Advanced age does not increase morbidity in pancreaticoduodenectomy

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Background: Due to rising life expectancy of population, very complex surgical procedures such as pancreaticoduodenectomy (PD), are more commonly being performed in elderly patients. The objective of this study was to evaluate the safety of PD in patients older than 75 years old and the risk factors associated with severe complications.

Methods: Patients who underwent PD for periampullary tumors were retrospectively reviewed and divided into two groups, A (<75 years) and B (>75 years). The primary endpoint was severe postoperative complications (Clavien 3 or greater). Secondary endpoints were mortality and any complications.

Results: Ninety consecutive patients underwent PD for periampullary tumors in the studied period, 70 in group A and 20 in group B. Clinical and pathological characteristics of both groups were equivalents except for age. There were no difference regarding the incidence of severe complications (17% *vs.* 10%, P=0.72) or all complications (50% *vs.* 50%, P>0.999). Although mortality was greater in group A (8.6% *vs.* 0%), it was not statistically significant (P=0.333). On multivariate analyses, only male sex, obesity and American Society of Anesthesiology Score of 3 or 4 were associated with severe postoperative complications.

Conclusions: Poor clinical status, obesity and male gender are associated with severe complications in PD, but not age greater than 75 years, therefore PD can be considered safe in elderly patients and age itself should not be a contraindication for PD.

Keywords: Pancreaticoduodenectomy (PD); morbidity; elderly; risk factors

Introduction

Periampullary cancer predominantly affects elderly patients, with 40% aged more than 75 years at the time of diagnosis (1). Since the 90's, several studies have demonstrated low mortality rates after pancreaticoduodenectomy (PD), however morbidity still remains high (40%) (2,3). As surgery is the only curative treatment available for these tumors, it is essential to consider the survival benefit in elderly patients against the risks of severe complications.

Previous studies reported contradictory data regarding morbidity and mortality associated with PD in elderly patients (3,4). Although some authors have found similar complication rates between groups, others have shown that elderly patients usually have longer stay in the intensive care unit (ICU) and require more readmissions after PD (4-6). Recent publications are focused in establishing perioperative factors associated with overall morbidity and classifying severity of the complications, as mild ones have little clinical significance (7-9).

The aim of this study was to assess the safety of surgical treatment for periampullary cancer in patients older than 75 years in such demanding procedures.

Methods

This present study was approved by the institutional ethics committee. Consecutive patients with periampullary tumors who underwent pancreaticoduodenectomy between January 2009 and October 2014 were retrospectively reviewed from a prospectively maintained database. The cohort was divided into two groups according to age: <75 and ≥75 years old.

Primary outcome was severe complications. Secondary outcomes were overall complications, length of ICU and hospital stay, readmission rate and 30-day mortality. Preoperative factors, intraoperative data and postoperative outcomes were compared between groups. Pancreatic fistula and delayed gastric emptying were defined according to the International Study Group of Pancreatic Surgery definitions (10,11). Complications were recorded using the Clavien-Dindo classification system (12). Severe complication was defined as Clavien-Dindo classification ≥3.

All patients underwent open PD and the pylorus was preserved whenever possible. Reconstruction was performed with a double jejunal loop technique, as standardized in our institution since 1976 (13). All procedures were performed by the same team of three experienced pancreatic surgeons.

Quantitative variables were expressed as mean ± standard deviation (SD) or median and compared using Student t-test. Qualitative variables were expressed as number and percentage and compared by means of chi-square or Fisher exact test, when appropriate. The significance level was set as $P<0.05$. Additionally, multivariate logistic regression was used to generate odds ratio for factors associated with major complication. Statistical analysis was carried out with SPSS software version 20.0 (SPSS, Inc. Chicago, IL).

Results

A total of 90 patients who underwent PD were included in the final analysis. Among these, 20 (22.2%) were aged ≥75 years (median age: 78.9±3.2 years). Patient demographic characteristics and preoperative variables are shown in *Table 1*. Except for the age itself, there were no statistically significant differences between groups.

Intra-operative outcomes are outlined in *Table 2*. Although there was no difference in preoperative hemoglobin level,

elderly patients received more red blood cells transfusion (17.1% *vs.* 45.0%; P=0.016). No difference was observed in terms of operative technique, operative time and vascular resection.

As shown in *Table 3*, overall and specific complications, such as pancreatic fistula and gastroparesis, were similar in both groups. Although the incidence of severe complications (17.1% *vs.* 10.0%; P=0.727) and 30-day mortality (8.6% *vs.* 0%; P=0.331) was higher in younger patients, these differences were not statistically significant. The elderly group had no re-operation, no mortality and only 2 cases (10.0%) of severe complication (acute kidney failure after pancreatic fistula and gastrointestinal bleeding after cardiogenic shock), but a higher rate of readmission (20%) was observed, although not statistically significant. Furthermore, the younger group had 12 (17.1%) patients with severe complications: 4 related to pancreatic fistula, 2 extra-luminal bleeding, 2 intestinal obstruction and the other 4 due to clinical complications. Early re-operation were required in 6 of these patients.

Risk factors that were predictive of complications are shown in *Tables 4* and *5*. Considering any complication (Clavien-Dindo ≥1), multivariate analysis showed that smoking is an independent risk factor (P=0.028), but higher albumin values (P=0.023) and pancreatic duct dilation (P<0.001) are protective factors for any complications. Furthermore, in multivariate analysis for severe complication (Clavien-Dindo ≥3), male gender (P=0.003), BMI >25 kg/m^2 (P=0.006) and American Society of Anesthesiologists (ASA) physical status classification system score 3 or 4 (P=0.039) were noted to be independent risk factors. Moreover, older age (P=0.030) was found to be a protective factor against it.

Pre- and post-operative variables for 30-day mortality are disposed in *Table 6*. None of these were associated with mortality.

Discussion

Contrary to previous studies that have shown older age to be a risk factor for morbidity and mortality after PD (8,9,14), our study found that patients aged ≥75 years old have the same rates of severe complications and 30-day mortality as younger patients. As there are dissonant results in the literature, it is difficult to make an assumption based on the current data, but we believe that careful selection of elderly patients is of paramount importance to find better results in these patients.

Table 1 Baseline characteristics of study patients

Characteristics	Age <75 years (n=70)	Age ≥75 years (n=20)	P
Demographics			
Male gender	34 (48.6)	9 (45.0)	0.778
Age (years)	60.7±7.8	78.9±3.2	0.001
BMI (kg/m^2)	25.4±4.4	24.8±3.7	0.555
Tumor histology			0.804
Duodenal adenocarcinoma	6 (8.6)	1 (5.0)	
Pancreatic duct adenocarcinoma	21 (30.0)	6 (30.0)	
Ampullary adenocarcinoma	36 (51.4)	12 (60.0)	
Distal bile duct cancer	7 (10.0)	1 (5.0)	
Comorbidities and risk factors			
ECOG performance status			0.434
0	33 (47.1)	11 (55.0)	
1	24 (34.3)	7 (35.0)	
2	8 (11.4)	2 (10.0)	
3	5 (7.1)	0	
4	0	0	
ASA score			0.393
1	8 (11.4)	1 (5.0)	
2	39 (55.7)	9 (45.0)	
3	22 (31.4)	10 (50.0)	
4	1 (1.4)	0	
Diabetes	20 (28.6)	5 (25.0)	0.753
Smoking	17 (24.3)	3 (15.0)	0.545
Pre-operative lab			
Hemoglobin (g/dL)	12.1±2.1	11.7±1.7	0.410
Albumin (g/dL)	3.6±0.8	3.5±0.8	0.453
Billirubin (mg/dL)	4.2±6.2	6.3±9.1	0.337

Data are shown as number (percentage) or mean ± standard deviation. BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; ASA, American Society of Anesthesiology.

Table 2 Intraoperative outcomes

Variables	Age <75 years (n=70)	Age ≥75 years (n=20)	P
Pylorus preserving surgery	46 (65.7)	8 (40.0)	0.638
Operative time (min)	297±61	298±65	0.950
Portal vein resection	7 (10.0)	0	0.331
IO blood transfusion	12 (17.1)	9 (45.0)	0.016

Data are shown as number (percentage) or mean ± standard deviation. IO, intraoperative.

Table 3 Post-operative outcomes

Outcomes	Age <75 years (n=70)	Age ≥75 years (n=20)	P
Length of ICU stay (days)	3.0±3.4	3.4±1.9	0.699
Length of hospital stay (days)	14.6±9.8	12.3±6.1	0.311
Overall complication	35 (50.0)	10 (50.0)	>0.999
Severe complication (Clavien-Dindo ≥3)	12 (17.1)	2 (10.0)	0.727
Readmission	4 (5.7)	4 (20.0)	0.070
Reoperation	6 (8.6)	0	0.331
30-day mortality	6 (8.6)	0	0.331
Pancreatic fistula	18 (25.7)	4 (20.0)	0.727
Grade A	12 (66.7)	2 (50.0)	
Grade B	4 (22.2)	2 (50.0)	
Grade C	2 (11.1)	0	
Gastroparesis	23 (32.9)	7 (35.0)	0.858
Grade A	10 (43.5)	2 (28.6)	
Grade B	7 (30.4)	3 (42.9)	
Grade C	6 (26.1)	2 (28.6)	

Table 4 Multivariate analysis identifying predictive factors of any complication (Clavien-Dindo ≥1)

Variables	OR	95% CI	P
Albumin	0.43	0.21–0.89	0.023
Pancreatic duct dilation	0.12	0.04–0.38	<0.001
Smoking	3.96	1.16–13.53	0.028

Table 5 Multivariate analysis identifying predictive factors of severe complication (Clavien-Dindo ≥3)

Variables	OR	95% CI	P
Male gender	15.44	2.57–92.72	0.003
Age (years)	0.92	0.85–0.99	0.030
BMI >25 kg/m^2	11.04	1.99–61.15	0.006
ASA (3/4)	5.15	1.09–24.38	0.039

ASA, American Society of Anesthesiology.

In our series, increased ASA score was an important risk factor for severe complications, in accordance with previous studies (8,14). However, it must be considered that elderly patients have more comorbidities and use of medication, so ASA score alone should not be used as an exclusion criteria for surgical treatment, as done by Sulpice *et al.* (9) Prior to PD in elderly, it is important to perform a geriatric assessment (GA) to identify individuals who are at higher risk and treat reversible conditions to improve outcome, as recently shown by Dale *et al.* (15). Even though other studies chose age cutoff as 80 years old (7,14), we used 75 years old because it is considered by geriatricians as the threshold in patient management and it is the life expectancy in Brazil (16).

Male gender and higher BMI are known risk factors for complications after PD. In a recent study by Okano *et al.* (17), both variables were independently associated with infectious complications. Previous studies showed male gender to be related to specific complications, such as surgical site infection, pancreatic fistula and delayed gastric emptying (17-19). Recent studies have shown visceral fat as a predictor for pancreatic fistula and postoperative mortality (20,21). Knowing that both male gender and higher BMI are associated with visceral fat, this could be an important pre-operative data in further studies. Restricted by the limited number of patients and low incidence of complications, our study could not calculate the specific complications associated with preoperative risk factors.

Table 6 Analysis of pre- and post-operative risk factors for 30-day mortality

Variables	30-day mortality		Univariate analysis	
	No (n=84)	Yes (n=6)	OR (95% CI)	P
Male gender [n (%)]	39 (90.7)	4 (9.3)	2.31 (0.40–13.29)	0.349
Age (years)	64 [34–87]	60 [48–70]	0.94 (0.87–1.02)	0.131
BMI >25 kg/m^2 [n (%)]	40 (90.9)	4 (9.1)	2.20 (0.38–12.67)	0.377
Hemoglobin (mg/dL)	12.3 (7.0–17.2)	11.9 (9.6–14.3)	0.95 (0.63–1.44)	0.818
Albumin (g/dL)	3.7 (1.5–5.0)	3.6 (2.8–4.2)	0.88 (0.27–2.86)	0.826
Pancreatic duct dilation [n (%)]	44 (93.6)	3 (6.4)	0.91 (0.17–4.77)	0.910
ASA 3/4 [n (%)]	29 (87.9)	4 (12.1)	3.79 (0.66–21.96)	0.137
ECOG 2/3 [n (%)]	13 (86.7)	2 (13.3)	2.73 (0.45–16.48)	0.273
Diabetes [n (%)]	23 (92.0)	2 (8.0)	1.33 (0.23–7.74)	0.754
Smoking [n (%)]	18 (90.0)	2 (10.0)	1.83 (0.31–10.82)	0.503
Pylorus preserving surgery [n (%)]	56 (96.6)	2 (3.4)	0.25 (0.04–1.45)	0.122
Operative time (min)	310 [170–420]	285 [225–400]	1.00 (0.99–1.02)	0.663

ASA, American Society of Anesthesiology.

As observed by de la Fuente *et al.* (8), elderly patients had a higher incidence of intraoperative blood transfusion despite of same preoperative hemoglobin levels. This fact is not necessarily a sign of bleeding or poor surgical performance, but it is more likely linked to lower volume variation tolerance during surgery due to baseline chronic diseases.

Although no elderly patient died during the study, the difference in mortality between both groups was not statistically significant. As mortality was a rare event and the number of patients in this study is limited, we were not able to establish any risk factor associated with that.

Despite prospectively collected, this study was limited by its observational design derived from a single center. Different from previous studies (9,22,23), we selected patients only with periampullary neoplasms to avoid confounding factors. Our judicious selection of patients for comparison and the decreasing rate of PD indication in elderly (24) may be the reasons for our limited number of patients despite being in a referral oncologic center.

In conclusion, our study revealed PD to be safe in patients aged ≥75 years old. Severe complication was found to be associated with clinical preoperative variables such as male gender, higher ASA score and overweight. In clinical practice, the decision to perform a major abdominal surgery must not be based only on chronological age, but in clinical and functional scores and discussed in a multidisciplinary context.

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