Age 80 years and over is not associated with increased morbidity and mortality following pancreaticoduodenectomy

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ABSTRACT

Background: Pancreaticoduodenectomy (PD) is associated with high morbidity which is perceived to be increased in the elderly. To our knowledge there have been no Australian series that have compared outcomes of patients over the age of 80 undergoing PD to those who are younger.

Methods: Patients who underwent PD between January 2008 and November 2015 were identified from a prospectively maintained database.

Results: A total of 165 patients underwent PD of whom 17 (10.3%) were aged 80 or over. The pre-operative health status, according to American Society of Anaesthesiologists class was similar between the groups (p=0.420). The 90-day mortality rates (5.9% in the elderly and 2% in the younger group; p=0.355) and the post-operative complication rates (64.7% in the elderly versus 62.8% in the younger group; p=0.88) were similar. Overall median length of hospital stay was also similar between the groups, but older patients were far more likely to be discharged to a rehabilitation facility than younger patients (47.1% versus 12.8%; p<0.0001). Older patients with pancreatic adenocarcinoma (n=10) had significantly lower median survival than the younger group (n=69) (16.6 months versus 22.5 months; p=0.048).

Conclusion: No significant differences were seen in the rate of complications following PD in patients aged 80 or over compared to younger patients, although there appears to be a shorter survival in the elderly patients treated for pancreatic cancer. Careful selection of elderly patients and optimal peri-operative care, rather than age should be used to determine whether surgical intervention is indicated in this patient group.

INTRODUCTION

The population aged 80 or over is increasing worldwide, constituting around 1% of the overall population[1] and is predicted to increase 4-fold by 2050[1-3]. This has imposed a new challenge for the healthcare system, given that 70% of cancer is expected to occur in the elderly.[2] Pancreatic cancer has an incidence that increases with the age[1, 4] and therefore surgical options such as pancreaticoduodenectomy (PD) need to be considered more frequently in the elderly.

In the last two decades, the outcomes of PD have improved with better surgical techniques and optimal post-operative care of patients[1]. Given that pancreatic cancer has a poor prognosis, offering major surgery to elderly patients has been considered controversial.[1] It is estimated that the 5-year survival rate after resection of pancreatic cancer is only 12% to 24%.[5, 6,7] There are several recent studies from the United States, Germany and Italy[1,8, 9] that have retrospectively analysed data on outcomes of elderly patients treated by PD compared with younger subgroups generally suggesting greater post-operative complications and mortality in the older group. As far as we are aware, there have been no Australian series that have reported on such an outcome that will allow comparisons with other reported literature.

METHODS

Patients

Patients treated at Austin Health, Melbourne, Australia who underwent PD between January 2008 and November 2015 were included in this study. Patients were managed post operatively by standard enhanced recovery techniques. This study was approved by the Austin Health Human Ethics Committee. Follow-up data was complete as of May 2016 for all patients.

Pathology

The histopathological diagnoses of the resected specimens were identified and categorised into benign and malignant lesions. Pancreatic ductal adenocarcinoma (PDAC) was the most common malignant tumour treated. A microscopic positive margin (R1) was defined as the presence of tumour at any inked surgical margin at the time of histological examination.

Preoperative Assessment

Patients' demographic information was recorded including age, sex, body mass index, American Society of Anesthesiologists (ASA) classification and pre-morbid conditions.

Operative Details

Information including operative technique, duration of surgery, estimated blood loss, intra-operative blood transfusion and use of epidural or intrathecal morphine were recorded.

Post-operative Outcome

Post-operative outcomes such as morbidity, mortality, length of hospital stay, length of intensive care unit (ICU) stay, re-operation and hospital readmissions within 90 days after discharge were recorded.

Complications and severity

Patient complications were recorded and the severity of post-operative complications were analysed using Comprehensive Complication Index (CCI) calculator as previously described, [10] utilising an online calculator (http://www.assessurgery.com/about_cci-calculator/). Post-operative complications were further categorised into general and PD-specific. Delayed gastric emptying (DGE), post-operative pancreatic fistula (POPF) and haemorrhage were defined using the International Study Group of Pancreatic Surgery criteria[11, 12].

Statistical Analysis

All the statistical analyses were performed using SPSS (IBM SPSS Statistics Version 22). Categorical variables were assessed using the chi-squared or Fisher's exact test. Comparisons of continuous data were performed with the use of Student's t test for normally distributed data, otherwise the Mann-Whitney U test was used. Values were reported as mean and standard deviation or median with range. Kaplan-Meier method was used to create survival curves which were then compared using a univariate Log-rank test. Statistical significance was considered when p-value <0.05.

RESULTS

Patients

The patient characteristics are shown in Table 1. There were 165 patients who underwent PD of which 17 (10.3%) patients who were aged 80 or over. The two groups did not show differences in ASA classifications (p = 0.420), but the older group was far more likely to be hypertensive pre-operatively [Odds Ratio (OR) 3.2, 95% Confidence Interval (CI):1.09-9.66, p = 0.028]. Significantly more patients in the older group (76.5%) underwent biliary stent insertion pre-operatively than the younger group (44.6%) (p = 0.019). This may be partly related to a greater proportion of PDAC cases (Table S1) or anticipated delays to surgery. Our unit generally avoids biliary stenting prior to surgery, when timely access to operative sessions are available and bilirubin levels are below 200 μmol/L.

Pathology

Pathology details are noted in Table S1. The majority of elderly patients with malignant diseases had PDAC (71.4%), with similar nodal and R1 status as their younger counterparts.

Operative Details

There was no difference between younger and older patients in terms of duration of surgery, intra-operative blood loss, intra-operative blood transfusion, use of epidural and intrathecal analgesia, reported pancreatic texture or pancreatic duct diameter (Table S2).

Mortality

One patient died within 90-days of surgery in the elderly group (5.9%) compared to 3 (2%) in the younger group with no statistical difference between the two groups (p = 0.355) (Table 2).

Post-operative complications

Post-operative complications were compared between the two groups as Table 2shows. The overall complications were similar in the two populations (p = 0.88).

PD-specific complications

No differences were found in PD-specific complications, as shown in Table 2.

Length of Stay

The median length of hospital stay for the older population was 15 days and that of the younger population was 12 days, which was not significantly different (p = 0.162) (Table S3)

Discharge

There was a significant difference in the discharge destinations between the two groups (Table S3). In total, 47.1% of older patients were discharged to rehabilitation facilities whereas this was required in only 12.8% of younger patients (p<0.0001).

Survival

At follow-up, there were 10 (58.8%) patients deceased in the older cohort and 60 (40.5%) deaths in the younger group (p = 0.078) (Table 2). The majority of deaths were related to malignant disease recurrence. The median survival in patients aged 80 or over was 19.1 months which was not significantly lower than younger patients at 61.1 months, p = 0.067. The 1-, 3-, and 5-year survival rates were 82.4%, 27.9% and 27.9%, respectively, in the older group and 80.8%, 59.1% and 51.8% , respectively, in the younger group (p = 0.067) (Figure 1A).

At the time of follow-up 80.0% of the older group with PDAC were deceased compared with 59.4% of younger patients with PDAC, p = 0.210. Among these patients, cancer recurrence was noted in 87.5% of patients in the older group and 70% in the younger cohort, p = 0.081 (Table 2). The adjuvant chemotherapy treatment rates were similar between the groups 6(60%) in the older group versus 48(69.6%) in the younger group; p=0.543). Patients in the older group with PDAC had a median survival of 16.6 months, compared with 22.5 months in the younger group (p = 0.048). The survival rate in the older group at 1-year was 80.0%, with no 3-year or 5-year survivors. This is compared to a 1-year survival of 71.4%, 3-year 37.4%, 5-year 27.6% for those in the younger group (p = 0.048) (Figure 1B).

DISCUSSION

PD can improve quality of life and is the only potentially curative option for peri-ampullary or pancreatic malignancy.[13] PD is however associated with a high morbidity ranging from 41% to 52% in some large series[14,6,15] with a reluctance of offering surgery in some centres to older patients. Despite improved operative techniques and low post-operative mortality, the rate of post-operative morbidity remains high. Our study showed the rates of post-operative complications at 64% in elderly and 62% in younger patients, which were statistically similar between the two populations. Even though there is a high rate of complications, the vast majority of patients have these detected early and treated successfully to prevent mortality.

The PD-specific complications that impact patient outcomes include POPF, DGE, bile leakage and haemorrhage[11,16]. Risk factors for developing POPF include soft texture of the pancreas and the size of the pancreatic duct. It has been shown previously that the age has no effect on the incidence of POPF.[3] This finding is consistent with our results where none of the elderly patients developed POPF. DGE is another potential PD-specific complication which was reported to be increased in the elderly population in some series,[1, 6] possibly due to global reduction in gastrointestinal motility in elderly patients.[17] It is, however, inconsistent across the reported literature,[18, 19] possibly related to differences in the definitions used. With regard to other PD-specific complications such as delayed gastric emptying, bile leakage and haemorrhage, we found no differences between our groups, which are in keeping with other published reports.[3,19]

The median length of hospital stay was not significantly different between the elderly and the younger cohorts, which may be reflective of similar post-operative complication rates in each of the groups. The median length of hospital stay in our study in elderly patients was comparable to large United States series of PD, possibly reflecting our utilisation of enhanced recovery pathways.[6, 20] Johns Hopkins Medical Centre showed a decline in the length of stay in patients from 21 days to 10 days[20] with more streamlined post-

operative care. It should however be noted that elderly patients were far more likely to be discharged to a rehabilitation facility than home. This finding is consistent with other reported series.[21,22] A study conducted at Mayo Clinic[23] noted that despite the increased need for rehabilitation in the elderly population following PD, the patients were mostly independent in their ambulatory status and were discharged to home after generally a short period at the rehabilitation facilities.

Other studies have reported higher mortality associated with PD in patients aged 80 years and older, often reflecting a higher ASA status.[1, 6] This was not the case in our study and may reflect the similar pre-operative medical status of the patients based on ASA score. Although our unit does not use age *per se* when determining whether to offer PD, it is possible that many elderly patients with perceived major comorbidities were excluded from surgery, which we were unable to identify due to the retrospective nature of this study. There were no standard pre-operative objective tests routinely used to assess patient's fitness for surgery in our unit. Cardiorespiratory function testing was undertaken selectively. We could not determine the absolute number patients with potentially resectable tumours who were not offered surgery due a perceived lack of fitness. In addition, it is probable that some elderly patients with a diagnosis of pancreatic cancer may not be referred to our unit for consideration of surgery due to primary physician biases.

The long-term survival of patients undergoing PD aged 80 years and older compared to younger patients has been analysed in a limited number of series.[15, 24] There appear to be major variations in survival following PD in the published literature which may be related to the inclusion of different pathologies in the analysis.[18, 25] In our study, the overall survival was significantly decreased in the older cohort treated by PDAC compared to younger patients. This included a small number of patients, but the tumour staging was similar between the two groups. There is some suggestion that the tumour biology in the elderly patients may be more aggressive for unknown reasons.[26] Comparison of survival in elderly populations with resectable tumour treated by palliative chemotherapy compared to surgical resection would provide further insights.

This could not however be undertaken from the data available to us for this study. A reduction in the survival in older patients may also relate to age-related predicted lower life expectancy in those aged 80 years and older .The general population's life expectancy in Australia is trending up and men and women aged 80 or over are expected to live for another 10 years,[27] while the life expectancy in people aged 65 is double that of those 80 years and over.[27,28].Nevertheless, given the life expectancy of up to 10 or more years in the octogenarian or older population, consideration for surgery appears a valid option in highly selected patients operated on by experienced surgeons in tertiary hospitals. The median survival of 16.6 months in patients over the age of 80 years undergoing PD for treatment of pancreatic cancer appears to be better that those of patients with non-metastatic pancreatic cancer treated by chemotherapy alone. [29]

CONCLUSION

In a large Australian series of PD, 10% of those offered surgery were aged 80 years or older and had similar comorbidities to younger patients. The overall post-operative morbidity, mortality, ICU and hospital stay was similar between the two groups. The older patients were, however, more likely to require rehabilitation following surgery. Long-term survival was lower in the older patients treated for pancreatic cancer, which may reflect disease biology and inherent lower life-expectancy with increasing age, rather than being directly related to surgical factors. Careful selection of patients aged 80 or over for PD appears be the major determinant of surgical outcomes rather than the patients' age alone. Therefor older patients should not be excluded from surgical intervention solely due to their age.

LEGENDS

Figure 1

Kaplan-Meier survival curve for patients undergoing pancreaticoduodenectomy. **A.** The overall survival rates for those aged 80 years and over (n=17) were not statistically significantly different to the younger patients (n=148) (p = 0.067) (Log-Rank Test) **B.** In patients with pancreatic ductal adenocarcinoma the survival rate for those aged 80 years and over (n=10) and was significantly less than the younger patients (n=69) (p = 0.048) (Log-Rank Test)

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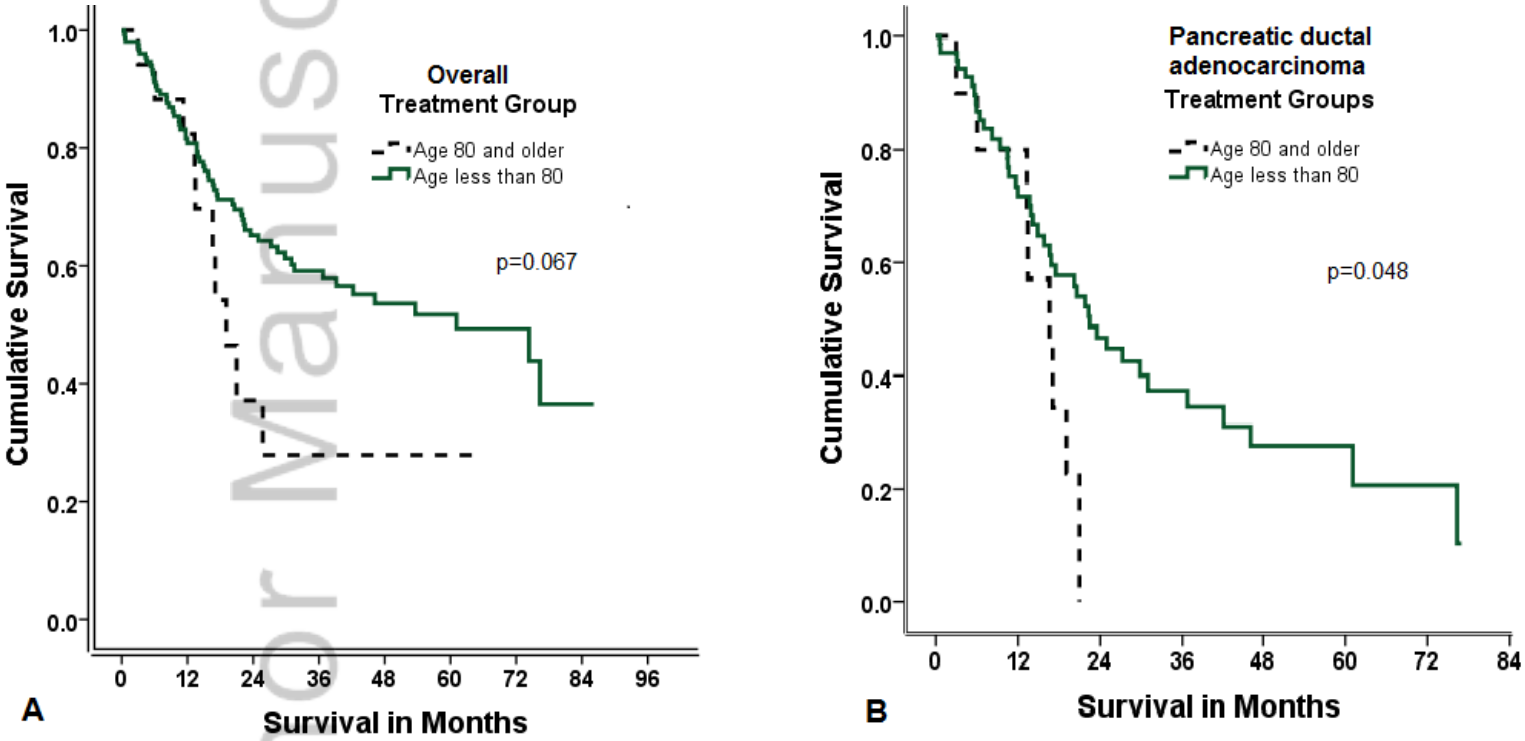

Fig 1.tif

Table 1. Clinicopathological and surgical characteristics of patients treated by pancreaticoduodenectomy according to age group. Data are displayed as number (%), median (range) or mean ± standard deviation.

	≥80 years old (n= 17)	<80 years old (n = 148)	P-value
Sex (Male)	9 (52.9%)	82 (55.4%)	0.847
Age	81(80-86)	66 (15-79)	**<0.0001**
BMI[a]	24.2 ± 0.7	25.7 ± 0.5	0.059
ASA[b] Class I	0 (0.0%)	5 (3.4%)	0.420
II	2 (11.8%)	36 (24.3%)	
III	15 (88.2%)	103 (69.6%)	
IV	0 (0%)	4 (2.7%)	
History of Pancreatitis	1 (5.9%)	24 (16.2%)	0.260
Diabetes Mellitus	5 (29%)	40 (27%)	0.834
Hypertension	12 (70.6%)	63 (42.6%)	***0.028**
Ischaemic Heart Disease	5 (29.4%)	18 (12.2%)	0.052
COPD[c]	1 (5.9%)	13 (8.8%)	0.684
Chronic Renal Failure	1 (5.9%)	6 (4.1%)	0.723
Pre-operative stent insertion	13 (76.5%)	66(44.6%)	***0.019**
Pre-operative Laboratory Tests			
Haemoglobin, g/L	121.4 ± 12.2	124.0± 28.9	0.103
White Cell Count, $x10^9$/L	8.6 ± 3.4	7.9 ± 3.7	0.854
Platelets, $x10^9$/L	299.3 ± 124.4	296.0 ± 106.5	0.998
Bilirubin, µmol/L	47.1 ± 84.7	58.8 ± 94.8	0.615
Albumin, g/L	33.1 ± 9.6	36.3 ± 8.1	0.250
Urea, mmol/L	6.9 ± 3.0	5.6 ± 2.43	0.616
Creatinine, µmol/L	85.6 ± 33.8	74.0 ± 28.3	0.163
Types of Operation			
Pylorus preserving	3 (17.6%)	33 (22.3%)	0.660
Non-pylorus preserving	14 (82.4%)	115 (77.7%)	
Portal vein resection			
Partial/total	2 (11.8%)	19 (12.8%)	0.900

[a]BMI = Body Mass Index [b]ASA = American Society of Anaesthesiologist
[c]COPD = Chronic Obstructive Pulmonary Disease

Table 2. Post-operative outcomes of patients treated by pancreaticoduodenectomy according to age group.

	≥80 years old (n = 17)	**<80 years old (n = 148)**	**P-value**
Any complication	11 (64.7%)	93 (62.8%)	0.880
Myocardial infarction	1 (5.9%)	4 (2.7%)	0.469
Arrhythmia	5 (29.4%)	20 (13.5%)	0.083
Acute pulmonary oedema	2 (11.8%)	8 (5.4%)	0.298
Pneumonia	2 (11.8%)	12 (8.8%)	0.686
Acute renal failure	0 (0.0%)	7 (4.7%)	0.359
Urinary tract infection	0 (0.0%)	3 (2.0%)	0.554
Wound infection	3 (17.6%)	16 (10.8%)	0.403
Sepsis	2 (11.8%)	13 (8.8%)	0.686
Peritonitis	0 (0.0%)	2 (1.4%)	0.630
Confusion/delirium	1 (5.9%)	9 (6.1%)	0.974
Re-operation	0 (0.0%)	9 (6.1%)	0.296
Re-admission	4 (23.5%)	24 (16.2%)	0.447
PD-Specific Complications	**≥80 (n= 17)**	**<80 (n = 148)**	**P-value**
Delayed gastric emptying	0 (0.0%)	14 (9.5%)	0.185
POPF[a]/Leak	0 (0.0%)	11 (7.4%)	0.245
Haemorrhage	0 (0.0%)	8 (5.4%)	0.326
Bile leak	0 (0.0%)	7 (4.7%)	0.359
Complications scoring	**≥80 (n= 11)**	**<80 (n = 93)**	**P-value**
Clavien-Dindo classification			0.061
I	0 (0%)	4 (4.3%)	
II	8 (72.7%)	64 (68.8%)	
III	0 (0%)	18 (19.4%)	
IV	3 (27.3%)	5 (5.4%)	
V	0 (0%)	2 (2.2%)	
CCI[e] score Mean ± Std[f]	33.4 ± 15.3	35.8 ± 17.0	0.878
90-Day Mortality	1 (5.9%)	3 (2%)	0.355
Mortality at follow-up	10 (58.8%)	60 (40.5%)	0.078
Mortality at follow-up in Patients with PDAC	**≥80 (n = 8 of 10) 80%**	**<80 (n = 41 of 69) 59.4%**	0.210
Recurrence at time of death	7 (87.5%)	25 (70%)	0.081

[a]POPF = Post-operative pancreatic fistula, [e]CCI = Comprehensive Complication Index score, [f]Std = Standard deviation