

Comparisons of Outcomes Between Adolescent and Young Adult with Older Patients After Radical Resection of Pancreatic Ductal Adenocarcinoma by Propensity Score Matching: A Single-Center Study

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Purpose: Adolescent and young adult (AYA) pancreatic ductal adenocarcinoma (PDAC) occurs in patients below 40 years old. Whether AYA patients have worse outcomes compared with older patients is still controversial. The purpose of this study is to compare the outcomes of AYA patients and older patients after radical surgery for PDAC.

Methods: A single-center, retrospective, cohort study was conducted in patients who underwent radical surgery for PDAC in Xiangya Hospital Central South University from January 2007 to December 2019. The clinicopathological data and results of patients with PDAC were collected and analyzed retrospectively. They were divided into AYA group and older group based on age (<40, AYA group; ≥40, older group). Based on all the considered covariates except age, we estimated 1:2 case propensity score matching (PSM).

Results: A total of 1033 cases were enrolled, 46 cases (4.45%) in the AYA group. Both before and after PSM, the AYA patients have a higher preoperative CA19-9 than the older patients ($P < 0.001$) and ($P < 0.001$). Pathological results showed that AYA group had a higher microvascular invasion rate ($P < 0.001$ and $P = 0.045$) than older group. The median time of overall survival (OS) in AYA group and older group were 13 months (95% $CI = 11.50-14.50$) and 14 months (95% $CI = 13.50-14.50$), respectively. Additionally, AYA group have a worse 2-year OS rate than older group (8.70% vs 25.23%, $P = 0.011$ and 8.70% vs 25.00%, $P = 0.023$). According to the Log rank test, AYA group have a worse cumulative OS rate than older group ($P = 0.002$) and ($P = 0.030$), respectively.

Conclusion: PDAC might be more aggressive in AYA, and the cumulative OS after radical PDAC surgery in AYA patients is worse than that in older patients.

Keywords: adolescent and young adult, AYA, pancreatic ductal adenocarcinoma, PDAC, propensity score matching, PSM, total pancreaticoduodenectomy, TPD, overall survival, OS

Introduction

In recent years, the incidence rate of cancer has been increasing all over the world. Compared with the elderly, young cancer patients are often ignored. However, increasing studies have been reported that cancer is showing a younger trend. The American Cancer Society predicts that in 2020, there will be about 89,500 new cancer cases and 9270 new cancer deaths among young people aged 15–39.¹ AYA Cancer is defined by the National Cancer Institute (NCI)'s AYA Oncology Progress Review Group for the patients diagnosed between 15 and 39 years old.² Approximately 70,000 new cases of invasive cancer were diagnosed annually in AYAs.³ Compared with cancer in the other

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age groups, AYA cancer is unique for the important differences in tumor biology and molecular features.^{4,5} However, the understanding of the AYA cancers is limited currently, and whether there is a worse prognosis than other age groups is still controversial.^{6,7}

Pancreatic cancer (PC) is still one of the deadliest malignant cancers in the world.⁸ In the United States, PC is the third leading cause of cancer death, and the 5-year survival rate is less than 10%, with only marginal improvement during the last decades.⁹ Epidemiological prediction models estimate PC will become the second cause of cancer-related death by 2030.¹⁰ Pancreatic ductal adenocarcinoma (PDAC) accounts for more than 90% of all PC. Therefore, PDAC contributes to the major mortality of PC.¹¹ Typically, PDAC is considered to be a disease in the elderly, the median onset age of PDAC is around 68 years old in the US, and it rarely affects the young people.¹² Although young patients diagnosed with PDAC is a small fraction, but this group dramatically contributes to the societal burden of PDAC, because of the greater number of years of potential life lost.¹³ In addition, the incidence of PDAC in AYAs has increased in recent years.¹⁴ However, the research on AYAs is limited, and the difference in tumor biology between the AYA group with PDAC and older groups with PDAC is still uncertain. Therefore, we conducted a retrospective analysis to compare the clinicopathological features and survival outcomes between patients with PDAC in AYAs and the older patients, who underwent radical resection for PDAC.

Patients and Methods

This research complied with the Declaration of Helsinki. This research was performed in accordance with the 1964 Helsinki Declaration, and the study was approved by the Ethics Committee of Xiangya Hospital Central South University, China (reference: 202012196). Due to the retrospective nature of this research, there was no requirement for informed consent from the patients. The data of the patients in the survey was kept confidential.

Patient Selection

This retrospective cohort study retrieved 3596 patients diagnosed with space-occupying lesions of pancreatic who were admitted to Xiangya Hospital Central South University from January 2007 to December 2019. Patients who had not undergone radical resection (R1/R2 resection), neoadjuvant therapy and incomplete information (lost to follow-up patients) were excluded firstly, leaving 1883 cases. Secondly, according to the postoperative pathological results, patients with non-

PDAC were excluded, with 1033 cases remaining. The patients were divided into the AYA group and the older group according to the age less than 40 years old and greater than or equal to 40 years old, 46 cases in the AYA group, 987 cases in the older group. After propensity score matching (PSM), there were 46 cases in the AYA group, 92 cases in the older group. The design of this study is shown in Figure 1.

Observation Indicators

The clinical data of patients were collected, including gender, age, body mass index (BMI), smoking, drinking, family history, symptoms, comorbidity (including coronary artery disease (CAD), hypertension, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), chronic renal insufficiency (CRI)), albumin, hemoglobin, carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA). The imaging (abdominal ultrasound, abdominal CT, MRI/magnetic resonance cholangiopancreatography (MRCP)), operation status (including the location of the tumor, tumor size, surgery types, vascular invasion, and blood loss), and pathological results (including tumor size, degree of differentiation, lymph nodes status and microvascular invasion status) are also required. Treatment regimen, perioperative mortality and postoperative hospital stay were also included. Postoperative tumor stage based on the 8th American Joint Committee on Cancer (AJCC) tumor TNM stage¹⁵ was obtained. Postoperative complications (including postoperative pancreatic fistula (POPF), intraabdominal abscess (IAA), postpancreatectomy hemorrhage (PPH), delayed gastric emptying (DGE), and perioperative mortality), and overall survival (OS) were essential indices.

Postoperative complications were defined as follows:

- Perioperative mortality: death within 30 days of surgery or during the hospitalization.¹⁶
- POPF: drain output of any measurable volume of fluid and amylase level > three times the upper limit of institutional normal serum amylase activity and have clinically relevant development/condition directly related to the postoperative pancreatic fistula.¹⁷
- IAA: the culture results of abdominal drainage or puncture fluid were positive, and there were clinical manifestations of fever.
- PPH: refers to the consensus on postpancreatectomy hemorrhage (PPH) proposed by the International Study Group of Pancreatic Surgery (ISGPS) in 2007.¹⁸
- DGE: refers to the consensus on delayed gastric emptying (DGE) proposed by the International Study Group of Pancreatic Surgery (ISGPS) in 2007.¹⁹

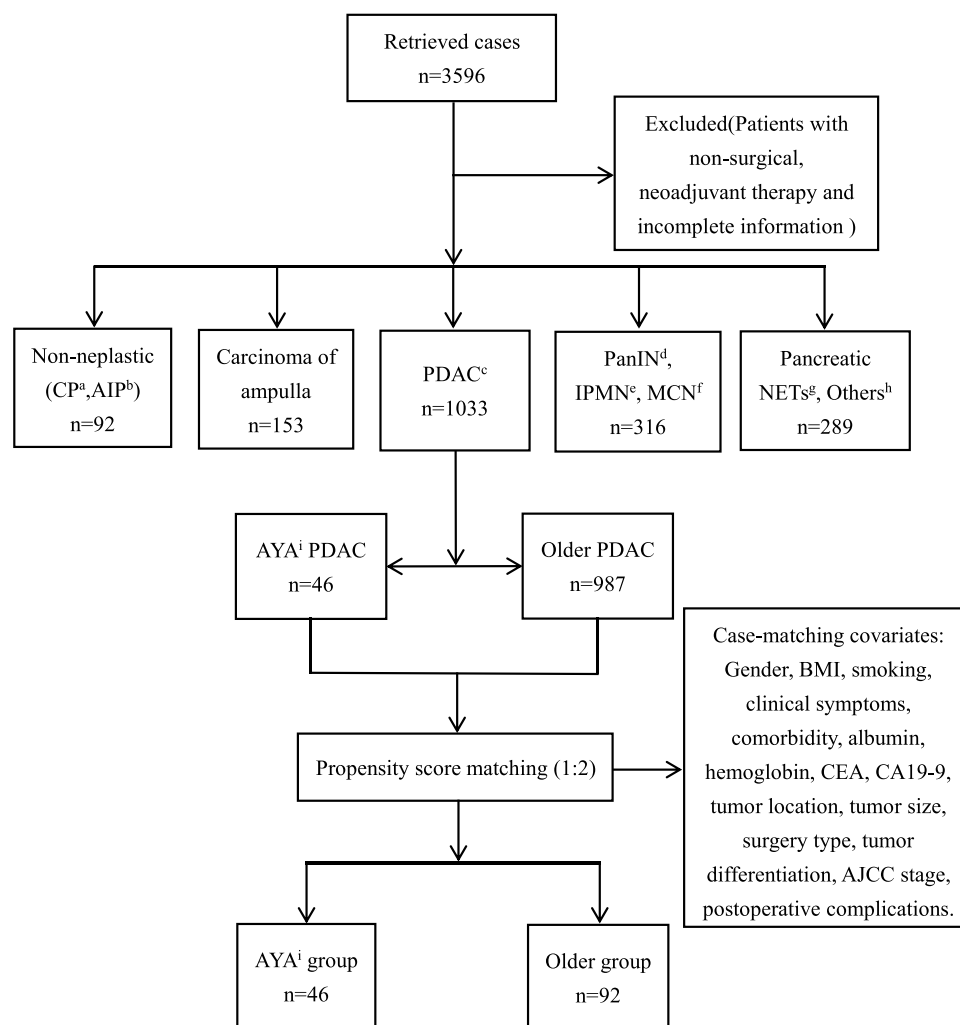


Figure 1 Study flow chart. Search results of patients with space-occupying lesions of pancreatic who hospitalized in Xiangya Hospital Central South University from January 2007 to December 2019. A total of 1033 cases meet the inclusion and exclusion criteria. AYA PDAC 46 cases, older PDAC 987 cases. After propensity score matching (PSM), there were 46 cases in AYA group, 92 cases in Older group.

Abbreviations: aCP, chronic pancreatitis; bAIP, autoimmune pancreatitis; cPDAC, pancreatic ductal adenocarcinoma; dPanIN, pancreatic intraepithelial neoplasia; eIPMN, intraductal papillary mucinous neoplasm; fMCN, mucinous cystic neoplasm; gNETs, neuroendocrine tumours; hOther, solid pseudopapillary neoplasm, undifferentiated carcinoma, mucinous cystadenocarcinoma mixed ductal-neuroendocrine carcinoma; iAYA, adolescent and young adult.

Surgical Technique

All operations are performed by experienced pancreatic surgeons. The operation is performed under general anesthesia. Choose the appropriate surgical method according to the location of the tumor, such as pancreaticoduodenectomy (PD), distal pancreatectomy (DP) and splenectomy, and total pancreaticoduodenectomy (TPD); all patients underwent standard radical resection of PDAC, and all of these patients have a R0 resection, with corresponding intraoperative dissection lymph nodes.

Follow-Up

The follow-up period was the time between the surgery to the last follow-up. During follow-up period, patients

underwent CT or MRI/MRCP every 3 months in the first year, every 6 months in the second year and then once a year to monitor survival and recurrence. For those patients who did not come to the outpatient clinic, we asked them the general conditions, survival and recurrence by telephone. OS was defined as the time interval (months) from operation to death or the last follow-up.

Propensity Score Matching and Statistical Analysis

In order to reduce potential selection bias and confounding factors in retrospective observational studies, we performed PSM between the AYA group and the older group. PSM analysis is a popular approach that uses the propensity scores

calculated by logistic regression models to form matched sets with similar distributions.²⁰ Moreover, SPSS version 3.0.4 (Felix Thoemmes, Cornell University/University of Tübingen) and Stata 15.0 (Stata Corp, College Station, TX) are used for propensity score matching analysis and stratification analysis with interaction tests, respectively. Specifically, open SPSS version 3.0.4 and select “PS Matching of analyze”. Then, enter the grouping variable age in the “Propensity Score Matching dialog box” and select it into “Binary Indicator”, where 1 represents the AYA group and 0 represents the older group. The covariates sex, BMI, smoking, drinking, family history, symptoms, comorbidity, albumin, hemoglobin, CEA, CA19-9, tumor location, tumor size, surgery types, vascular invasion, blood loss, treatment regimen, grade differentiation, lymph node status, microvascular invasion, AJCC stage, grade differentiation, postoperative complications (POPF, IAA, PPH, DGE), perioperative mortality, postoperative hospital stay used to calculate the propensity score were selected as covariates, set the caliper value to 0.05. “Histogram of standardized differences”, “Dotplot of standardized mean differences”, “Line plot of individual differences” were checked under plots to plot SD distribution histogram, univariate SD scatter plot, and line plot of standardized differences, respectively. Under output datasets, check paired datasets by “matched_id”, under Include, select Matched cases, and under balance statistics, select “Detailed - Under Match Ratio”, then, select “Match 1: many”, enter 2, and select “Random for the Matching” order drop-down box. Finally, click “OK” to finish matching.

Data were analyzed with IBM SPSS Statistics 22.0 (IBM, Inc., Armonk, NY). Continuous variables were presented as means \pm standard deviation (SD), then compared via Student's *t*-test. Categorical variables were compared using the Chi square test. All statistical analyses were two-tailed, *P*-values <0.05 were considered to be statistically significant differences. The overall survival curves were determined by the Kaplan–Meier method and compared by the Log rank test.

Results

Patients Characteristics

A total of 1033 patients who underwent radical surgery for PDAC were included after screening, all of them had a R0 resection, and the screening method is shown in Figure 1. Pathological results were obtained in all cases and all of them were diagnosed as PDAC. The mean age of onset of patients in the AYA group and the older group was $36.22 \pm$

2.21 and 63.84 ± 7.95 years old. The clinicopathological characteristics of patients, both before and after PSM, are presented in Table 1.

Before PSM, 46 (4.45%) patients were in AYA group, 987 (95.55%) patients were in older group. AYA group had a higher incidence of male (73.91% vs 59.17%, $P < 0.05$). The incidence of stomachache was higher in the AYA group (80.43% vs 34.65%, $P < 0.05$). Compared with the AYA group, the older group had a higher incidence of hypertension, CAD and COPD, which were as follows: 33.94% vs 4.35%, $P < 0.001$, 12.66% vs 2.17%, $P = 0.034$ and 16.62% vs 2.17%, $P = 0.009$ (Table 1). The preoperative mean CA19-9 in the AYA group and the older group were 234.69 ± 209.57 vs 125.22 ± 164.53 , $P < 0.001$. There were no significant differences between the AYA group and older group for the following patient characteristics: BMI (21.95 ± 2.18 vs 21.88 ± 2.20 , $P = 0.873$), smoking (63.04% vs 55.32%, $P = 0.303$), drinking (65.22% vs 54.91%, $P = 0.169$), family history (8.70% vs 4.46%, $P = 0.182$), obstructive jaundice (71.74% vs 56.35%, $P = 0.372$), weight loss (39.18% vs 40.12%, $P = 0.893$), diabetes mellitus chronic (DM) (32.61% vs 36.27%, $P = 0.613$), preoperative albumin (38.53 ± 3.36 vs 38.16 ± 2.77 , $P = 0.396$), hemoglobin (12.20 ± 1.23 vs 12.10 ± 0.74 , $P = 0.374$), CEA (6.22 ± 12.83 vs 5.51 ± 10.85 , $P = 0.667$) (Table 1).

After 1:2 PSM, 46 patients were in AYA group, 92 patients were in older group. The two groups did not significantly differ for any tested variables except for the presence of preoperative mean CA19-9 (234.69 ± 209.57 vs 123.28 ± 166.32 , $P < 0.001$).

Intraoperative and Postoperative Results

Surgery types include PD, DP and splenectomy, and TPD. The intraoperative tumor size in the AYA group and older group was divided into <2.0 cm, 2.0–4.0 cm and >4.0 cm. Postoperative pathological results showed that all patients underwent radical surgery for PDAC, and all of them had a R0 margin.

Whether before PSM or after 1:2 PSM, AYA group and older group had no significant difference in tumor locations, tumor size, surgery types, intraoperative vascular invasion status, lymph node metastasis status, intraoperative bleeding, treatment regimen, tumor differentiation degree, AJCC clinical stage, postoperative complications, postoperative hospital stay and perioperative mortality (Tables 2 and 3). However, both before PSM and after 1:2 PSM, the postoperative pathological results showed that the proportion of microvascular invasion in the AYA group and the older

Table 1 Characteristics of Patients Performed PDAC Radical Resection According to Age Group

| Investigated Parameters | Before Propensity Score Matching | | | After Propensity Score Matching | | |
|--------------------------|----------------------------------|-----------------|---------|---------------------------------|----------------|---------|
| | AYA (N = 46) | Older (N = 987) | P value | AYA (N = 46) | Older (N = 92) | P value |
| Age (Years) | 36.22 ± 2.21 | 63.84 ± 7.95 | <0.001* | 36.22 ± 2.21 | 63.70 ± 6.50 | <0.001* |
| Sex | | | 0.046* | | | 0.890 |
| Male, n (%) | 34 (73.91) | 584 (59.17) | | 34 (73.91) | 69 (75.00) | |
| Female, n (%) | 12 (26.09) | 403 (40.83) | | 12 (26.09) | 23 (25.00) | |
| BMI (kg/m ²) | 21.95±2.18 | 21.88±2.20 | 0.873 | 21.95±2.18 | 21.75±2.29 | 0.617 |
| Smoking, n (%) | 29 (63.04) | 546 (55.32) | 0.303 | 29 (63.04) | 57 (61.96) | 0.901 |
| Drinking, n (%) | 30 (65.22) | 542 (54.91) | 0.169 | 30 (65.22) | 61 (66.30) | 0.899 |
| Family history, n (%) | 4 (8.70) | 44 (4.46) | 0.182 | 4 (8.70) | 5 (5.43) | 0.465 |
| Symptoms | | | | | | |
| Jaundice, n (%) | 33 (71.74) | 645 (65.35) | 0.372 | 33 (71.74) | 65 (70.65) | 0.894 |
| Stomachache, n (%) | 37 (80.43) | 342 (34.65) | <0.001* | 37 (80.43) | 73 (79.35) | 0.881 |
| Weight loss, n (%) | 18 (39.13) | 396 (40.12) | 0.893 | 18 (39.13) | 38 (41.30) | 0.806 |
| Comorbidity | | | | | | |
| Hypertension, n (%) | 2 (4.35) | 335 (33.94) | <0.001* | 2 (4.35) | 10 (10.87) | 0.200 |
| DM, n (%) | 15 (32.61) | 358 (36.27) | 0.613 | 15 (32.61) | 31 (33.70) | 0.898 |
| CAD, n (%) | 1 (2.17) | 125 (12.66) | 0.034* | 1 (2.17) | 2 (2.17) | 1.000 |
| COPD, n (%) | 1 (2.17) | 164 (16.62) | 0.009* | 1 (2.17) | 2 (2.17) | 1.000 |
| Albumin (g/dl) | 38.53±3.36 | 38.16±2.77 | 0.396 | 38.53±3.36 | 38.44±2.72 | 0.877 |
| Hemoglobin (g/dl) | 12.20±1.23 | 12.10±0.74 | 0.374 | 12.20±1.23 | 12.26±0.68 | 0.742 |
| CEA (ng/mL) | 6.22±12.83 | 5.51±10.85 | 0.667 | 6.22±12.83 | 5.40±11.37 | 0.701 |
| CA19-9 (U/mL) | 234.69±209.57 | 125.22±164.53 | <0.001* | 234.69±209.57 | 123.28±166.32 | 0.001* |

Note: *P < 0.05.

Abbreviations: BMI, body mass index; DM, diabetes mellitus; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRI, chronic renal insufficiency; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Table 2 Surgical Outcomes

| Investigated Parameters | Before Propensity Score Matching | | | After Propensity Score Matching | | |
|---------------------------|----------------------------------|-----------------|---------|---------------------------------|----------------|---------|
| | AYA (N = 46) | Older (N = 987) | P value | AYA (N = 46) | Older (N = 92) | P value |
| Location of tumor | | | 0.979 | | | 0.983 |
| Head, n (%) | 33 (71.74) | 696 (70.52) | | 33 (71.74) | 64 (69.57) | |
| Body, n (%) | 5 (10.87) | 96 (9.73) | | 5 (10.87) | 12 (13.04) | |
| Tail, n (%) | 7 (15.22) | 170 (17.22) | | 7 (15.22) | 15 (16.30) | |
| Whole pancreas, n (%) | 1 (2.17) | 25 (2.53) | | 1 (2.17) | 1 (1.09) | |
| Tumor size (cm) | | | 0.893 | | | 0.461 |
| <2.0, n (%) | 9 (19.57) | 182 (18.44) | | 9 (19.57) | 24 (26.08) | |
| 2.0 to 4.0, n (%) | 32 (69.56) | 715 (72.44) | | 32 (69.56) | 54 (58.70) | |
| >4.0, n (%) | 5 (10.87) | 90 (9.12) | | 5 (10.87) | 14 (15.22) | |
| Surgery types | | | 0.853 | | | 0.880 |
| PD, n (%) | 36 (78.26) | 736 (74.57) | | 36 (78.26) | 73 (79.34) | |
| DP and splenectomy, n (%) | 9 (19.57) | 225 (22.80) | | 9 (19.57) | 18 (19.57) | |
| WPD, n (%) | 1 (2.17) | 26 (2.63) | | 1 (2.17) | 1 (1.09) | |
| Vascular invasion | | | 0.736 | | | 0.862 |
| Negative, n (%) | 35 (76.09) | 796 (80.65) | | 35 (76.09) | 66 (71.74) | |
| Positive, n (%) | 5 (10.87) | 82 (8.31) | | 5 (10.87) | 12 (13.04) | |
| Unknown, n (%) | 6 (13.04) | 109 (11.04) | | 6 (13.04) | 14 (15.22) | |
| Blood loss (mL) | 488.04±140.71 | 481.26±123.68 | 0.718 | 488.04±140.71 | 488.59±127.98 | 0.982 |

Abbreviations: PD, pancreaticoduodenectomy; DP, distal pancreatectomy; WPD, total pancreaticoduodenectomy.

Table 3 Postoperative Outcomes

| Investigated Parameters | Before Propensity Score Matching | | | After Propensity Score Matching | | |
|------------------------------------|----------------------------------|-----------------|---------|---------------------------------|----------------|---------|
| | AYA (N = 46) | Older (N = 987) | P value | AYA (N = 46) | Older (N = 92) | P value |
| Treatment regimen | | | 0.574 | | | 0.672 |
| Surgical, n (%) | 36 (78.26) | 805 (81.56) | | 36 (78.26) | 69 (75.00) | |
| Surgical and Chemotherapy, n (%) | 10 (21.74) | 182 (18.44) | | 10 (21.74) | 23 (25.00) | |
| AJCC stage | | | | | | |
| T stage | | | 0.893 | | | 0.461 |
| T1 | 9 (19.56) | 81 (8.21) | | 9 (19.56) | 24 (26.08) | |
| T2 | 32 (69.57) | 576 (58.36) | | 32 (69.57) | 54 (58.70) | |
| T3 | 5 (10.87) | 330 (33.43) | | 5 (10.87) | 14 (15.22) | |
| N stage | | | 0.818 | | | 0.496 |
| N0 | 15 (32.61) | 289 (29.28) | | 15 (32.61) | 38 (41.31) | |
| N1 | 18 (39.13) | 388 (39.31) | | 18 (39.13) | 25 (27.17) | |
| N2 | 10 (21.74) | 204 (20.67) | | 10 (21.74) | 20 (21.74) | |
| Unknown, n (%) | 3 (6.52) | 106 (10.74) | | 3 (6.52) | 9 (9.78) | |
| TNM stage | | | 0.881 | | | 0.872 |
| I, n (%) | 4 (8.70) | 108 (10.94) | | 4 (8.70) | 12 (13.04) | |
| 2, n (%) | 12 (26.09) | 213 (21.58) | | 12 (26.09) | 25 (27.17) | |
| 3, n (%) | 24 (52.17) | 540 (54.71) | | 24 (52.17) | 45 (48.92) | |
| Unknown, n (%) | 6 (13.04) | 126 (12.77) | | 6 (13.04) | 10 (10.87) | |
| Grade differentiation | | | 0.339 | | | 0.340 |
| Well, n (%) | 4 (8.69) | 81 (8.21) | | 4 (8.69) | 3 (3.26) | |
| Moderate, n (%) | 22 (47.83) | 576 (58.36) | | 22 (47.83) | 51 (55.43) | |
| Poor, n (%) | 20 (43.48) | 330 (33.43) | | 20 (43.48) | 38 (41.31) | |
| Microvascular invasion | | | <0.001* | | | 0.045* |
| Negative, n (%) | 21 (45.65) | 776 (78.62) | | 21 (45.65) | 61 (66.31) | |
| Positive, n (%) | 18 (39.13) | 122 (12.36) | | 18 (39.13) | 19 (20.65) | |
| Unknown, n (%) | 7 (15.22) | 89 (9.02) | | 7 (15.22) | 12 (13.04) | |
| Postoperative complications | | | | | | |
| POPF, n (%) | 2 (4.35) | 55 (5.57) | 0.722 | 2 (4.35) | 4 (4.35) | 1.000 |
| IAA, n (%) | 2 (4.35) | 65 (6.59) | 0.547 | 2 (4.35) | 7 (7.61) | 0.465 |
| PPH, n (%) | 1 (2.17) | 21 (2.13) | 0.983 | 1 (2.17) | 1 (1.09) | 0.614 |
| DGE, n (%) | 1 (2.17) | 46 (4.66) | 0.429 | 1 (2.17) | 4 (4.35) | 0.519 |
| Perioperative mortality, n (%) | 0 (0.00) | 28 (2.84) | 0.247 | 0 (0.00) | 0 (0.00) | |
| Postoperative hospital stay (days) | 11.57±3.03 | 13.51±3.89 | 0.073 | 11.57±3.03 | 12.52±4.20 | 0.171 |
| Overall survival rate | | | | | | |
| 1-Year, n (%) | 30 (65.22) | 719 (72.85) | 0.257 | 30 (65.22) | 63 (68.48) | 0.700 |
| 2-Year, n (%) | 4 (8.70) | 249 (25.23) | 0.011* | 4 (8.70) | 23 (25.00) | 0.023* |
| 5-year, n (%) | 0 (0.00) | 95 (9.63) | 0.027* | 0 (0.00) | 7 (7.61) | 0.055 |

Note: * $P < 0.05$.

Abbreviations: POPF, postoperative pancreatic fistula; IAA, Intraabdominal abscess; PPH, Postpancreatectomy hemorrhage; DGE, delayed gastric emptying; OS, overall survival.

group was significantly different (45.65% vs 78.62%, 39.13% vs 12.36% and 15.22% vs 9.02%, $P < 0.001$) and (45.65% vs 66.31%, 39.13% vs 20.65% and 15.22% vs 13.04%, $P = 0.045$) (Table 3).

Overall Survivals

Before PSM, the median time of OS after radical surgery in the AYA group and the older group was 13 months (95%

$CI = 11.50$ – 14.50) and 14 months (95% $CI = 13.50$ – 14.50), respectively. Although there was no significant difference in the 1-year OS rates between the AYA group and the older group (65.22% vs 72.85%, $P = 0.257$), but the 2-year and 5-year OS rates in the AYA group were worse than those in the older group (8.70% vs 25.23%, $P = 0.011$ and 0.00% vs 9.63%, $P = 0.027$) (Table 3). In addition, according to the Log-rank (Mantel-Cox) test, there was significant a difference in

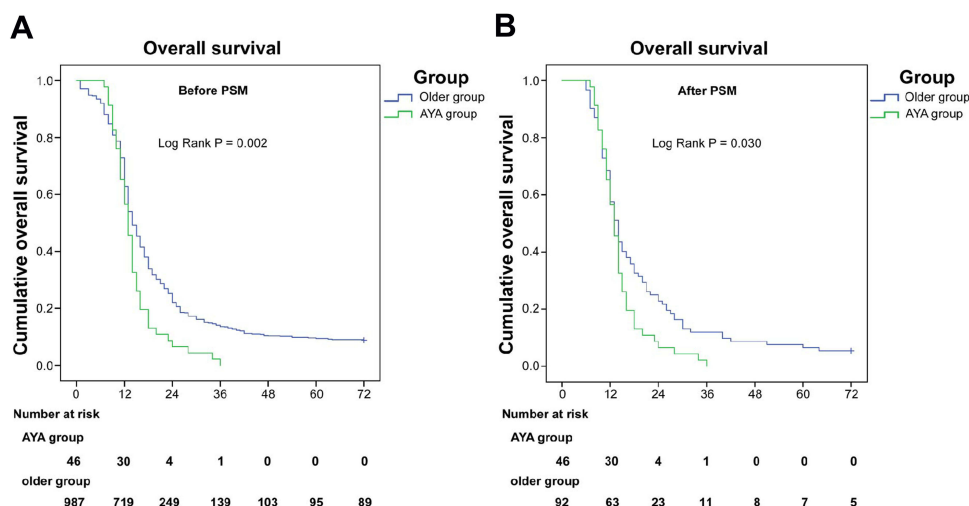


Figure 2 Kaplan–Meier survival curve of overall survival in AYA group and older group. **(A)** Kaplan–Meier survival curve of overall survival in AYA group and older group before PSM. **(B)** Kaplan–Meier survival curve of overall survival in AYA group and older group after PSM.

the cumulative OS rates between the AYA group and the older group ($P = 0.002$) (Figure 2A).

After 1:2 PSM, the median time of overall survival after radical surgery in the AYA group and the older group was 13 months (95% $CI = 11.50$ – 14.50) and 14 months (95% $CI = 13.50$ – 14.50), respectively. There was no significant difference in the 1-year OS rate and 5-year OS rate between the AYA group and the older group (65.22% vs 68.48%, $P = 0.700$ and 0.00% vs 7.61%, $P = 0.055$), respectively, but the 2-year OS rate in the AYA group was worse than that in the older group (8.70% vs 25.00%, $P = 0.023$) (Table 3). According to the Log-rank (Mantel-Cox) test, there was a significant difference in the cumulative OS rates between the AYA group and the older group ($P = 0.030$) (Figure 2B).

Discussion

Pancreatic cancer (PC) is one of the deadliest cancers, despite the molecular tumor-associated technologies and novel therapeutic strategies have been enhanced over the past years.²¹ Because of the insidious onset of PC, its special anatomical location and high malignancy, more than 80% of patients are lost the opportunities to surgery at the time of diagnosis because of local invasion or metastasis. Despite the fact that PC having a low surgical resection rate, surgical resection remains the only curative treatment option for patients with PC, regardless of their age.²² Usually, PDAC is diagnosed in patients aged 65 to 75 years and seldom observed in patients in their 30s or 40s.²³ However, in our study, the average age of patients who underwent radical PDAC surgery was 62.61 ± 9.65 years old, which may be due to the

fact that some elderly patients with comorbidity did not perform surgical treatment and were excluded from the study.

Young-onset cancer act as a hallmark of many familial cancer syndromes. Kieran et al²⁴ reported the risk of PC was higher in members of family history of PC family lines with early-onset cases than in members of family history of pancreatic cancer family lines without early-onset cases. Additionally, Abe et al²⁵ reported the cumulative incidence of PC was significantly higher among individuals with an identifiable deleterious germline mutation in a PC susceptibility gene than it was among individuals with a strong family history but no identified mutation. Eguchi et al²⁶ conducted a retrospective analysis showing that AYA patients accounted for 1.5% of all PDAC patients. However, in this study, we found the AYA group accounted for 4.45% of all patients who underwent radical PDAC surgery in our center. This may be due to our single-center study and our center's conservative attitude towards elderly patients undergoing radical PDAC surgery, or the onset age of PDAC is relatively early in our country. In addition, we did not observe a significant difference in family history between patients in the AYA group and those in the older group. Research on the genetic factors associated with early-onset pancreatic cancer should include a large number of pancreatic family patients to study the difference between the onset time of pancreatic cancer in their offspring and the general population.

Radical resection of localized lesions provides the chance for long-term survival for PDAC.²² But, most patients are not candidates for surgery. However, with the advent of gemcitabine and FOLFIRINOX on pancreatic

cancer chemotherapy regimens, the overall survival time of pancreatic cancer patients is significantly longer than before.^{27,28} Strobel et al²⁹ reported that surgical resection combined with systemic adjuvant chemotherapy currently provides the only chance of long-term survival for PDAC patients. Barbas et al¹⁶ reported that neoadjuvant and adjuvant therapy prolonged overall survival and were independent predictors of better overall survival. However, the number of AYA patients who received neoadjuvant therapy in our center is very small, and chemotherapy regimens were inconsistent in our center before the gemcitabine regimen was proposed. Therefore, this study excluded neoadjuvant therapy patients to ensure the comparability of the study and subgroup analysis of adjuvant therapy was not performed in this study. But, it is undeniable that neoadjuvant therapy and adjuvant therapy can prolong the OS time of PDAC patients. What is more, early screening and early diagnosis can increase the surgical resection rate of PDAC patients, thereby prolonging the OS time. In addition, several reports indicate that the incidence of postoperative complication of surgical resection in elderly patients is similar to those in younger patients.^{30–32} In this study, the postoperative complication rates in the AYA group and the older group had no significant difference, which was similar to other studies. The main complications after radical resection of PDAC include POPE, PPH, IAA and DGE, and most of these complications are not life-threatening if they are properly managed. According to this, all patients suspected with PDAC, regardless of age, should be screened and diagnosed as soon as possible, and comprehensive therapy should be considered to prolong the OS time.

Many studies indicate that younger cancer patients have more aggressive cancer cells, so younger cancer

patients are thought to have a worse prognosis than older patients.^{33–36} However, the OS rates of younger and older patients with PDAC were still controversial.^{22,37–39} Table 4 shows the survival prognosis compared with the previous studies. Although in some studies the survival prognosis between the two groups was not statistically significant, overall their findings showed that the survival prognosis of younger PDAC patients was not consistent with that of older PDAC patients. He et al²² have reported that the younger group did better than the older group in estimated median survival (19 vs 16 months, $P = 0.007$) and actual 5-year OS rate (24 vs 11%, $P = 0.005$). Some studies also reported the same results as He et al reported.^{39,40} However, another study reported that compared with older PC patients, younger PC patients were more often diagnosed at advanced stages, and had a worse overall survival rate.²⁶ Additionally, many studies showed there was no significant difference in survival prognosis between AYA group and older group.^{41–43} In our study, although there was no significant difference in median postoperative survival time (13 vs 14, $P = 0.326$). However, no matter before PSM or after PSM, the pre-operative CA19-9 of the AYA group was higher than the older group and the postoperative pathological results showed a higher proportion of microvascular invasion. It suggested that PDAC in AYA patients was more aggressive. What's more, the AYA group had a worse cumulative OS rate.

Limitation of the present study is that the single-center study may be biased. In addition, the retrospective nature of the study may be associated with the risk of selection bias. However, the proportion of AYA patients in this study is higher than that in other studies, which may be

Table 4 The Survival Outcomes Compared with the Previous Studies

| | Early-Onset Definition | Groups | | Median Survival (Month) | | P value |
|--------------------------------|------------------------|---------------|------------------|-------------------------|-------|---------|
| | | Younger (n) | Older (n) | Younger | Older | |
| He et al. ²² | <45 | 75 (7.9%) | 874 (92.1%) | 19 | 16 | 0.01 |
| Eguchi et al. ²⁶ | <40 | 526 (1.5%) | 35,619 (98.5) | 12 | 15 | 0.168 |
| Tingstedt et al. ⁴¹ | <50 | 33 (5.7%) | 543 (94.3%) | 5.7 | 5.3 | 0.840 |
| Piciucchi et al. ⁴² | <50 | 25 (8.5%) | 268 (91.5%) | 11 | 9 | 0.28 |
| Kang et al. ³⁷ | <45 | 34 (4.9%) | 660 (95.1%) | 17 | 32 | 0.54 |
| Ntala et al. ⁴³ | <50 | 35 (9.5%) | 334 (90.5%) | 12 | 9 | 0.168 |
| Ramai et al. ⁴⁰ | <40 | 1181 (0.87%) | 134,919 (99.23%) | 7 | 6 | 0.004 |
| Ordenez et al. ³⁹ | <50 | 12,137 (5.9%) | 194,925 (94.1%) | 9.2 | 6 | <0.001 |
| This study | <40 | 46 (4.45%) | 987 (95.55%) | 13 | 14 | 0.326 |

due to the fact that we are more active in the surgical treatment of AYA patients and do not perform surgical treatment in elderly patients with severe concomitant diseases. However, in order to increase comparability, we have performed PSM on the two groups to increase persuasiveness, so the conclusions drawn in this study are more reliable. Genetic testing for PDAC was not widely utilized in our center during the study period, which could provide useful data on the pattern and behavior of PDAC in this AYA group.

In conclusion, our findings show that PDAC may be more aggressive in AYA patients and AYA patients have a worse cumulative OS than older patients. Early screening, early diagnosis, early treatment and comprehensive therapy should be considered to prolong the OS time of PDAC patients.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors of this article report no conflicts of interest in this work.

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