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Outcomes of pancreatic resection for elderly patients with pancreatic cancer
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Abstract:
Background
Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease with poor, albeit gradually improving, prognosis. We evaluated predictive clinicophysiological outcomes of elderly patients with PDAC.

Methods
We retrospectively examined 260 patients who underwent pancreatic resection classified into two groups: (A) those ≤ 80 (B) and those > 80 years. Operative characteristics, preoperative clinicophysiological parameters (body mass index, jaundice decompression, total bilirubin, albumin, creatinine, HbA1c, amylase, C-reactive protein, white blood cells, lymphocytes, hemoglobin, platelets, cancer antigen 19-9, carcinoembryonic antigen, neutrophil/lymphocyte ratio, prognostic nutritional index, platelet/lymphocyte ratio, and CRP/Alb ratio), disease-free survival (DFS), and overall survival (OS) were reported.

Results
There were no differences noted in morbidity, mortality, and preoperative clinicophysiological parameters. Median DFS of groups A and B were 15.4 and 15.5 months respectively. One year and 3-year OS of groups A and B were 86.7/68% and 88.4/69.3%, respectively. There were no differences between the groups for DFS and...
**Conclusion**

Curative resection for PDAC can be safely performed in elderly and younger patients and elderly patients with PDAC can benefit from curative surgery without a significant decrease in survival rates.
Original Article
Outcomes of pancreatic resection for elderly patients with pancreatic cancer

Running head: elderly patients with pancreatic cancer

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Original Article

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Running head: elderly patients with pancreatic cancer
Abstract

**Background:** Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease with poor, albeit gradually improving, prognosis. We evaluated the predictive clinicophysiological outcomes of elderly patients with PDAC.

**Methods:** We retrospectively examined 260 patients who underwent pancreatic resection classified into two groups: (A) those ≤ 80 (B) and those > 80 years. Operative characteristics, preoperative clinicophysiological parameters (body mass index, jaundice decompression, total bilirubin, albumin, creatinine, HbA1c, amylase, C-reactive protein, white blood cells, lymphocytes, hemoglobin, platelets, cancer antigen 19-9, carcinoembryonic antigen, neutrophil/lymphocyte ratio, prognostic nutritional index, platelet/lymphocyte ratio, and CRP/Alb ratio), disease-free survival (DFS), and overall survival (OS) were reported.

**Results:** There were no differences in morbidity, mortality, and preoperative clinicophysiological parameters between both groups. Median DFS of groups A and B were 15.4 and 15.5 months, respectively. One-year/3-year OS of groups A and B were
86.7/68\% and 88.4/69.3\%, respectively. There were no differences in DFS and OS between the groups.

**Conclusion:** Curative resection for PDAC can be safely performed in elderly and younger patients, and elderly patients with PDAC can benefit from curative surgery without a significant decrease in survival rates.

**Keywords:** pancreatic cancer, elderly patient, clinicophysiological parameters, disease-free survival, overall survival
Introduction

Treatment for patients with cancer has become a major public concern as the aging population continues to grow. This is especially true in Japan, where the aging population is growing more rapidly compared to the US and other European countries (1). From 2007 to 2011, the overall pancreatic ductal adenocarcinoma (PDAC) incidence rates were stable after slowly increasing for most of the past decade, and the death rate for PDAC increased slightly by 0.3% per year (2). As the population ages were older, more and more elderly patients were being diagnosed with PDAC and referred for treatment of their disease. In the Western population, two-thirds of patients with PDAC are older than 65 years (3). In Japan, the age-specific incidence of PDAC from age distribution in those <70 years old was 47.5% (<70/all ages number), and for those ≤80 years old, it was 17.9% (≤80/all ages number) based on data from 10 population-based cancer registries (4).

On the other hand, PDAC had a bad prognosis. In global surveillance of trends, age-standardized five-year net survival estimates were generally in the range 5–15% throughout 2000 to 2014 (5). The 5-year survival rate after curative resection of PDAC in
recent decades (2001 to 2007) has been reported to be 18.8% in the Japan pancreatic cancer registry (6). Furthermore, surgical resection has proven to be the only effective means of curing PDAC (3,7). For radically resected PDAC, the 5-year survival rate is 21.3–44.1%, which was recently improved by adjuvant chemotherapy and aggressive combined vessel resection (7-9). Previous studies have addressed the safety of pancreatic resection in patients aged 80 years or older with various comorbid disorders; however, the optimal therapeutic strategy for very elderly patients with PDAC remains to be determined (10).

As elderly patients increase in number, medication treatment of older patients with PDAC is becoming more and more important. We aimed to evaluate the predictive clinicophysiological outcomes of elderly patients with PDAC.

Methods

Between 2007 and 2015, 260 consecutive patients who underwent pancreatic resection for pancreatic cancer at the Ibaraki Medical Center and the University Hospital, Tokyo Medical University, were retrospectively examined. All patients were classified into two
groups: (A) patients < 80 years (B) patients ≥ 80 years. Outcomes, including operative characteristics, operative procedures, postoperative pancreatic fistula, length of hospital stay, morbidity, mortality, preoperative clinicophysiological parameters, disease-free survival (DFS), and overall survival (OS) were reported. All patients had pathologically confirmed PDAC. Data on clinicophysiological parameters such as body mass index (BMI), jaundice decompression, total bilirubin, albumin, creatinine, HbA1c, amylase, C-reactive protein (CRP), white blood cells (WBC), lymphocytes, hemoglobin, platelets, cancer antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), neutrophil/lymphocyte ratio (NLR), prognostic nutritional index (PNI), platelet/lymphocyte ratio (PLR), and CRP/Alb ratio (CAR), were collected.

Patients with a performance status of 3 or 4 were ineligible for surgical intervention in all generations. If they had an American Society of Anesthesiologists’ physical status system score of 1, 2, or 3 under general operative conditions, pancreaticoduodenectomy (PD) was performed in all generations. Postoperative main complications of this study were classified as grades 3-5 by the Clavien-Dindo’s classification (11). Delayed gastric
emptying in this study was defined as grade B/C of the International Study Group of Pancreatic Surgery (12). Postoperative pancreatic fistula was defined based on the International Study Group on Pancreatic Fistula definition (13).

**Statistical analysis**

Continuous variables were compared using the Student's t-test and Chi-square test.

Kaplan–Meier survival curves were generated and compared using log-rank tests. Cox proportional hazard models were used to perform multivariate analyses. P-values of <0.05 were considered statistically significant. The SPSS statistical software package, version 22.0 (IBM Corp., Chicago, IL, USA) was used for statistical analyses.

**Ethical conduct**

This study was approved by the Research Ethics Committee of Ibaraki Medical Center, Tokyo Medical University (acceptance number 16-26). All procedures performed in studies involving human participants were in accordance with the ethical standards of the
institutional research committee and with the 1964 Helsinki Declaration. This article does not contain any study performed on animals by any of the authors. The requirement for obtaining written informed consent from each patient was waived because of the study’s retrospective design. We provided the patients with the opportunity to Opt-Out.

Results

The mean patient age was 68.15 years (range: 36–88 years), and the cohort included 160 men and 100 women. Surgical methods included primary distal pancreatectomy in 79 patients (including en bloc celiac axis resection in 10), PD in 172 patients (pylorus-preserving in 10, subtotal stomach-preserving in 149, and conventional in 13), and total pancreatectomy in nine patients. The analyses of the operative background relationship between Group A and B are shown in Table 1. Groups A and B consisted of 220 and 40 patients, respectively. The average age was $65.55 \pm 0.62$ years in group A and $82.50 \pm 0.35$ years in group B. There were 142 males and 78 females in group A and 18 males and 22 females in group B. There were significant differences in age and sex. Operative
procedures in both groups (pancreaticoduodenectomy/ distal pancreatectomy/ total pancreatectomy) were 149/63/8 in group A and 23/16/1 in group B ($p = 0.35$). The stages in both groups (0/Ia/Ib/IIa/IIb/III/IV) were 7/5/48/154/0/5 in group A and 2/0/12/23/0/2 in group B ($p = 0.444$). The preoperative background in these groups did not differ in terms of location, biliary decompression, modified Glasgow Prognostic Score (mGPS), stage, and resectability (R). There were no differences in any of the preoperative clinicophysiological parameters, as shown in Table 2. Preoperative inflammation and immunological findings such as CRP, WB, NLR, PLR, CAR were not significantly different and nutritional findings such as albumin and PNI were not significantly different either. In this study, neoadjuvant therapies were administered in 39 cases (15%) as follows: 25 with radiation+gemcitabine+S-1, 8 with gemcitabine+S-1, 3 with gemcitabine+nab-paclitaxel, 2 with radiation+gemcitabine, and 1 with gemcitabine. Adjuvant chemotherapies were administered in 179 cases (68.8%) as follows: 97 cases with S-1, 75 with gemcitabine+S-1, 62 with gemcitabine, 4 with gemcitabine+cisplatin, 2 with gemcitabine+nab-paclitaxel, and 1 with Tegafur/Uracil. Neoadjuvant therapies in group A were significantly more than those
in group B. As shown in Table 3, there was no significant difference between groups A and B in postoperative variables such as adjuvant chemotherapies, morbidity, mortality, postoperative pancreatic fistula, and length of hospital stay. The median DFS of groups A and B was 15.4 and 15.5 months \((p = 0.764)\), respectively (Figure 1). One-year/3-year OS of groups A and B was 86.7/68\% and 88.4/69.3\% \((p = 0.412)\), respectively (Figure 2).

There were no differences between these groups in terms of DFS and OS.

**Discussion**

The safety of pancreatic resection has improved in recent years due to improvements in surgical techniques, perioperative care, and postoperative management. Resection has become a feasible procedure even for elderly patients (14-16). Contrary to previous studies that suggest that age is not an independent risk factor for patients undergoing PD (17,18), postoperative morbidity and mortality of elderly patients were significantly higher than that of younger patients in several previous reports (19-21). Turrini et al. reported that elderly patients might obtain comparable advantages from pancreatectomies for PDAC than did
younger patients and healthy elderly patients with resectable PDAC should not be excluded from surgical resection of PDAC solely because of their age (22). In previous reports, several diseases involved periampullary lesions. Outcomes for pancreatectomies of PDAC with dissection of extended lymph nodes were different than those of pancreatectomies for other diseases such as distal bile duct cancer, ampulla of Vater cancer, and duodenal cancer.

Therefore, we aimed to evaluate the predictive clinicophysiological outcomes for only PDAC in elderly patients.

Several meta-analyses and systematic reviews have evaluated the clinicophysiological outcomes of elderly patients who underwent PDAC. Sukharamwala et al. found that patients ≥80 years of age had a higher rate of postoperative mortality and incidence of pneumonia compared to younger patients after PD (23). Casadei et al. suggested that patients ≥80 years of age have increased postoperative mortality and morbidity rates, as well as the incidence of cardiac complications and longer length of hospital stays than younger patients. They also suggested that pancreatic resection could be recommended only in a selected group of patients ≥80 years of age (24). Oguro et al. studied 561 patients,
including 22 patients ≥80 years of age who underwent PD for pancreatic cancer and found that patients in this age range should be carefully selected since these patients had a higher incidence of severe postoperative complications but only a slightly better long-term survival (25). These researchers revealed that elderly patients had a higher risk of mortality, morbidity, and some complications than did younger patients, and therefore, an appropriate selection of elderly patients was important.

We investigated recent reports evaluating the outcomes in patients ≥80 years who underwent pancreatic resection after 2010 (Table 4) (10,16,21,22,25-28). The results of these 12 studies showed that the difference in morbidity between elderly patients and younger patients has gradually decreased over time, and that overall mortality rates of elderly patients undergoing this procedure have decreased.

An analysis of short-term outcomes revealed that elderly patients developed more postoperative anorexia and cachexia, thus compromising their nutritional and functional status more frequently than did younger patients (17).

There were no differences in postoperative complications such as pancreatic fistula and...
delayed gastric empty between older patients and younger patients (29,30). Postoperative cardiac complications in several studies were significantly more frequent in patients 80 years or older than in younger patients (24). However, the incidences of cardiopulmonary complications, re-intervention rate, and re-admission rate in another meta-analysis were similar in these groups (22). In this study, there was no significant difference between variables, including hospital stay ($p = 0.869$), morbidity ($p = 0.449$), and mortality ($p = 0.285$). Sho reported that the postoperative prognosis in older patients was not as good as that in younger patients, possibly due to less frequent completion of adjuvant chemotherapy (10). As our report revealed, similar to younger patients, older patients could have received adjuvant chemotherapies; there were no differences between older and younger patients in terms of DFS and OS in our study. Our study also indicated no difference in complications between younger and elderly patients (Table 4).

The 5-year survival rate after curative resection of PDAC in recent decades (2001 to 2007) has been reported to be 18.8% (5). The results in Table 3 show that there was no difference in OS among patients included in the study; however, the OS of elderly patients and
younger patients was prolonged. Patients also need to be aware that surgical resection is the only curative option for PDAC (19). Moreover, the main cause of death in elderly patients who underwent pancreatectomy was PDAC recurrence, similar to younger patients (17). In reasonably healthy patients, the benefit of surgical resection for PDAC does not decrease with age, and these patients can experience long-term survival and good quality of life (19,31). Therefore, the life-limiting factor in these elderly patients with resected PDAC has more to do with their cancer than their age (15,16,22).

There are several limitations associated with our study. First, the criteria for selecting elderly patients were not standardized among the hospitals. Hence, additional multicenter investigations involving larger patient populations are needed before definitive conclusions can be drawn. Though the research design was retrospective, our PDAC cases were consecutive.

Conclusions

Pancreatic curative resection for PDAC can be safely performed in both elderly and
younger patients. Furthermore, the benefits that elderly patients receive from curative surgery for PDAC and overall survival rates are comparable to those received by younger patients.

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Figure Legends

Figure 1

Kaplan-Meier curves for disease-free survival of patients with PDAC between group A (≤80) and group B (80<); there were no significant differences (p = 0.764)

Figure 2

Kaplan-Meier curves for overall survival of patients with PDAC between group A (≤80) and group B (80<); there were no significant differences (p = 0.412).
Figure 1

Survival (%) vs. Time (days)

Group A

Group B
Figure 2

![Survival Rate over Time Graph]

- **Group A**
- **Group B**
| Variable                  | factors       | Group A (≤80) | Group B (>80) | P value |
|--------------------------|---------------|---------------|---------------|---------|
| number                   |               | 220           | 40            |         |
| Age                      |               | 65.55±0.62    | 82.50±0.35    | p<0.001 |
| Sex                      | Male          | 142           | 18            | 0.022   |
|                          | Female        | 78            | 22            |         |
| Location                 | Total         | 8             | 1             | 0.35    |
|                          | Head          | 149           | 23            |         |
|                          | Body/tail     | 63            | 16            |         |
| operative procedure      | pancreaticoduodenectomy | 149  | 23 | 0.35 |
|                          | distal pancreatectomy   | 63    | 16 |     |
|                          | total pancreatectomy    | 8     | 1  |     |
| jaundice decompression   | (-)            | 124           | 27            | 0.224   |
|                          | (+)            | 96            | 13            |         |
| mGPS                     | 0,1            | 194           | 33            | 0.287   |
|                          | 2              | 24            | 7             |         |
| Stage                    | 0              | 1             | 0             | 0.444   |
|                          | I a            | 7             | 2             |         |
|                          | I b            | 5             | 0             |         |
|                          | II a           | 48            | 13            |         |
|                          | II b           | 154           | 23            |         |
|                          | III            | 0             | 0             |         |
|                          | IV             | 5             | 2             |         |
| R                        | 0              | 183           | 28            | 0.119   |
|                          | 1              | 33            | 10            |         |
|                          | 2              | 4             | 2             |         |

mGPS: modified Glasgow Prognostic Score, R: resectability

Table 1 The analyses of operative background relationship between Group A and B
Table 2 The analyses of preoperative clinicophysiological background factors relationship between group A and B

| Variable          | Group A(≤80) | Group B(80<) | P value |
|-------------------|-------------|-------------|---------|
| BMI(kg/m²)        | 21.82±0.21  | 21.75±0.55  | 0.073   |
| Total bilirubin(mg/dl) | 1.34±0.11    | 1.16±0.27   | 0.553   |
| Creatine(mg/dl)   | 3.74±0.03    | 3.74±0.08   | 0.97    |
| HbA1C(%)          | 6.64±0.13    | 6.25±0.22   | 0.144   |
| Amylase(IU/L)     | 100.77±8.01  | 97.50±10.55 | 0.806   |
| CRP (mg/dl)       | 1.03±0.17    | 1.08±0.49   | 0.932   |
| WBC (/µl)         | 5614.55±125.17 | 5690.00±284.65 | 0.809   |
| Lymphocytes(/µl)  | 1473.11±37.24 | 1355.58±80.89 | 0.192   |
| Hemoglobin (g/dl) | 12.15±0.11   | 12.07±0.23  | 0.758   |
| Platelets (×104/µl) | 21.55±0.53    | 20.48±1.10  | 0.385   |
| CA19-9 (U/ml)     | 444.18±76.21 | 531.53±150.24 | 0.606   |
| CEA (ng/ml)       | 4.93±0.45    | 4.26±0.67   | 0.408   |
| NLR               | 2.78±0.13    | 3.34±0.39   | 0.181   |
| PNI               | 44.70±0.38   | 44.13±1.01  | 0.601   |
| PLR               | 163.06±5.53  | 178.78±17.79 | 0.403   |
| CAR               | 0.32±0.05    | 0.35±0.17   | 0.849   |

±SD

BMI: body mass index, CRP:: C-reactive protein ,WBC: white blood cell, CA19-9: cancer antigen 19-9 , CEA: carcinoembryonic antigen, NLR: neutrophil/lymphocyte ratio, PNI: prognostic nutritional index, PLR: platelet/lymphocyte ratio, CAR: CRP/Albmin ratio ,

Table 2 The analyses of preoperative clinicophysiological background factors relationship between group A and B
Table 3 The analyses of postoperative factors relationship between Group A and B

| Variable                                      | factors      | Group A (≤80) | Group B (≥80) | P value |
|-----------------------------------------------|--------------|---------------|---------------|---------|
| number                                        |              | 220           | 40            |         |
| Neoadjuvant therapies                         | (-)          | 182           | 39            | 0.016   |
|                                               | (+)          | 38            | 1             |         |
| Adjuvant therapies                            | (-)          | 65            | 16            | 0.189   |
|                                               | (+)          | 155           | 24            |         |
| Morbidity (%)                                 |              |               |               | 0.449   |
| Mortality (%)                                 |              | 0.45          | 2.5           | 0.285   |
| postoperative main severe complication        | cardiac complication | 0 | 0 |         |
|                                               | respiratory complication | 0 | 2 |         |
|                                               | infectious complication | 9 | 0 |         |
|                                               | brain infarction | 1 | 0 |         |
|                                               | cholangitis | 3 | 1 |         |
|                                               | bleeding | 10 | 0 |         |
|                                               | delayed gastric emptying | 7 | 0 |         |
| postoperative pancreatic fistula              | (-), biochemical leak | 203 | 36 | 0.542 |
|                                               | B/C         | 17            | 4             |         |
| length of stay in hospital                    |              | 25.48±1.29    | 26.05±4.00    | 0.869   |
| Author       | Indication            | operation | age | N   | Morbidity (%) | Mortality (%) | 5-year DFS (%) | DFS (media n:months) | 5-year OS (%) | OS (media n:months) | OS: P value |
|--------------|-----------------------|-----------|-----|-----|----------------|---------------|-----------------|----------------------|---------------|---------------------|-------------|
| Hatzaras     | 2011                  | Pancreatic malignancy | PD and DP | <80 | 490            | 59            | 3.7             | -                    | 34.8          | 21.9                | 0.18        |
| de la Fuente | 2011                  | periampullary neoplasms | PD | <80 | 5700           | 35.8          | 2.7             | -                    | -             | -                   | -           |
| Stauffer     | 2011                  | periampullary neoplasms | PD | <80 | 434            | -             | -               | -                    | -             | -                   | -           |
| Belyaev      | 2013                  | Benign and Malignant PD, DP and TP | PD | <80 | 1705           | 42            | 2.5             | -                    | -             | -                   | -           |
| Oguro        | 2013                  | periampullary malignancy | PD | <80 | 539            | 9.6           | 0.9             | -                    | 51            | 65                  | 0.277       |
| Turrini      | 2013                  | PDAC PD, DP and TP | <80 | 868 | -              | -             | 3.1             | -                    | 33.2          | 35.3                | 0.16        |
| Frakes       | 2014                  | PDAC PD | <70 | 106 | -              | -             | 17.2            | -                    | 15.6          | 26.7                | 0.62        |
| Sho          | 2016                  | PDAC PD, DP and TP | <80 | 1302 | 23            | 2             | -               | -                    | 16.6          | 0.006               |
| our study    | 2020                  | PDAC PD, DP and TP | <80 | 220 | 29.1           | 0.45          | 20.1            | -                    | 15.4          | 55.2                | 0.412       |

Table 4 recent reports evaluating the outcomes in patients aged 80 years and older undergoing pancreatic resection after 2010

**Table 4** recent reports evaluating the outcomes in patients aged 80 years and older undergoing pancreatic resection after 2010

PDAC: pancreatic ductal adenocarcinoma, PD: pancreaticoduodenectomy, DP: distal pancreatectomy, TP: total pancreatectomy, OS: overall survival, DFS: Disease free survival