fistulas. The thickness at the resection site of the pancreas was measured using preoperative CT images. The thickness of the pancreas was similar in patients with or without pancreatic fistulas in the hand-sewn suture and bipolar scissors groups. However, the thickness at the resection site of the pancreas in the stapler closure group was 14.5 ± 2.8 mm in patients with pancreatic fistulas and 10.8 ± 2.7 mm in patients with no pancreatic fistula. The thickness of the pancreas was significantly associated with the incidences of pancreatic fistulas after DP in the stapler closure group ($P < .0001$). The receiver operating characteristics indicated that a thickness of more than 12 mm was the cutoff value for the prediction of pancreatic fistulas after DP using stapler closure (Fig. 1). The sensitivity and specificity of cutoff level were 81%, and 83%, respectively.

### The association between pancreatic fistulas and stapler closure based on the thickness of the pancreas

The study investigated whether the thickness of the pancreas influences the incidence of pancreatic fistulas in DP using stump closure. Table 4 shows the association between pancreatic fistulas and stapler closure based on the thickness of the pancreas. Although 13 (72%) of 18 patients with a pancreas thicker than 12 mm had pancreatic fistula, only 3 (11%) of 27 of those with a pancreas thinner than 12 mm had a pancreatic fistula. Stapler closure significantly increased pancreatic fistulas when the thickness of the pancreas was more than 12 mm ($P < .001$).

### Risk factors of pancreatic fistulas after distal pancreatectomy using stapler closure

Univariate and multivariate analyses were used to reveal the risk factors for pancreatic fistulas after DP using stapler

**Table 3** Association between the thickness* of the pancreas and type of stump closure in patients with pancreatic fistula

| | Pancreatic fistula† | | |
|---|---|---|---|
| | (−) | (+) | *P* Value |
| Hand-sewn closure (n = 32) | 11.9 ± 2.6 mm | 12.4 ± 3.3 mm | .642 |
| Bipolar scissors (n = 45) | 13.4 ± 3.6 mm | 13.8 ± 5.0 mm | .717 |
| Stapler closure (n = 45) | 10.8 ± 2.7 mm | 14.5 ± 2.8 mm | <.0001 |

*Thickness at the resection site of pancreas, which was measured by preoperative CT images.
†Pancreatic fistula is defined based on ISGPF.

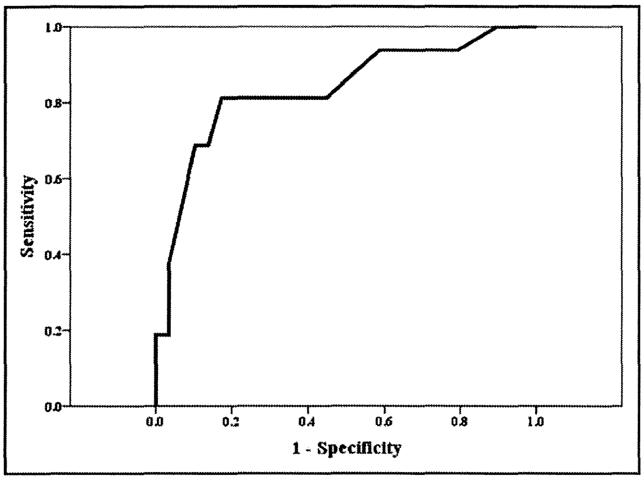


**Figure 1** Receiver operating characteristic curves for pancreatic thickness to predict pancreatic fistulas. Analysis of the the sensitivity and specificity of pancreatic thickness revealed an area under the receiver operating characteristic curve of .835 ($P < .001$; 95% confidence interval, .702–.969). A pancreas thicker than 12 mm was suggested to be the best cutoff for predicting pancreatic fistulas after stapler closure.

closure. Table 5 shows the results of the 12 parameters in the univariate analysis of risk factors for the 16 patients with pancreatic fistulas vs the 29 patients without pancreatic fistulas. Patients with a pancreatic thickness greater than 12 mm had a significantly high incidence of pancreatic fistulas in the stapler closure group ($P < .0001$).

Multivariate logistic regression analysis revealed that pancreatic thickness greater than 12 mm ($P = .006$; odds ratio = 15.6; 95% confidence interval [CI], 2.2–112.4) was the only independent risk factor of pancreatic fistulas after DP using stapler closure.

### Risk factors influencing the incidence of pancreatic fistulas after DP with a pancreas thicker than 12 mm in all 122 patients

Univariate and multivariate analyses were used to reveal risk factors for pancreatic fistulas after DP using stapler

**Table 4** The association between pancreatic fistulas and stapler closure in patients with pancreatic fistula based on the thickness* of the pancreas

| | Pancreatic fistula† | | |
|---|---|---|---|
| | (−) (n = 29) | (+) (n = 16) | *P* value |
| Thickness of pancreas (%) | | | <.001 |
| ≤12 mm (n = 27) | 24 (89) | 3 (11) | |
| >12 mm (n = 18) | 5 (28) | 13 (72) | |

*Thickness at the resection site of pancreas.
†Pancreatic fistula is defined based on ISGPF.

closure. Table 6 shows the results of the 12 parameters in the univariate analysis of risk factors for the 29 patients without pancreatic fistulas vs the 28 patients with pancreatic fistulas. Male sex, BMI greater than 25 $kg/m^2$, and stapler closure were significantly associated with an increase in the incidence of pancreatic fistula patients with a pancreas thicker than 12 mm ($P$ = .022, .043, and .018, respectively).

A multivariate logistic regression analysis revealed that male sex ($P = .025$; odds ratio = 4.2, 95% CI, 1.2–14.6), BMI greater than 25 $kg/m^2$ ($P = .037$; odds ratio = 4.0; 95% CI, 1.1–14.9), and stapler closure ($P = .049$; odds ratio = 3.8; 95% CI, 1.0–14.7) were independent risk factors of pancreatic fistulas after DP with a pancreas thicker than 12 mm.

## Comments

A thick pancreas may not be suitable for pancreatic stump closure using a stapler. The incidence of pancreatic fistulas was analyzed in the current series of DP. This study compared 3 different stump closure techniques. The results showed a significant difference between the thickness of the pancreas and the incidence of pancreatic fistulas in the stapler closure group only, with significant differences between the hand-sewn suture and bipolar scissors groups. This is the first study to clarify whether the thickness of the pancreas influences the incidence of pancreatic fistula formation among 3 different stump closure techniques.

The appropriate stump closure technique for use in DP to reduce the incidence of pancreatic fistulas remains controversial. Stapler closure is currently the standard technique used for stump closure.[15–18] Two meta-analyses of techniques for closure of the pancreatic remnant after DP did not show a statistically significant reduction in the incidence of pancreatic fistulas after DP.[29,30] In addition, a multicenter, randomized DISPACT trial proposed that stapler closure does not significantly reduce the incidence of pancreatic fistulas after DP compared with hand-sewn closure (stapler closure [32%] vs hand-sewn closure [28%]).[24]

There are 2 reasons that transection of a thick pancreas using stapler closure could influence the incidence of pancreatic fistulas. First, a thick pancreatic parenchyma easily tears with compression during stapler closure because the pancreas is a fragile organ. Second, a thick pancreatic parenchyma may be less likely to hold staples well and allows persistent extravasation of the pancreatic juice because of incomplete sealing of the small duct. On the other hand, the mechanism underlying the formation of pancreatic fistulas after hand-sewn suture in DP is thought to involve minimal ischemic necrosis of the sutured surgical stump. Bipolar scissors may cause thermal injury to the cut surface, and the subsequent tissue damage may lead to coagulation necrosis. Therefore, these 2 stump closure techniques do not influence the incidence of pancreatic fistulas associated with the thickness of the pancreas. In

**Table 5** Risk factors influencing pancreatic fistula after distal pancreatectomy using stapler closure

| | Pancreatic fistula | | | |
|---|---|---|---|---|
| | (−) (n = 29) | (+) (n = 16) | Univariate analysis | Multivariate analysis |
| Age | | | | |
| ≤75 | 21 | 11 | | |
| >75 | 8 | 5 | .795 | |
| Sex | | | | |
| Male | 14 | 12 | | |
| Female | 15 | 4 | .082 | |
| Diabetes | | | | |
| Yes | 9 | 6 | | |
| No | 20 | 10 | .660 | |
| BMI (kg/m$^2$) | | | | |
| ≤25 | 25 | 11 | | |
| >25 | 4 | 5 | .161 | |
| Histology | | | | |
| Benign | 8 | 5 | | |
| Malignant | 21 | 11 | .795 | |
| Operative time (min) | | | | |
| ≤240 | 18 | 12 | | |
| >240 | 11 | 4 | .378 | |
| Intraoperative bleeding (mL) | | | | |
| ≤1,000 | 22 | 14 | | |
| >1,000 | 7 | 2 | .350 | |
| Red blood cell transfusion | | | | |
| Yes | 2 | 0 | | |
| No | 27 | 16 | .283 | |
| Pancreatic texture | | | | |
| Soft | 21 | 14 | | |
| Hard | 8 | 2 | .244 | |
| Operative procedure | | | | |
| DP-CAR | 6 | 1 | | |
| DP | 23 | 15 | .201 | |
| Contiguous organ resection | | | | |
| Yes | 5 | 0 | | |
| No | 24 | 16 | .078 | |
| Thickness of pancreas (mm) | | | | |
| ≤12 | 26 | 5 | | |
| >12 | 3 | 11 | <.0001 | .006 |

Contiguous organ refers to the stomach and transverse colon.
BMI = body mass index; DP = distal pancreatectomy; DP-CAR = distal pancreatectomy with en bloc celiac axis resection.

1 study, stump closure using a white cartridge (compressible thickness to 1.0 mm) significantly decreased the incidence of pancreatic fistulas in comparison to that performed with a green cartridge (compressible thickness to 2.0 mm) (5% vs 31%).[31] The cutoff point (>12 mm) used in the current study may have been influenced by staple size. However, Echelon 60 with a gold cartridge (compressible thickness to 1.8 mm) is standard and widely used in DP; therefore, the current results should be relevant to all types of staplers.

A few other methods, including absorbable mesh reinforcement[23] and the use of seromuscular patches,[32] are used to reinforce the staple line and reduce the incidence of pancreatic fistulas. A randomized clinical trial reported that covering the stapled pancreatic remnants with seromuscular patches significantly decreases the overall rate of pancreatic-related complications.[32] However, patients with a thick or fibrotic pancreatic parenchyma were excluded from that study. Therefore, stump closure techniques other than stapler closure should be performed when the pancreatic parenchyma is too thick.

Several studies have reported that BMI is a statistically significant risk factor associated with the incidence of pancreatic fistulas and postoperative complications after pancreatic surgery.[3,4,33,34] On the other hand, several other studies have reported that BMI is not an independent risk factor for the development of postoperative complications after pancreatic surgery.[35] In our study, 21 of 57 patients (37%) with a thick pancreas (>12 mm) had a BMI greater than 25 kg/m$^2$. Fourteen of the 21 patients (67%) with a

**Table 6** Risk factors influencing pancreatic fistulas after DP with a pancreas thicker than 12 mm

| | Pancreatic fistula | | | |
|---|---|---|---|---|
| | (−) (n = 29) | (+) (n = 28) | Univariate analysis | Multivariate analysis |
| Age | | | | |
| ≤75 | 24 | 21 | | |
| >75 | 5 | 7 | .473 | |
| Sex | | | | |
| Male | 12 | 20 | | |
| Female | 17 | 8 | .022 | .025 |
| Diabetes | | | | |
| Yes | 10 | 10 | | |
| No | 19 | 18 | .922 | |
| BMI | | | | |
| ≤25 | 22 | 14 | | |
| >25 | 7 | 14 | .043 | .037 |
| Histology | | | | |
| Benign | 12 | 9 | | |
| Malignant | 17 | 19 | .470 | |
| Operative time (min) | | | | |
| ≤240 | 19 | 17 | | |
| >240 | 10 | 11 | .707 | |
| Intraoperative bleeding (mL) | | | | |
| ≤1,000 | 22 | 21 | | |
| >1,000 | 7 | 7 | .940 | |
| Red blood cell transfusion | | | | |
| Yes | 4 | 1 | | |
| No | 25 | 27 | .173 | |
| Pancreatic texture | | | | |
| Soft | 25 | 24 | | |
| Hard | 4 | 4 | .957 | |
| Operative procedure | | | | |
| DP | 27 | 24 | | |
| DP-CAR | 2 | 4 | .363 | |
| Contiguous organ resection | | | | |
| Yes | 2 | 2 | | |
| No | 27 | 26 | .971 | |
| Type of stump closure | | | | |
| Stapler closure | 5 | 13 | | |
| Other closure type | 24 | 15 | .018 | .049 |

Contiguous organ refers to the stomach and transverse colon.
BMI = body mass index; DP = distal pancreatectomy; DP-CAR = distal pancreatectomy with en bloc celiac axis resection.

BMI greater than 25 kg/m$^2$ had pancreatic fistulas, and the patients with a BMI greater than 25 kg/m$^2$ exhibited a significantly increased incidence of pancreatic fistulas compared with those with a BMI less than or equal to 25 kg/m$^2$ (67% vs 39%, $P$ = .043). The sample size in this study is too small to draw any conclusions concerning an association between BMI and the incidence of pancreatic fistulas or postoperative complications after pancreatic surgery.

This study did not find that any of the 3 different stump closure techniques significantly reduced the incidence of pancreatic fistulas. Increasing experience might improve this operative technique and also reduce the number of postoperative complications. In fact, there might be some bias associated with the present study because of the increasing experience over time (including the 3 periods of the study) concerning the operative time, intraoperative bleeding, and red blood cell transfusion. Previous studies suggest a soft pancreas to be a risk factor of pancreatic fistulas.[14,19] In the present study, no significant difference was observed between a soft pancreas and a hard pancreas concerning the occurrence of pancreatic fistulas (soft pancreas [42%] vs hard pancreas [26%], $P$ = .127). As a result, there may be no statistical significance between the textures of the pancreas because the rate of a hard pancreas was only 27 of 122 patients (22.1%). Moreover, the small sample size in the subgroup analysis is a limitation of this study concerning the analysis of pancreas thickness associated with stapler closure.

In conclusion, stratifying the results of this study according to pancreas thickness revealed that stapler closure for transection of a thick pancreas (>12 mm) significantly increases the incidence of pancreatic fistulas after DP compared with hand-sewn suture or bipolar scissor techniques. In contrast, stapler closure for stump closure of a thin pancreas (<12 mm) is a quick, simple, and secure procedure. The present study is a prospective comparison and not a randomized comparison. Therefore, a randomized controlled trial should be undertaken to confirm the present results. However, stapler closure is a beneficial choice for DP during resection of a thin pancreas (<12 mm).

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# Surgical strategy for patients with pancreatic body/tail carcinoma: Who should undergo distal pancreatectomy with en-bloc celiac axis resection?

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***Background.*** *Indications for distal pancreatectomy with en-bloc celiac axis resection (DP-CAR) in pancreatic carcinoma remain controversial.*
***Methods.*** *Fifty-two consecutive patients with pancreatic cancer who underwent distal pancreatectomy, including 36 standard distal pancreatectomies (standard DP) and 16 DP-CAR were reviewed retrospectively.*
***Results.*** *After standard DP, microscopically positive margins were identified at the dissection sites around the transection margins of the splenic arteries and were detected more frequently in the patients with tumors within 10 mm from the root of the splenic artery (14%). After DP-CAR, the estimated overall survival rate in patients who were pathologically negative for portal venous and artery invasion* (n = 7) *was greater than that of the other patients* (n = 9; P = .023, *log-rank test). The estimated overall 1- and 2-year survival rates after standard DP/DP-CAR were 81/81% and 52/53%, and the median survival times were 32/25 months, respectively, with no differences noted between the groups. There were no differences in the mortality rates and the incidence of each complication between the 2 groups except for delayed gastric emptying.*
***Conclusion.*** *DP-CAR was a feasible and safe procedure, similar to standard DP. DP-CAR should be reserved for patients without tumor infiltrating either the portal venous or arterial systems. (Surgery 2013;153:365-72.)*

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THE OVERALL 1- AND 5-YEAR SURVIVAL RATES in patients with pancreatic carcinoma are generally <20% and <5%, respectively,[1-3] with radical surgical resection (R0) remaining the most important factor impacting the long-term survival. Unfortunately, most patients with pancreatic body/tail carcinoma tend to be diagnosed in more advanced stages, such as when there is tumor involvement of the celiac axis and of the root of the common hepatic artery.[4-7] The indications for distal pancreatectomy with en-bloc celiac axis resection (DP-CAR) were extended recently to increase the R0 rate for advanced pancreatic body/tail carcinoma,[8,9] with reports suggesting that DP-CAR can provide an R0 resection rate of 91%, a mortality rate of 0%, and an estimated 5-year survival probability of 42%.[10] According to previous reports, the most important predictor of long-term survival in patients with locally advanced pancreatic carcinoma is whether an R0 was possible.[11-16] Because most pancreatic carcinomas recur systemically, tumor involving arterial structures recur rapidly even after the complete resection.[17] One should consider whether the presence of just an R0 resection should be the primary issue of cure in borderline resectable pancreatic carcinoma. Therefore, the impact and indications for DP-CAR in patients with potentially resectable pancreatic body/tail carcinoma remain undefined. The aim of the present study was to clarify who should and who should not undergo DP-CAR in patients with potentially resectable/borderline resectable pancreatic carcinoma.

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## PATIENTS AND METHODS

**Patient characteristics.** Between January 2005 and February 2010, 52 consecutive patients underwent distal pancreatectomy with D2 node dissection, including 36 standard DP and 16 DP-CAR, for pancreatic body/tail carcinoma at Wakayama Medical University Hospital. We do not resect para-aortic lymph nodes, but do resect the D2 lymph nodes along the hepatic artery, celiac axis, and superior mesenteric artery in the present study.[18] The stages of pancreatic carcinoma were based on the TNM classification. Among the patients who underwent standard DP, there was 1 patient with stage IA, 2 with stage IB, 15 with stage IIA, 17 with stage IIB, and 1 with stage IV disease; among the patients undergoing DP-CAR, 9 patients were stage IIA, 5 were stage IIB, and 2 were stage III (Table I).[19] During this time, no patients with pancreatic body/tail carcinoma received neoadjuvant therapy; all were recommended to receive postoperative adjuvant chemotherapy by systemic intravenous gemcitabine. The dosage and schedule were based on the CONKO-001 study.[20] The safety and outcomes of DP-CAR are discussed in terms of the stage, curability, complications, and survival compared with standard DP.

**Table I.** Patient characteristics and surgical outcomes

| *Procedure* | *Standard DP* (n = *36)* | *DP-CAR* (n = *16)* | P *value* |
|---|---|---|---|
| Age at surgery, yrs (mean) | 68 | 63 | .276 |
| Gender | | | |
| Male | 23 | 11 | .734 |
| Female | 13 | 5 | |
| Histopathology | | | |
| IDC | 32 | 15 | |
| Anaplastic | 1 | 1 | |
| Adenosquamous | 2 | 0 | |
| Mucinous | 1 | 0 | |
| Stage | | | |
| IA | 1 | 0 | |
| IB | 2 | 0 | |
| IIA | 15 | 9 | |
| IIB | 17 | 5 | |
| III | 0 | 2 | |
| IV | 1 | 0 | |
| Preoperative diagnosis | | | |
| Potentially resectable | 36 | 0 | |
| Borderline resectable | 0 | 16 | |
| Operative time (min) | 203 | 298 | <.001 |
| EBL (mL) | 700 | 1165 | .102 |
| R0 | 29 | 5 | .002 |
| R1, 2 | 7 | 11 | |

*Anaplastic*, Anaplastic ductal carcinoma; *DP*, distal pancreatectomy; *DP-CAR*, distal pancreatectomy with en-bloc celiac axis resection; *EBL*, estimated blood loss; *IDC*, invasive ductal carcinoma; *stage*, the stage based on the TNM classification.

All tissue specimens were reviewed after resection. Microscopically positive sites of the peripancreatic tissue margin were identified by macroscopic/microscopic histopathologic examination of the pathologic specimens. In patients with standard DP, the distances between the proximal edge of the tumor and the root of the splenic artery (SA) were measured by computed tomography. Every patient was followed up in the outpatient clinic every 1–3 months. The clinical data and follow-up information for every patient were obtained from the medical records.

**Indications for and surgical procedures of standard DP and DP-CAR.** In patients where resectable body/tail tumors had not invaded the plexus around the common hepatic artery, the root of the SA, or the celiac axis, we employed a standard DP, whereas we employed DP-CAR in patients where the tumors had invaded 1 of these regions. Our DP-CAR procedure basically included en bloc resection of the celiac, common hepatic, and left gastric arteries, the celiac plexus, the left-sided nerve plexus along the superior mesenteric artery, a part of the crus of the diaphragm, and Gerota's fascia. In addition, the resection included the retroperitoneal fat tissues bearing lymph nodes above the renal vein, the transverse mesocolon covering the body of the pancreas, and the inferior mesenteric vein. Resection of the portal and the middle colic vessels and the left adrenal gland was performed when necessary. In general, no reconstruction of the arterial system was required because of the early development of the collateral arterial pathways via the pancreaticoduodenal arcades from the superior mesenteric artery. Basically, all patients were expected to undergo preoperative coil embolization of the common hepatic artery regardless of the diameter of the gastroduodenal artery to enlarge the collateral pathways and prevent ischemia-related complications,[21] but embolization was not possible in 4 patients because of the arterial anatomy, including replaced right hepatic artery. In addition, with preservation of the stomach, no reconstruction of the alimentary tract was required.

**Statistical analysis.** Descriptive statistics were employed to examine the demographic characteristics of the study population. Data are expressed as medians (minimum to maximum). A value of $P < .05$ was considered to suggest significance, but we acknowledge that the series is small in number and follow up is still short (median, 25 months).

Survival times were measured from the date of operation, and death from all causes (without discrimination between deaths resulting from pancreatic carcinoma or other causes) was used as the outcome. Survival curves were traced with the Kaplan–Meier method and the comparison of survival curves was based on the log-rank test. All of the analyses were performed using the statistical software package SPSS II (version 11.0; SPSS, Inc., Chicago, IL).

## RESULTS

**Patient characteristics.** Table I presents the characteristics of the 52 consecutive patients with pancreatic body/tail carcinoma. All patients underwent a peritoneal cytologic evaluation just after laparotomy; only 1 patient had positive cytology. All but 1 patient underwent what seemed to be a macroscopically curative resection without any residual tumor.

In the standard DP group, segmental resection of the portal vein was performed in 1 patient. The median duration of the operation was 203 minutes (range, 128–276), and the median blood loss was 700 mL (range, 10–2,850). Twenty-nine patients (81%) achieved an R0 resection, 6 (17%) R1, and 1 an R2 resection.

In the DP-CAR group, the portal vein was resected in 4 patients, including 3 segmental and 1 tangential resection. The median duration of the operation was 298 minutes (range, 212–465), and the median blood loss was 1,170 mL (range, 410–2,240). In this group, only 5 patients achieved an R0 (31%).

**Postoperative complications.** Table II presents the postoperative complications after standard DP and DP-CAR. The incidence of postoperative pancreatic fistula based on the International Study Group on Pancreatic Fistula definition[22] revealed no differences between the groups, but delayed gastric emptying was more common in the DP-CAR group (13% vs 0%). After DP-CAR, no hepatic abscess or hepatic failure was observed nor were there any gastric ulcers observed. A duodenal perforation presumably from ischemia occurred 1 week postoperatively was in 1 patient after DP-CAR; this complication was treated successfully by endoscopic clipping and percutaneous drainage without reoperation. Otherwise, there were no differences in mortality rate and the incidence of each complication between groups.

**Survival.** The median follow-up for all patients was 25 months. The estimated 1-year survival rate after standard DP was 81%, the 2-year survival rate was 52%, and the estimated median survival time was 32 months. The estimated 1-year survival rate after DP-CAR was 81%, the 2-year survival rate was 53%, and the estimated median survival time was also 25 months. Recurrence free-survival of all

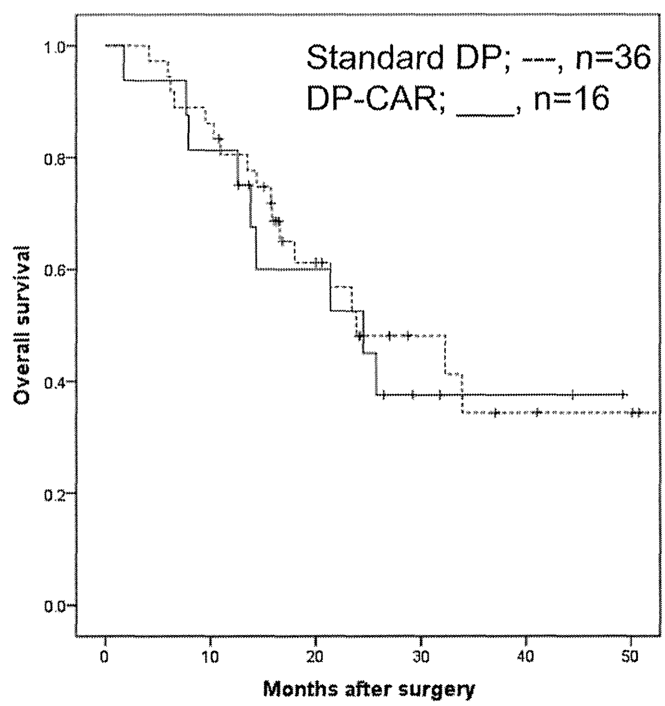
**Table II.** Postoperative complications and outcomes

| | *Standard DP* (n = *36*) | *DP-CAR* (n = *16*) | P *value* |
|---|---|---|---|
| Pancreatic fistula* | 10 (27.8%) | 3 (18.8%) | .49 |
| Grade A | 4 (11.1%) | 2 (12.5%) | .89 |
| Grade B | 6 (16.7%) | 1 (6.25%) | .31 |
| Grade C | 0 | 0 | |
| Delayed gastric emptying* | 0 | 2 (12.5%) | .03 |
| Grade A | 0 | 2 (12.5%) | .03 |
| Grade B | 0 | 0 | |
| Grade C | 0 | 0 | |
| Intra-abdominal abscess | 2 (5.6%) | 0 | .99 |
| Intra-abdominal hemorrhage* | 1 (2.8%) | 0 | .99 |
| Grade A | 0 | 0 | |
| Grade B | 1 (2.8%) | 0 | .99 |
| Grade C | 0 | 0 | |
| Wound infection | 0 | 1 (6.3%) | .31 |
| Pulmonary complications | 1 (2.8%) | 0 | .99 |
| Cardiac complications | 1 (2.8%) | 0 | .99 |
| Percutaneous drainage | 7 (19.4%) | 0 | .09 |
| Delirium | 0 | 1 (6.3%) | .31 |
| Edema of lower extremity† | 1(2.8%) | 0 | .99 |
| Reoperation | 0 | 0 | |
| Mortality | 0 | 0 | |

*Pancreatic fistula, delayed gastric emptying, and intra-abdominal hemorrhage are defined according to the International Study Group of Pancreatic Surgeons.
†One patient underwent portal vein reconstruction using an iliac vein graft.
*DP*, Distal pancreatectomy; *DP-CAR*, distal pancreatectomy with en-bloc celiac axis resection.

cases was 13 months; 7 patients are alive with local (DP-CAR; $n$ = 1), hepatic (standard DP; $n$ = 2), lung (standard DP, $n$ = 1; DP-CAR, $n$ = 1), lymph node (DP-CAR; $n$ = 1), and peritoneum (DP-CAR; $n$ = 1) recurrent disease. There were no differences in survival between patients who underwent standard DP and DP-CAR ($P$ = .650, log-rank test; Fig 1). Comparison of survival curves according to the curability of patients with standard DP revealed no differences between R0 ($n$ = 29) and R1 and R2 patients ($n$ = 7; $P$ = .694, log-rank test; Fig 2, *A*). According to the curability of DP-CAR, the mean estimated survival time (the median survival time could not be calculated) was 37 months in the 5 patients who underwent an R0 resection and 18 months in 11 patients with R1 and R2 resections (log-rank $P$ = .217; Fig 2, *B*). The estimated recurrence-free survival in all patients was greater in patients after R0 ($n$ = 34) than after R1/R2 ($n$ = 18; log-rank $P$ = .010; Fig 3). Thirty-six of 52 (10 after DP-CAR and 26 after standard DP) patients finished adjuvant chemotherapy as scheduled; the others refused because of poor general condition ($n$ = 8), early recurrence ($n$ = 5), and prolonged hospitalization ($n$ =3). The preoperative mean CA19-9 value of all patients was 171 U/mL (DP-CAR group, 208; standard DP group, 172). The preoperative CA 19-9 value was not a prognostic factor on survival.

**Tumor residual (R1) sites in the patients who underwent standard DP.** Positive margins in the peripancreatic tissue dissections were found in 7 patients who underwent standard DP. Two patients were positive in the peripancreatic tissue around the invasion site into another organ (stomach, colon). Five patients were positive around the transection margin of the SA, and the tumors of these 5 patients were situated near the root of the SA. The distance between the proximal edge of the tumor and the root of the SA in each patient was 23 mm (case 1), 10 mm (case 2), 9 mm (case 3), 8 mm (case 4), and 5 mm (case 5; Fig 4, *A*).




Patients at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| Standard DP | 36 | 31<br>(5) | 15<br>(13) | 7<br>(16) | 4<br>(18) | 3<br>(18) |
| DP-CAR | 16 | 13<br>(3) | 8<br>(6) | 3<br>(9) | 2<br>(9) | 0<br>(9) |

**Fig 1.** Comparison of the survival curves according to procedure revealed no differences between patients who underwent standard distal pancreatectomy (standard DP; –; $n$ = 36) and distal pancreatectomy with en-bloc celiac axis resection (DP-CAR; ___; $n$ = 16; $P$ = .755, log-rank test). The number listed below patients at risk represents the cumulative number of death.

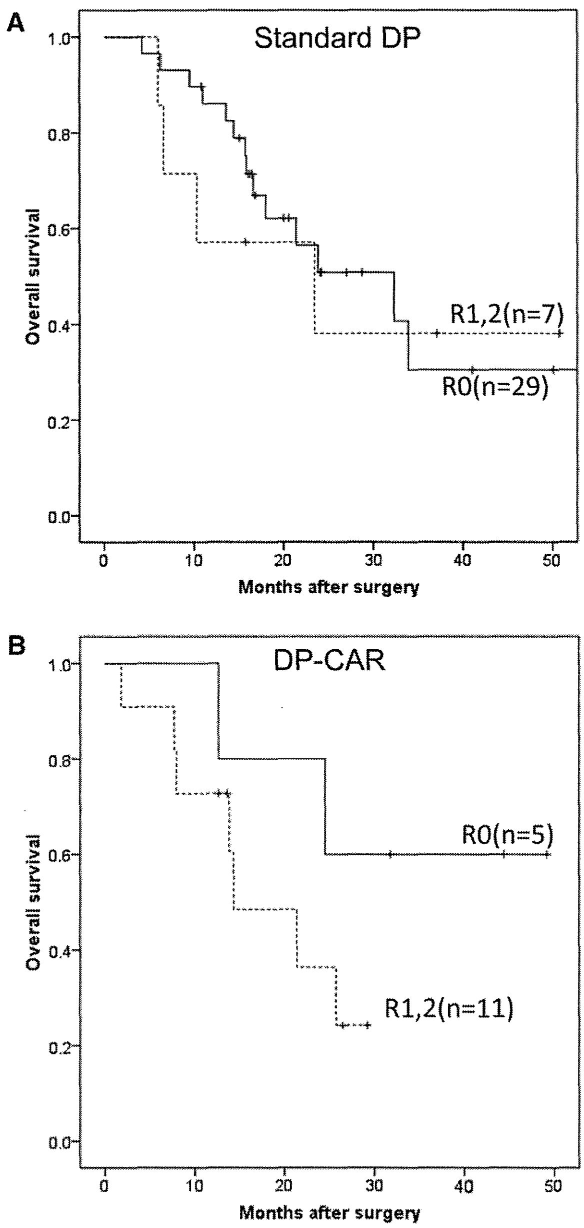
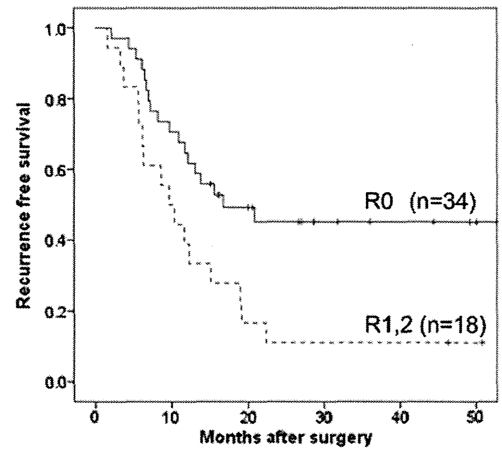



**Fig 2.** Comparison of survival curves according to (*A*) the curability of patients with standard DP revealed no differences between patients who achieved R0 (___; *n* = 29) and R1/R2 (–; *n* = 7) resections (*P* = .694, log-rank test) and (*B*) the curability in the DP-CAR group. Patients with R0 resections (___; *n* = 5) showed a better survival than those with R1 or R2 resections (–; *n* = 11; *P* = .217, log-rank test).

**The distance between the edge of the tumor and the SA in subjects who underwent standard DP.** The relationship between curability and the distance between the edge of the tumor and the SA root in patients who underwent standard DP is shown in Fig 4, *B*. The microscopically positive margins were detected more frequently in the patients with tumors situated ≤10 mm from the SA than those with a distance of >10 mm from the SA (*P* = .001; $\chi^2$ test).




Patients at risk

| | 0 | 10 | 20 | 30 | 40 | 50 |
|---|---|---|---|---|---|---|
| R0 | 34 | 24 (10) | 13 (17) | 7 (18) | 5 (18) | 3 (18) |
| R1,2 | 18 | 9 (9) | 3 (15) | 2 (16) | 2 (16) | 1 (16) |

**Fig 3.** Estimated recurrence-free survival curves according to the curability of all patients revealed that the estimated recurrence-free survival of R0 curability (___; *n* = 34) was greater than that of R1/R2 curability (–; *n* = 18; *P* = .010, log-rank test). The number listed below patients at risk represents the cumulative number of recurrence.

**Residual (R1) sites in DP-CAR.** Histopathologic examination revealed positive margins for tumor infiltration in 10 patients (63%). Microscopically positive margins, except for the pancreatic margin, were identified frequently in 2 dissected sites. The surface in front of the aorta at the root of the celiac axis in the periarterial nerve plexuses was involved in 4 patients. The retropancreatic tissue around the periarterial nerve plexuses of the celiac artery was involved in 6 patients. These positive margins were situated at the posterior extent of the resected specimens. The sites of first recurrence included the pancreatic margin (*n* = 4), liver (*n* = 4), lymph node (*n* = 2), peritoneum (*n* = 2), and lung (*n* = 1); all of whom have died. The other 3 patients are still alive without any evidence of recurrence.

**Prognostic factors for patients who underwent DP-CAR.** Univariate analysis using the Kaplan–Meier method and log-rank test showed a relationship between the clinicopathologic features and survival of patients with pancreatic carcinoma undergoing DP-CAR. The patient survival correlated negatively with the portal venous system invasion (*P* = .023). The estimated overall survival rate in patients with pathologically negative