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# Resected pancreatic adenocarcinoma: An Asian institution's experience

Kennedy Yao Yi Ng[1] | Edwin Wei Xiang Chow[1] | Bochao Jiang[1] | Cindy Lim[2] | Brian Kim Poh Goh[3,4,5] | Ser Yee Lee[6] | Jin Yao Teo[3,5] | Damien Meng Yew Tan[5,7] | Peng Chung Cheow[3,4,5] | London Lucien Peng Jin Ooi[3,4,5] | Pierce Kah Hoe Chow[3,4,5] | Joycelyn Jie Xin Lee[1] | Juinn Huar Kam[3] | Ye Xin Koh[3] | Prema Raj Jeyaraj[3] | Ek Khoon Tan[3] | Su Pin Choo[1,8] | Chung Yip Chan[3,5] | Alexander Yaw Fui Chung[3,4,5] | David Tai[1,5]

[1]Division of Medical Oncology, National Cancer Centre Singapore, Singapore

[2]Division of Clinical Trials and Epidemiological Sciences, National Cancer Centre Singapore, Singapore

[3]Department of Hepatopancreatobiliary and Transplantation Surgery, Singapore General Hospital, Singapore

[4]Division of Surgical Oncology, National Cancer Centre Singapore, Singapore

[5]Duke-NUS Graduate Medical School, Singapore

[6]Surgical Associates, National Cancer Centre Singapore, Singapore

[7]Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore

[8]Curie Oncology, Graduate Medical School, Singapore General Hospital, Singapore

**Correspondence**
David Tai, Division of Medical Oncology, 11 Hospital Drive, National Cancer Centre Singapore, Singapore 169610, Singapore.
Email: david.tai.w.m@singhealth.com.sg

## Abstract

**Background:** Pancreatic adenocarcinoma (PDAC) is highly lethal. Surgery offers the only chance of cure, but 5-year overall survival (OS) after surgical resection and adjuvant therapy remains dismal. Adjuvant trials were mostly conducted in the West enrolling fit patients. Applicability to a general population, especially Asia has not been described adequately.

**Aim:** We aimed to evaluate the clinical outcomes, prognostic factors of survival, pattern, and timing of recurrence after curative resection in an Asian institution.

**Methods and Results:** The clinicopathologic and survival outcomes of 165 PDAC patients who underwent curative resection between 1998 and 2013 were reviewed retrospectively. Median age at surgery was 62.0 years. 55.2% were male, and 73.3% had tumors involving the head of pancreas. The median OS of the entire cohort was 19.7 months. Median OS of patients who received adjuvant chemotherapy was 23.8 months. Negative predictors of survival include lymph node ratio (LNR) of >0.3 (HR = 3.36, $P$ = .001), tumor site involving the body or tail of pancreas (HR = 1.59, $P$ = .046), presence of perineural invasion (PNI) (HR = 2.36, $P$ = .018) and poorly differentiated/undifferentiated tumor grade (HR = 1.86, $P$ = .058). The median time to recurrence was 8.87 months, with 66.1% and 81.2% of patients developing recurrence at 12 months and 24 months respectively. The most common site of recurrence was the liver.

**Conclusion:** The survival of Asian patients with resected PDAC who received adjuvant chemotherapy is comparable to reported randomized trials. Clinical characteristics seem similar to Western patients. Hence, geographical locations may not be a necessary stratification factor in RCTs. Conversely, lymph node ratio and status of PNI ought to be incorporated.

Kennedy Yao Yi Ng and Edwin Wei Xiang Chow contributed equally to the manuscript.

KEYWORDS
pancreatic adenocarcinoma, prognostic factors, resected

## 1 | INTRODUCTION

Pancreatic adenocarcinoma (PDAC) is a highly lethal malignancy. It is the eighth leading cause of cancer-related deaths in men and the ninth leading cause of cancer-related deaths in women worldwide.[1] PDAC often presents in advanced stages due to its aggressive biology and non-specific symptoms.

The prognosis is poor even among patients with resectable disease, with a 5-year survival of 10% to 30%.[2] Current staging and prognostic tools rely on the American Joint Committee of Cancer (AJCC) TNM staging system eighth edition.[3] Numerous other prognostic factors have been identified to better prognosticate patients with resected PDAC such as neutrophil/lymphocyte ratio,[4] lymph node ratio,[5] presence of lymphovascular invasion (LVI) or perineural invasion (PNI),[6] and resection margin status.[7,8] The standard operation for tumors of the pancreatic head is a pancreaticoduodenectomy (Whipple procedure), whereas tumors of the body or tail can be resected using a distal pancreatectomy.[9] These procedures are associated with high operative mortality and morbidity.[9] Advancement in surgical technique and perioperative management of patients has led to a reduction in the morbidity and mortality associated with the above-mentioned surgeries. Moreover, with the improvement of imaging technique and the employment of a multidisciplinary team approach, better selection of suitable patients for surgery could be done.[10] Surgical outcomes at high-volume centers have been shown to be superior compared to outcomes at low-volume centers. In spite of that, many patients relapse at both local and distant sites after resection. Hence, adjuvant chemotherapy is crucial in the management of these patients as demonstrated in multiple randomized controlled trials (RCT).[11-15,17,18,38] Often, these trials stratify patients by geographical locations, resection margins, T-stage and lymph node status. Adjuvant chemotherapy or chemoradiotherapy was conducted primarily in West enrolling fit patients with preserved organ functions and good performance status. Applicability to a general population especially in an Asian population has been inadequately described.

Pattern, timing, and predictors of recurrence after curative resection have been described primarily in Western populations.

We aimed to evaluate the clinical outcomes, prognostic factors of survival, pattern, and timing of recurrence after curative resection in an Asian institution.

We also compared the resected PDAC series from both Asian and Western populations.

## 2 | METHODS

Patients who underwent resection with curative intent in our center between 1998 and 2013 were identified from a retrospective database. Patients eventually noted to have R2 resection or stage 4 disease were excluded. We collected clinicopathological and operative data of 165 patients. Follow-up and data collection extended to December 2015.

Following surgery, all specimens underwent histopathological review, and features such as histology subtype, pathological AJCC stage and grade, resection margin status, tumor size, LVI and PNI. Resection margin involvement was defined according to the Royal College of Pathologists guidelines, with microscopic evidence of tumor within 1 mm of a resection margin (RM) being classified as R1.[19] Laboratory parameters such as CA 19-9 and carcinoembryonic antigen (CEA) were measured preoperatively and postoperatively (patients without tests done within 3 months before or after the surgery was excluded from the analysis). The development of a hypointense mass in the resection site was considered as evidence of local recurrence. Similarly, detection of a new hypointense nodule/mass in the liver, lung, or peritoneum was considered evidence of distant recurrence. No biopsies were performed in this series to confirm the diagnosis of recurrent cancer. If the CT findings were non-specific, a follow-up CT would be performed, and the date of recurrence will be taken as the date of the follow-up CT that demonstrate enlargement of the nodule or mass. Our study was approved by the Centralized Institutional Review Board of our institution.

### 2.1 | Statistical analysis

Continuous variables were summarized using median and range. Categorical variables were summarized using frequency and percentage. Overall survival (OS) was calculated as the time from surgery to death from all causes. Patients who were alive at last follow-up were censored at date of last follow-up. Median OS was estimated using the Kaplan-Meier method. Differences in survival curves were tested using the log-rank test. Univariable and multivariable analyses were performed using the Cox proportional hazards model. For multivariable analysis, variable selection was performed using a forward selection procedure. All variables, regardless of significance in univariable analysis, were entered as candidate variables in the forward selection procedure. Only variables with more than 10% missing data were excluded. The proportional hazards assumption was tested on the final multivariable model using a test based on Schoenfeld residuals. A *P*-value of less than .05 was taken as statistically significant in the univariable analyses. For the forward selection procedure, a *P*-value of less than .10 was used for addition of variables into the multivariable model. *P*-values for Cox models were calculated using the likelihood ratio test. All analyses were performed in Stata 15.0 (StataCorp, College Station, Texas).

## 3 | RESULTS

### 3.1 | Study population characteristics

Our study population consisted of 165 patients with resected pancreatic ductal adenocarcinoma. Median age at surgery was 62.0 (41-84) years. 55.2% were male and 44.8% were female. The ethnic proportion of our study population was 77.6% Chinese, 4.8% Malay, 4.2% Indian, and 12.7% of other races. The median follow-up time was 15.5 months. Regarding grade of differentiation, 10.9% had well differentiated, 75.2% moderately differentiated, 12.1% poorly differentiated, and 0.6% undifferentiated histology. Majority (73.3%) of patients had tumors involving the head of pancreas. Whipple operation or pylorus-preserving pancreaticoduodenectomy (PPPD) was the most common form of surgery (73.3%) followed by distal pancreatectomy in 22.4%, and total pancreatectomy in 2.4%. The institution's surgical outcomes and details were previously published.[20,21] Only 50.9% of patients who underwent curative resection eventually received adjuvant therapy. Of these, 55 (33.3%) received adjuvant chemoradiotherapy, 33 (20.0%) received only adjuvant chemotherapy and 1 (0.6%) received only adjuvant radiotherapy. No patients received neoadjuvant chemotherapy or chemoradiotherapy. All patients who received adjuvant chemotherapy received gemcitabine or 5-fluorouracil (5-FU)/oral capecitabine monotherapy. Patients receiving adjuvant chemoradiotherapy received either concurrent radiotherapy with radiosensitizing 5-FU or gemcitabine followed by gemcitabine or 5-FU monotherapy. Patient demographic and clinicopathologic characteristics of the cohort are detailed in Table 1.

### 3.2 | Recurrence pattern

After median follow-up of 15.5 months, 112 patients (67.9%) developed recurrence. The median time to recurrence was 8.87 months. 66.1% and 81.2% of patients developed recurrence at 12 and 24 months, respectively. (Figure S1).

Majority of patients developed distant recurrence as the first site of relapse. Seventy-three (44.2%) had recurrence in a distant site, 20 (12.1%) had both local (defined as resection bed) and distant recurrences and 19 (11.5%) had solely local recurrence.

The most common site of recurrence was the liver (n = 58; 35.2%), followed by local recurrence (n = 39; 23.6%), distant lymph nodes (n = 31, 18.8%), peritoneum (n = 22, 13.3%), and lungs (n = 19; 11.5%).

### 3.3 | Univariable analysis of OS

The median OS of the entire patient cohort was 19.7 months (95%CI: 16.9-23.7). Median OS of patients who did not receive adjuvant therapy after curative resection was 15.7 months (95%CI: 11.7-26.9). Median OS of patients who received adjuvant chemoradiotherapy or chemotherapy were 20.1 months (95%CI: 15.7-28.2) and 23.8 months

**TABLE 1** Patient demographics and clinical characteristics

| Characteristic | Frequency | Percentage |
|---|---|---|
| Total number of patients | 165 | 100 |
| Age at surgery (years) | | |
| Median (Range) | 62 (41–84) | |
| Gender | | |
| Male | 91 | 55.2 |
| Female | 74 | 44.8 |
| Race | | |
| Chinese | 128 | 77.6 |
| Malay | 8 | 4.8 |
| Indian | 7 | 4.2 |
| Others | 21 | 12.7 |
| Unknown | 1 | 0.6 |
| Smoking status | | |
| Never | 86 | 52.1 |
| Ex | 30 | 18.2 |
| Current | 10 | 6.1 |
| Unknown | 39 | 23.6 |
| Alcohol consumption | | |
| Never | 96 | 58.2 |
| Ex | 9 | 5.5 |
| Current | 19 | 11.5 |
| Unknown | 41 | 24.8 |
| Charlson comorbidities index | | |
| Median (Range) | 3 (1–9) | |
| Symptoms | | |
| Loss of weight | 42 | 25.5 |
| Loss of appetite | 27 | 16.4 |
| Fever | 4 | 2.4 |
| Abdominal pain | 48 | 29.1 |
| Abdominal distension | 5 | 3.0 |
| Diarrhea | 4 | 2.4 |
| Jaundice | 84 | 50.9 |
| Malaena | 1 | 0.6 |
| Tumor site | | |
| Head involved | 121 | 73.3 |
| Head not involved | 44 | 26.7 |
| AJCC TNM stage | | |
| IA | 5 | 3.0 |
| IB | 16 | 9.7 |
| IIA | 45 | 27.3 |
| IIB | 90 | 54.5 |
| III | 9 | 5.5 |
| T stage | | |
| T1 | 4 | 2.4 |
| T2 | 30 | 18.2 |
| T3 | 123 | 74.5 |
| T4 | 8 | 4.8 |

(Continues)

**TABLE 1** (Continued)

| Characteristic | Frequency | Percentage |
|---|---|---|
| N stage | | |
| N0 | 69 | 41.8 |
| N1 | 95 | 57.6 |
| NX | 1 | 0.6 |
| Histological grade | | |
| Well differentiated | 18 | 10.9 |
| Moderately differentiated | 124 | 75.2 |
| Poorly differentiated | 20 | 12.1 |
| Undifferentiated | 1 | 0.6 |
| Not stated/not determined | 2 | 1.2 |
| Type of surgery | | |
| Whipples operation or Pylori preserving pancreaticoduodenectomy (PPPD) | 121 | 73.3 |
| Pancreatectomy, distal or subtotal | 37 | 22.4 |
| Pancreatectomy, total | 4 | 2.4 |
| Pancreatectomy, NOS | 3 | 1.8 |
| Resection margins | | |
| R0 | 80 | 48.5 |
| R1 | 85 | 51.5 |
| Perineural invasion | | |
| No | 14 | 8.5 |
| Yes | 135 | 81.8 |
| Indeterminate | 6 | 3.6 |
| Unknown | 10 | 6.1 |
| Lymphovascular invasion | | |
| No | 80 | 48.5 |
| Yes | 62 | 37.6 |
| Indeterminate | 13 | 7.9 |
| NA | 10 | 6.1 |
| Lymph node resected | | |
| Median (Range) | 9 (0-36) | |
| Lymph node ratio (No. positive/No. resected) | | |
| Median (Range) | 0.08 (0–1) | |
| Unknown (no LN resected) | 5 | 3.0 |
| Tumor size (largest diameter) (cm) | | |
| Median (Range) | 3.0 (0.8-18.0) | |
| Not Reported | 18 | 10.9 |
| Posterior margins involved | | |
| No | 102 | 61.8 |
| Yes | 36 | 21.8 |
| Unknown | 27 | 16.4 |
| Type of adjuvant treatment | | |
| No adjuvant treatment | 76 | 46.1 |
| Radiotherapy only | 1 | 0.6 |
| Chemotherapy only | 33 | 20.0 |
| Chemoradiotherapy | 55 | 33.3 |

**TABLE 1** (Continued)

| Characteristic | Frequency | Percentage |
|---|---|---|
| Pre-op CEA (ng/mL)[a] | | |
| Median (range) | 3.3 (0.5-61.8) | |
| Unknown | 87 | 52.7 |
| Post-op CEA (ng/mL)[a] | | |
| Median (range) | 2.2 (0.7-14.9) | |
| Unknown | 124 | 75.2 |
| Pre-op CA19-9 (U/mL)[a,b] | | |
| Median (range) | 187.0 (<0.6->10 000) | |
| Unknown | 73 | 44.2 |
| Post-op CA19-9 (U/mL)[a,b] | | |
| Median (range) | 25.2 (<0.6-6825) | |
| Unknown | 66 | 40.0 |
| Pre-op albumin (g/L)[a] | | |
| Median (range) | 34 (16-48) | |
| Unknown | 34 | 20.6 |
| Post-op albumin (g/L)[a] | | |
| Median (range) | 24 (14-47) | |
| Unknown | 26 | 15.8 |
| Pre-op neutrophil/lymphocyte ratio[a] | | |
| Median (range) | 2.9 (0.6-36.5) | |
| Unknown | 29 | 17.6 |
| Post-op neutrophil/lymphocyte ratio[a] | | |
| Median (range) | 12.3 (0.8-49.6) | |
| Unknown | 23 | 13.9 |

Abbreviation: NOS, Not otherwise specified.
[a]Taken within 90 days before or after surgery.
[b]Values of <0.6, < 2.0, > 5000, and >10 000 were taken as 0.6, 2.0, 5000, and 10 000, respectively, for the calculation of median.

(95%CI: 19.1-31.5) respectively. 1-, 3-, and 5-year OS rates were 73.1% (95%CI: 65.1-79.5), 28.0% (95%CI: 20.3-36.1), and 14.8% (95% CI 7.6-22.0), respectively.

Factors which conferred a poorer prognosis on OS by univariable analysis were: poorly differentiated/undifferentiated tumor (HR 2.15, 95% CI: 1.24-3.74, $P$ = .013), non-pancreatic head tumors (HR 1.54, 95% CI: 1.04-2.29, $P$ = .037), N1 nodal status (HR 1.84, 95% CI: 1.24-2.72, $P$ = .002), lymph node ratio (LNR) of >0-0.3 (HR 1.68, 95% CI: 1.09-2.58, $P$ = .001), LNR > 0.3 (HR 3.06, 95% CI: 1.75-5.37, $P$ = .001), presence of PNI (HR 2.62, 95% CI: 1.20-5.73, $P$ = .006), LVI (HR 1.52, 95% CI: 1.01-2.29, $P$ = .045), pre-op CA 19-9 (>75 U/mL) (HR 2.39, 95% CI 1.23-4.63, $P$ = .005), post-op CA 19-9 (>75 U/mL) (HR 2.61, 95% CI: 1.56-4.38, $P$ = .001). (Table 2).

## 3.4 | Multivariable analysis of OS

The final multivariable model for OS revealed that LNR > 0-0.3 (HR 1.58, 95%CI: 1.00-2.49, $P$ < .001), lymph node ratio > 0.3-1 (HR 3.36, 95%CI: 1.83-6.16, $P$ = .001), non-pancreatic head tumors

**TABLE 2** Univariable and multivariable analysis of overall survival

| | | | | Univariable | | Multivariable | |
|---|---|---|---|---|---|---|---|
| | No. of events/ patients | Median OS, months (95% CI) | Log-rank *P*-value | Hazard ratio (95% CI) | Cox model *P*-value | Hazard ratio (95% CI) | Cox model *P*-value |
| All patients | 111/165 | 19.7 (16.9, 23.7) | | | | 98/146 | |
| Age at surgery (years) | | | | | | | |
| <65 | 66/97 | 19.7 (16.9, 24.4) | | 1 | | | |
| ≥65 | 45/68 | 20.1 (14.1, 24.9) | .389 | 1.18 (0.81, 1.74) | .392 | | |
| Gender | | | | | | | |
| Male | 59/91 | 19.7 (15.5, 24.4) | | 1 | | | |
| Female | 52/74 | 20.0 (16.8, 31.0) | .463 | 0.87 (0.60, 1.26) | .463 | | |
| Race | | | | | | | |
| Chinese | 93/128 | 20.1 (17.4, 24.1) | | 1 | | | |
| Non-Chinese | 18/36 | 13.5 (10.6, 31.5) | .198 | 1.40 (0.84, 2.33) | .216 | | |
| Smoking status | | | | | | | |
| Never | 58/86 | 21.4 (17.9, 31.0) | | 1 | | | |
| Former | 21/30 | 15.7 (12.8, 19.6) | | 1.73 (1.04, 2.88) | | | |
| Current | 6/10 | 31.6 (24.9, UD) | **.027** | 0.58 (0.25, 1.36) | .032 | | |
| Alcohol consumption | | | | | | | |
| Never | 64/96 | 20.0 (17.2, 28.2) | | 1 | | | |
| Former | 7/9 | 12.3 (6.9, 28.8) | | 1.70 (0.77, 3.73) | | | |
| Current | 14/19 | 26.4 (16.9, 36.1) | .406 | 1.02 (0.57, 1.84) | .465 | | |
| Charlson comorbidities index | | | | | | | |
| 1–2 | 46/63 | 19.7 (15.4, 28.8) | | 1 | | | |
| >2 | 65/102 | 19.7 (15.7, 23.7) | .463 | 1.16 (0.78, 1.71) | .462 | | |
| Tumor site | | | | | | | |
| Head involved | 74/121 | 21.1 (17.9, 24.9) | | 1 | | 1 | |
| Head not involved | 37/44 | 15.4 (11.4, 24.4) | **.031** | 1.54 (1.04, 2.29) | .037 | 1.59 (1.02, 2.48) | .046 |
| AJCC TNM stage | | | | | | | |
| I | 15/21 | 23.7 (11.4, 50.2) | | 1 | | | |
| II | 90/135 | 19.6 (15.7, 23.7) | | 1.16 (0.67, 2.02) | | | |
| III | 6/9 | 26.9 (8.9, UD) | .730 | 0.89 (0.34, 2.31) | .719 | | |
| T stage | | | | | | | |
| T1/T2 | 26/34 | 19.7 (11.4, 30.2) | | 1 | | | |
| T3/T4 | 85/131 | 19.7 (16.6, 24.4) | .505 | 0.86 (0.55, 1.34) | .511 | | |
| N stage | | | | | | | |
| N0 | 42/69 | 28.8 (20.4, 45.4) | | 1 | | | |
| N1 | 68/95 | 15.5 (13.2, 19.7) | **.002** | 1.84 (1.24, 2.72) | .002 | | |
| Histological grade | | | | | | | |
| Well/moderately differentiated | 95/142 | 21.1 (17.4, 24.9) | | 1 | | 1 | |
| Poorly differentiated/ Undifferentiated | 15/21 | 11.2 (7.6, 20.0) | **.005** | 2.15 (1.24, 3.74) | .013 | 1.86 (1.02, 3.38) | .058 |
| Type of surgery | | | | | | | |
| Whipples operation or PPPD | 77/121 | 20.1 (17.4, 24.1) | | 1 | | | |
| Pancreatectomy, distal or subtotal | 29/37 | 17.6 (11.4, 31.6) | | 1.29 (0.84, 1.98) | | | |
| Pancreatectomy, total | 3/4 | 4.3 (3.1, UD) | | 7.24 (2.22, 23.60) | | | |
| Pancreatectomy, NOS | 2/3 | 14.2 (14.2, UD) | **.002** | 1.31 (0.32, 5.37) | .057 | | |
| Resection margins | | | | | | | |
| R0 | 52/80 | 19.7 (16.9, 26.9) | | 1 | | | |
| R1 | 59/85 | 19.7 (14.2, 24.1) | .612 | 1.10 (0.76, 1.60) | .611 | | |

(Continues)

**TABLE 2** (Continued)

| | | | | Univariable | | Multivariable | |
|---|---|---|---|---|---|---|---|
| | No. of events/ patients | Median OS, months (95% CI) | Log-rank *P*-value | Hazard ratio (95% CI) | Cox model *P*-value | Hazard ratio (95% CI) | Cox model *P*-value |
| Perineural invasion | | | | | | | |
| No | 7/14 | 50.2 (17.2, UD) | | 1 | | 1 | |
| Yes | 94/135 | 19.1 (15.5, 22.6) | **.013** | 2.62 (1.20, 5.73) | .006 | 2.36 (1.07, 5.23) | .018 |
| Lymphovascular invasion | | | | | | | |
| No | 54/80 | 23.7 (17.7, 35.4) | | 1 | | | |
| Yes | 42/62 | 16.6 (11.7, 20.1) | **.042** | 1.52 (1.01, 2.29) | **.045** | | |
| Lymph node ratio | | | | | | | |
| 0 | 38/64 | 31.0 (20.1, 45.4) | | 1 | | 1 | |
| >0–0.3 | 49/70 | 17.9 (14.1, 22.0) | | 1.68 (1.09, 2.58) | | 1.58 (1.00, 2.49) | |
| >0.3 | 20/26 | 12.3 (7.5, 19.6) | <.001 | 3.06 (1.75, 5.37) | .001 | 3.36 (1.83, 6.16) | .001 |
| Tumor size (largest diameter) (cm) | | | | | | | |
| ≤3 | 50/78 | 23.7 (17.9, 28.8) | | 1 | | | |
| >3 | 51/69 | 14.1 (11.5, 21.1) | .017 | 1.61 (1.09, 2.38) | **.018** | | |
| Posterior margins involved | | | | | | | |
| No | 68/102 | 19.7 (15.7, 26.4) | | 1 | | | |
| Yes | 24/36 | 18.5 (10.8, 31.6) | .797 | 1.06 (0.67, 1.70) | .798 | | |
| Adjuvant treatment | | | | | | | |
| None | 48/76 | 15.7 (11.7, 26.9) | | 1 | | | |
| Chemotherapy only | 19/33 | 23.8 (19.1, 31.5) | | 0.74 (0.43, 1.26) | | | |
| Chemoradiotherapy | 43/55 | 20.1 (15.7, 28.2) | .528 | 0.89 (0.59, 1.35) | .520 | | |
| Pre-op CEA (ng/ml) | | | | | | | |
| ≤5 | 27/44 | 22.0 (17.6, 44.6) | | 1 | | | |
| >5 | 28/34 | 14.1 (10.0, 24.4) | .110 | 1.54 (0.90, 2.61) | .114 | | |
| Post-op CEA (ng/ml) | | | | | | | |
| ≤5 | 27/34 | 21.8 (14.7, 30.2) | | 1 | | | |
| >5 | 6/7 | 21.4 (3.1, UD) | .330 | 1.55 (0.64, 3.80) | .356 | | |
| Pre-op CA19-9 (U/ml) | | | | | | | |
| ≤75 | 13/28 | 55.5 (14.0, 74.4) | | 1 | | | |
| >75 | 51/64 | 19.1 (15.3, 22.0) | .008 | 2.39 (1.23, 4.63) | .005 | | |
| Post-op CA19-9 (U/ml) | | | | | | | |
| ≤75 | 48/72 | 22.6 (18.5, 30.2) | | 1 | | | |
| >75 | 22/27 | 13.2 (8.4, 19.4) | <.001 | 2.61 (1.56, 4.38) | **.001** | | |
| Pre-op albumin (g/L) | | | | | | | |
| >35 | 38/54 | 22.0 (14.2, 31.6) | | 1 | | | |
| ≤35 | 50/77 | 17.9 (14.1, 23.7) | .870 | 1.04 (0.68, 1.58) | .869 | | |
| Post-op albumin (g/L) | | | | | | | |
| >35 | 11/17 | 24.4 (17.6, 36.0) | | 1 | | | |
| ≤35 | 83/122 | 18.5 (14.7, 22.6) | .300 | 1.39 (0.74, 2.62) | .283 | | |
| Pre-op NLR | | | | | | | |
| ≤5 | 77/109 | 19.1 (15.4, 26.4) | | 1 | | | |
| >5 | 16/27 | 19.4 (12.8, 24.1) | .363 | 1.29 (0.74, 2.24) | .377 | | |
| Post-op NLR | | | | | | | |
| ≤5 | 14/18 | 22.6 (13.2, 50.0) | | 1 | | | |
| >5 | 83/124 | 19.4 (15.4, 24.1) | .861 | 1.05 (0.60, 1.86) | .861 | | |

Abbreviations: NLR, neutrophil-lymphocyte ratio; PPPD, pylori preserving pancreaticoduodenectomy; UD, undefined.
*Note:* For the multivariable analysis, only variables with less than 10% missing data were considered in the forward selection procedure. The criterion for variable addition was $P < .10$.

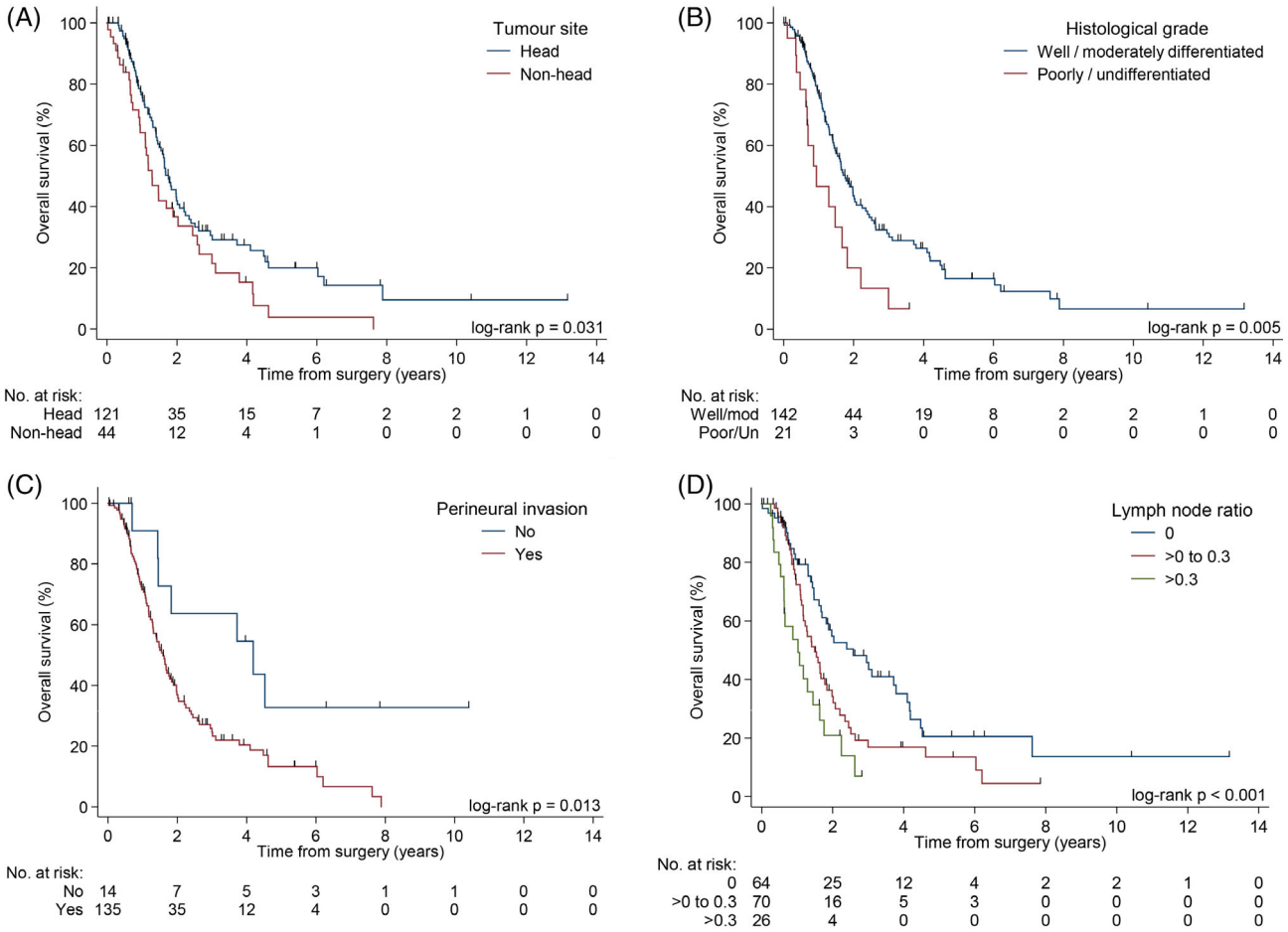


**FIGURE 1** Kaplan-Meier curves of OS by tumor site, A, tumor grade, B, PNI, C, LNR, D

(HR 1.59, 95%CI: 1.02-3.38, *P* = .046), presence of PNI (HR 2.36 95%CI: 1.07-5.23, *P* = .018), and poorly differentiated or undifferentiated tumor grade (HR 1.86, 95%CI: 1.02-3.38, *P* = .058) were negative predictors of survival. (Table 2) The Kaplan-Meier plot of the OS for the above-mentioned prognostic factors can be found in Figure 1.

## 4 | DISCUSSION

The median survival of patients in this study was 19.7 months (95% CI: 16.9-23.7) with a 5-year OS of 14.8% (95%CI: 7.6-22). This is comparable to the experience of major centers in both Western and Asian series with a median survival ranging from 13 to 24 months and a 5-year OS ranging from 4% to 27%. The patient characteristics and prognostics factors described in both Western and Asian series are also similar (Table 3).

Despite the benefits of adjuvant chemotherapy, only 50.9% of our patients received adjuvant treatment, which was comparable with other institutions and large series reporting rates of approximately 35% to 60%.[31-34] There are numerous reasons why patients do not receive adjuvant chemotherapy. These include post-operative complications leading to poor performance status post-surgery, tumor recurrence or metastases detected prior to initiation of adjuvant chemotherapy, and patient's preferences.[35-37] Patients who received adjuvant chemotherapy in our series had an OS of 23.8 months as compared to 15.7 months for those who did not receive adjuvant chemotherapy. This is comparable to that of the Phase 3 trials evaluating the efficacy of these regimes,[11,12,14,38] and consistent with real-world data described by other authors.[34,37] Given the low rates of receipt of adjuvant chemotherapy and early dissemination of disease in PDAC, a neoadjuvant approach may be advantageous.[39,40] Studies exploring this approach have conflicting results. The Phase 3 PREOPANC-1 trial randomized patients to preoperative chemoradiotherapy followed by surgery and four courses of adjuvant gemcitabine or to immediate surgery and six courses of adjuvant gemcitabine. There was no difference in the OS by intention to treat in both groups.[63] The Prep-02/JSAP-05 randomized Phase 2/3 trial randomized 362 patients with resectable PDAC to neoadjuvant gemcitabine and S-1 followed by surgery and adjuvant S-1 or initial surgery and adjuvant S-1. There was a significant benefit of neoadjuvant gemcitabine and S-1 followed by surgery and adjuvant S-1 compared with initial surgery and adjuvant S-1 therapy (median OS: 36.7 vs 26.6 months, HR 0.72 (95%CI: 0.55-0.94), *P* = .015).[64] However, this was done exclusively in Japanese

**TABLE 3** Series of resected pancreatic adenocarcinoma in Asian and Western Centers

| Series (Author, country) | Year | Number of Patients (N) | Median age | Gender (%) | Tumour site (%) | Stage (%) | Tumour | Lymph node (%) | Differentiation (%) | Adjuvant tx (%) | Median OS (mth) | 1-year OS (%) | 3-year OS (%) | 5-year OS (%) | Prognostic Factors (multivariable analysis) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Asian | | | | | | | | | | | | | | | |
| Liu et al, China[22] | 2007-2015 | 1223 | 62 | M: 57 | Head/Body: 56.9<br>Tail: 43.1 | IA: 9.4<br>IB: 30.9<br>IIA: 15.8<br>IIB: 33.7<br>III: 10.2 | Mean: 3.77 cm | N1: 43.9 | WD: 65.0<br>MD/PD: 35.0 | 82.5 | 18.7 | 64.0 | 28.7 | NR | Tumor grade<br>Post-operative (post-op) CA 19–9 |
| Yamamoto et al, Japan[23] | 2001-2015 | 100 | 70 | M: 58 | NR | IA: 5<br>IB: 3<br>IIA: 38<br>IIB 52<br>III: 1<br>IV: 1 | Median: 2.6 cm | N1: 53 | NR | 64.0 | NR | 79.7 | 40.9 | 22.6 | NR |
| You et al, Korea[5] | 2005-2017 | 351 | 63.3 | M: 57.8 | Head: 64.1<br>Non-head: 32.5<br>Overlapping: 3.4 | I: 19.1<br>II: 67.0<br>III: 12.8<br>IV: 1.1 | NR | N1: 57.3 | WD: 8.0<br>MD: 82.3<br>PD: 8.8<br>UD: 0.9 | 100.0[a] | 31.7 | NR | NR | NR | LNR<br>Tumor grade<br>Lymphovascular invasion (LVI)<br>Perineural invasion (PNI)<br>Tumor stage (T-stage)<br>Pre-operative (pre-op) CA 19-9 |
| Xu et al, China[24] | 2010-2014 | 353 | 61 | M: 56.9 | Head/body: 57.5<br>Tail: 42.5 | I: 24.4<br>IIA: 29.7<br>IIB: 45.9 | Mean: 4.13 cm | N1: 45.9 | WD/MD: 63.7<br>PD: 36.3 | Chemo (82.4)<br>ChemoRT (31.7) | 18.1 | 62.2 | 27.1 | - | Those with elevated post-op serum CA19-9: Tumour size, no adjuvant chemoradiotherapy (chemoRT), post-op CA125, no decrease in CA19-9 from pre-op<br>Those with normal post-op serum CA19-9: No adjuvant chemoradiotherapy, post-op CA125, post-op CEA |
| Haruki et al, Japan[25] | 2001-2011 | 113 | 66.8 (mean) | M: 61.9 | NR | 0:6.2<br>I: 2.7<br>II: 16.8<br>III: 48.7<br>IV: 25.7 | NR | NR | NR | NR | NR | NR | NR | 24.1 | CRP/albumin ratio<br>Higher TNM stage |
| Shin et al, Korea[26] | 2000-2007 | 528 | 61 | M: 60.2 | Head: 74.4<br>Non-head: 25.6 | | ≤3 cm: 51.3<br>>3 cm: 48.7 | N1: 42.0 | WD/MD: 78.0<br>PD: 15.2<br>Missing 6.8 | NR | NR | NR | NR | 15.5 | Tumor size<br>Tumor grade<br>Node-stage (N-stage)<br>PNI<br>LVI<br>Portal/mesenteric vein invasion |

**TABLE 3** (Continued)

| Series (Author, country) | Year | Number of Patients (N) | Median age | Gender (%) | Tumour site (%) | Stage (%) | Tumour | Lymph node (%) | Differentiation (%) | Adjuvant tx (%) | Median OS (mth) | 1-year OS (%) | 3-year OS (%) | 5-year OS (%) | Prognostic Factors (multivariable analysis) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Western | | | | | | | | | | | | | | | |
| Sohn et al, USA[27] | 1984-1999 | 616 | 64.3 (mean) | M: 54 | NR | NR | Mean: 3.2 cm | N1: 72.0 | WD/MD: 64.0<br>PD: 36.0 | 74.0 | 17.0 | 63.0 | 25.0 | 17.0 | Resection Margin<br>Tumor size<br>Intra-op blood loss<br>Tumor grade<br>Post-op chemoRT |
| Katz et al, USA[10] | 1990-2002 | 329 | 64 | M: 58 | Head: 92<br>Non-head: 8 | NR | Mean: 3.0 cm | N1: 52.0 | NR | 91.0 | 24.0 | NR | NR | 27.0 | N-stage<br>Prior attempts at resection |
| Schnelldorfer et al, USA[28] | 1981-2001 | 357 | 65 (mean) | M: 54 | Head: 100 | IA: 7.6<br>IB: 14.9<br>IIA: 27.4<br>IIB: 48.5<br>III: 0.8<br>IV: 0.8 | Mean: 3.2 cm | N1: 49.4 | WD: 0<br>MD: 21.9<br>PD: 55.8<br>UD: 22.3 | 77.0 | 17.0 | NR | NR | 18.0 | Tumour size<br>N-stage |
| Winter et al, USA[29] | 1990-1999 | 399 | NR | NR | NR | NR | NR | NR | NR | NR | 25.6 | 68.0 | NR | 20.0 | - |
| Winter et al, USA[29] | 2000-2009 | 625 | NR | NR | NR | NR | NR | NR | NR | NR | 24.5 | 68.0 | NR | 8.0 | - |
| Lewis et al, USA[6] | 2001–2011 | 424 | 67 | M: 50.5 | NR | IA: 3.8<br>IB: 6.8<br>IIA: 19.3<br>IIB 64.9<br>III: 2.4<br>IV: 2.6 | NR | N1: 68.4 | WD: 10.8<br>MD: 49.5<br>PD 39.7 | 76.4 | 21.3 | 76.0 | 34.0 | 23.0 | T-stage<br>N-stage<br>LNR<br>Tumor size<br>Tumor grade<br>LVI<br>PNI<br>Resection margin<br>Adjuvant treatment<br>Pre-op physiology |
| Konstantinidis et al, USA[30] | 1993-2008 | 517 | 67 | M: 47.2 | NR | NR | Median: 3.0 cm | N1: 31.5 | WD: 3.5<br>MD: 54.5<br>PD: 39.7<br>UD: 2.3 | NR | 19.7 | NR | NR | 17 | Size of tumour<br>Tumor grade<br>LVI<br>PNI<br>Resection margin<br>LNR |

Abbreviation: CRP, C-reactive protein; LNR, Lymph Node Ratio; LVI, Lymphovascular invasion; M, Male; MD, Moderately differentiated; NR, Not reported; PD, Poorly differentiated; PNI, Perineural invasion; UD, Undifferentiated; WD, Well differentiated

[a]Only patients who received adjuvant chemotherapy are included in this study.

**TABLE 4** Phase 3 randomized clinical trials evaluating efficacy of adjuvant treatment in resected pancreatic adenocarcinoma

| Randomized controlled trials | Arms | N | Stratifications | Clinico-pathological features described in patient characteristics Y: Yes, N: No | | | | | | | | | | | | Median OS (mths) | 5-year-OS (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Age | Gender | T-status | Nodal status | LNR | Resection status | Grade | Baseline CA19-9 | Post-operative CA19-9 | Site of primary | PNI | LVI | | |
| ESPAC 1[11] | Observation (Obs)<br>5-FU<br>ChemoRT<br>ChemoRT followed by 5-FU | 289 | Country<br>Resection margin | Y | Y | Y | Y | N | Y | Y | N | N | N | N | N | Obs: 16.9<br>5-FU: 20.1<br>ChemoRT: 15.9<br>ChemoRT followed by 5-FU: 19.9 | Obs: 11<br>5-FU: 29<br>ChemoRT: 7<br>ChemoRT followed by 5-FU: 13 |
| CONKO-001[12] | Gemcitabine (Gem)<br>Observation | 368 | Tumour stage: T1-2 vs T3-4<br>Nodal status: N0 vs N1<br>Resection margin: R0 vs R1 | Y | Y | Y | Y | N | Y | Y | N | N | N | N | N | Gem: 22.8<br>Obs: 20.2 | Gem: 20.7<br>Obs: 10.4 |
| RTOG 9704[13,45] | 5-FU-RT<br>Gem-RT | 451 | Tumor diameter: <3 cm vs ≥3 cm<br>Nodal status: N0 vs N1<br>Surgical margins: R0 vs R1 vs unknown | Y | Y | Y | Y | N | Y | Y | Y | N | Y | N | N | 5-FU-RT: 16.9<br>Gem-RT: 20.6 | 5FU: 18<br>Gem: 22 |
| ESPAC 3[14] | Gem<br>5-FU | 1008 | Country<br>Surgical margins: R0 vs R1 | Y | Y | Y | Y | N | Y | Y | N | Y | N | N | N | Gem:23.6<br>5-FU:23.0 | - |
| JASPAC-01[15] | Gem<br>TS-one | 377 | Study site<br>Surgical margin: R0 vs R1<br>Nodal status: N0 vs N1 | Y | Y | Y | Y | Y | Y | N | Y | N | N | N | N | Gem:25.5<br>TS-one: 46.5 | Gem: 24.4<br>TS-one: 44.1 |
| ESPAC-4[38,46]N | Gem<br>Gem/Cape | 730 | Country<br>R0 vs R1 | Y | Y | Y | Y | N | Y | Y | Y | Y | N | N | N | Gem: 25.5<br>Gem/Cape: 28.0 | Gem: 20.0<br>Gem/Cape: 28.0 |
| PRODIGE-24[18] | Gem<br>mFFX | 493 | Study site<br>Surgical margin: R0 vs R1<br>Nodal status: N0 vs N1<br>Post-op CA19-9 (≤90 U/mL vs 91-180 U/mL) | Y | Y | Y | N | N | Y | Y | N | Y | Y | Y | Y | Gem: 35.0<br>mFFX: 54.4 | - |
| APACT[17,47] | Gem<br>Gem/nab-paclitaxel | 866 | Country<br>Surgical margin: R0 vs R1<br>Nodal status: N0 vs N1 | Y | Y | Y | Y | N | Y | Y | Y | N | N | N | N | Gem: 37.7<br>Gem/nab-paclitaxel: 41.8 | - |

Abbreviations: 5-FU, 5-Flurouracil; Cape, Capecitabine; Gem, Gemcitabine; mFOLFIRINOX, modified 5-FU, leucovorin, oxaliplatin, irinotecan; nab-Paclitaxel, nanoparticle albumin-bound paclitaxel; Obs, Observation; TS-one, tegafur, gimeracil, oteracil.

patients and the generalizability of these data is debatable. The SWOG S1505 Phase 2 randomized trial randomized patients with resectable PDAC to perioperative FOLFIRINOX or perioperative gemcitabine and nab-paclitaxel. The primary outcome was 2-year OS. Each arm was compared against the historical threshold of 40%. The 2-year OS was 41.6% with mFOLFIRINOX ($P$ = .42) and 48.8% with gemcitabine/nab-paclitaxel ($P$ = .12).65 There are multiple other trials examining this question including the randomized Phase 2/3 NEPAFOX trial (ClinicalTrials.gov identifier: NCT02172976) which is evaluating neoadjuvant FOLFIRINOX, surgery, and adjuvant FOLFIRINOX compared with surgery and adjuvant gemcitabine in patients with resectable and borderline resectable pancreatic cancer. There is also the randomized Phase 2 NEONAX trial (ClinicalTrials.gov identifier: NCT02047513) which compares neoadjuvant gemcitabine and nab-paclitaxel followed by surgery and adjuvant gemcitabine and nab-paclitaxel compared with initial surgery and adjuvant gemcitabine and nab-paclitaxel. While no patients in our series received neoadjuvant treatment, it is a promising approach worth considering and we await the results of ongoing trials.

The pattern of recurrence in our series of patients is similar to that reported in the literature.[10] Most of the recurrences occurred within the first year after surgery as demonstrated in Figure S1. The most common sites of recurrence are the liver, local recurrence, distant lymph nodes, lungs, and peritoneum. 61.3% of patients in our study developed recurrence within 1 year after curative resection; this is reflective of the aggressive disease biology and presence of micrometastases at diagnosis.

In this study consisting of Asian patients, we identified four prognostic factors associated with poor prognosis: LNR > 0.3, poorly differentiated/undifferentiated tumor grade, location of tumor at the body or tail and the presence of PNI.

LNR has been found to be an independent prognostic factor in various studies.[5,41,42] Different groups have used different cutoffs for the LNR. Valsangkar et al demonstrated that increasing values of LNR of 0.2, 0.20 to 0.30 and ≥0.30 were associated with poor prognosis,[41] Huebner et al showed that a LNR of ≥0.17 had poorer prognosis.[42] We found that a LNR ≥0.30 was associated with a poorer prognosis. Patients with LNR of 0, >0 to 0.3 and > 0.3 had median OS of 31.0, 17.9, and 12.3 months, respectively. Total number of lymph nodes examined (TLN) may be of prognostic significance, especially in patients with pN0 disease. Slidell et al found that patients with pN0 disease could be further stratified based on the number of lymph nodes evaluated, with those with 11 or less LN examined having a poorer prognosis.[43] Another study showed that those with <12 TLN had a poorer prognosis, but this did not reach statistical significance.[44] In our study, however, we did not find that the TLN was a prognostic factor in patients with pN0 disease or in our entire cohort. While nodal status is incorporated as a stratification in a large proportion of randomized adjuvant trials in pancreatic cancer,[12,13,15,18] LNR could be a better stratification factor. LNR did not feature as a stratification factor in any of the randomized trials (Table 4). The only randomized trial, which included LNR in its patients' clinic-pathological characteristics, was JASPAC-01 trial.[15] Tumor grade is a known prognostic factor found in many studies, including various RCTs.[5,6,11,14,18,22,26,27,30,48,49] (Tables 3 and 4) Our study confirmed this finding. While Brennan et al found that tumors located at the head are associated with a worse prognosis, our results are contrary to this.[50] We found that patients with tumors at the body or tail had poorer prognosis. Multiple studies have suggested that the anatomical site is a prognostic factor; however, studies have been conflicting regarding which site is associated with a better prognosis.[51-54] Artinyan et al and Watanabe et al reported that patients with body/tail PDAC are more likely to be have unresectable or metastatic disease at presentation and consequently have poorer OS. This is attributed to the earlier onset of symptoms (eg, jaundice) in patients with head lesions.[52,53] Body/tail lesions were found to be a poorer prognostic factor compared with head lesions even in patients who had undergone surgical resection.[53] This may potentially be due to more aggressive tumor biology for lesions arising from the body/tail.[55] However, Lau et al, which utilized the Surveillance, Epidemiology, and End Results (SEER) registry, found that patients with local-stage pancreatic body/tail cancer had higher OS compared with local-stage pancreatic head cancer.[51]

Chatterjee et al found that the presence of PNI and LVI correlated with poorer outcomes. We found that the presence of PNI but not LVI was associated with poor prognosis. PNI is the presence of cancer cells along nerves and/or within the epineurial, perineurial, and endoneurial spaces of the neuronal sheath and is commonly found in PDAC.[56] The presence of PNI has been demonstrated as a negative prognostic factor in multiple studies.[5,6,26,30] (Table 3).

While the previously described factors are well described in the literature to be prognostic, the prognostic value of the resection margin remains controversial.[57]

Margin status has been identified as prognostic factor in multiple studies.[58,59] However, other studies have demonstrated no relationship between the resection margin and OS.[60,61] Conflicting results have also been found for the posterior resection margin.[58,62] Our study found that resection margin status (R0 vs R1) and the posterior resection margin status (R0 vs R1) were not independently associated with OS in the multivariable analysis. There are numerous postulations for the conflicting results. First, the definition of microscopic margin positivity differs from study to study.[19,60] Second, there are wide variability in the way different centers handle and sample the resection tissue.[57] Third, the definition of the posterior margin is also not standardized in multiple studies.[57]

Taking the above together, our study showed that our cohort had similar prognostic factors, recurrence patterns, and survival as other Western and Asian institutions.[5,6,10,22-30] (Table 3) In the APACT trial which recruits both Western and Asian patients, country was used as a stratification factor.[17] Given the similarity in clinical characteristics in Western and Asian patients with PDAC, using country as a stratification factor may not be necessary. On the other hand, LNR and presence of PNI have consistently been found to be a significant prognostic factor in RCTs or large series from high-volume centres[5,6,11,14,16,18,22,26,27,30,48,49] (Tables 3 and 4) and should perhaps be used as a stratification factor instead.

Our study has several limitations. While we managed to demonstrate applicability of adjuvant therapy in a general Asian population consistent with what has been reported in RCT, all the patients in this cohort received single agent systemic therapy (gemcitabine or 5FU). A number of RCT has since been reported providing evidence for doublet and triplet combination therapies.[17,18] Future population-based studies are needed to clarify its applicability to a general population. As this study is retrospective in nature, there may be recall bias. Furthermore, the study sample size is modest, perhaps explaining for lack of statistical significance in previously reported prognostic factors (eg, resection margins and presence of LVI). Finally, incomplete capture of variables may introduce bias in survival analysis.

In conclusion, the survival of Asian patients with resected PDAC who received adjuvant chemotherapy is comparable to reported randomized trials. Clinical characteristics of Asian patients with resected PDAC are similar to datasets described among patients from the West. Hence, geographical locations/country of origin may not be a necessary stratification factor in RCTs. Conversely, LNR and status of PNI ought to be incorporated.

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## CONFLICT OF INTEREST

Su Pin Choo has received research funding and speaking fees from Bristol-Myers Squibb (BMS) speaking fees from Lilly, research funding from Sirtex, and has participated on advisory boards for BMS, Sirtex, Lilly, Norvatis, Eisai, Bayer, Celgene. David Tai has received research funding for BMS and Sirtex, honorarium from Bayer and has participated on advisory boards for Eisai, Bayer, and Ipsen. Joycelyn Jie Xin Lee has received research funding from Bayer, honorarium from BMS and Ipsen, and has participated on advisory boards for Bayer and Ipsen.

## AUTHOR CONTRIBUTIONS

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization, K.Y.Y.N., E.W.X.C., D.T.; Methodology, K.Y.Y.N., E.W.X.C., D.T.; Investigation, K.Y.Y.N., E.W.X.C., B.J.; Formal Analysis, K.Y.Y.N., E.W.X.C., C.L.; Resources, D.T.; Writing - Original Draft, K.Y.Y.N., E.W.X.C., D.T.; Writing - Review & Editing, All authors: Visualization, K.Y.Y.N., E.W.X.C., D.T.

## ETHICAL STATEMENT

Our study was approved by the Centralized Institutional Review Board of our institution.

## DATA AVAILABILITY STATEMENT

The unidentified dataset is available upon reasonable requests made to the corresponding author.

## ORCID

*Kennedy Yao Yi Ng* https://orcid.org/0000-0001-6630-3803
*Edwin Wei Xiang Chow* https://orcid.org/0000-0001-6033-5724
*Bochao Jiang* https://orcid.org/0000-0002-2978-9725
*Cindy Lim* https://orcid.org/0000-0002-8036-4554
*Brian Kim Poh Goh* https://orcid.org/0000-0001-8218-4576
*Jin Yao Teo* https://orcid.org/0000-0002-0777-8128
*Damien Meng Yew Tan* https://orcid.org/0000-0002-7282-0900
*Peng Chung Cheow* https://orcid.org/0000-0002-8102-1203
*London Lucien Peng Jin Ooi* https://orcid.org/0000-0001-6777-8464
*Pierce Kah Hoe Chow* https://orcid.org/0000-0003-0584-2584
*Joycelyn Jie Xin Lee* https://orcid.org/0000-0002-1070-6125
*Juinn Huar Kam* https://orcid.org/0000-0002-2478-9689
*Ye Xin Koh* https://orcid.org/0000-0001-5006-4174
*Prema Raj Jeyaraj* https://orcid.org/0000-0003-3200-6450
*Ek Khoon Tan* https://orcid.org/0000-0002-5949-4741
*Su Pin Choo* https://orcid.org/0000-0002-8925-3922
*Chung Yip Chan* https://orcid.org/0000-0002-9397-0908
*Alexander Yaw Fui Chung* https://orcid.org/0000-0002-4598-6139
*David Tai* https://orcid.org/0000-0002-2612-0065

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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