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Research Article

Safety and Hazards of Middle-Life Robotic Pancreaticoduodenectomy

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Abstract

Pancreaticoduodenectomy procedures early done in young individuals, few days about the risk and survival after robotic pancreaticoduodenectomy.

Our goal was to report the results of robotic pancreaticoduenectomy in patients older than 50.

Methods: Our patients were split into two groups: younger patients (less than 50 years old) and older patients (more than 50 years old). A total of 555 patients were included in this study: 502 (90.5%) were in the elderly group and 53 (9.5%) were in the young group.

Results: 1- The incidence of periampulary carcinoma in younger ves older category is (32.1% vs. 76.5%).

2- Neuroendocrine tumors (15.1% vs. 3.6%).

3- Solid and pseudopapillary tumors (9.4% vs. 1.0%).

4- Soft pancreatic parenchyma (77.4% vs. 62.5%).

5- Non-dilated (≤3 mm) pancreatic ducts (77.4% vs. 46.3%), and were more prevalent in the young group.

6- The young group had a shorter length of stay (median, 16 vs. 20 days).

7- Survival following surgery results for overall periampullary adenocarcinoma favored the young group, with a 5-year survival rate of 76.4% vs. 46.7% in the old group.

8 -There were no significant differences in the other surgical outcomes.

Conclusions: Robotic pancreaticoduodenectomy is associated with favorable survival outcomes for periampullary cancer in younger people (<50 years) and equivalent surgical outcomes when compared to older individuals (≥50 years). These outcomes show that robotic pancreaticoduodenectomy is safe and effective for a subset of pediatric patients.

Following pancreaticoduodenectomy, juvenile robotic tumor adenocarcinoma numbers.

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Introduction

The complex and challenging pancreaticoduodenectomy, sometimes called the "Whipple operation" is typically performed on elderly patients with pancreatic cancer and periampullary diseases. Younger patients are rarely given pancreaticoduodenectomy procedures, and the impact of age on surgical and survival outcomes is still unclear [1].

Patients in their 30s or 40s are rarely found to have pancreatic duct adenocarcinoma, which is often detected in patients aged 65-75 years of age [2,3]. The influence of youth on surgical and survival outcomes following pancreaticoduodenectomy has not been thoroughly investigated, given its uncommon occurrence in younger patients. There is little literature in this field [1-5].

Traditionally, an open technique is used to perform pancreaticoduodenectomy using a high abdominal incision, right saber slash, or a lengthy upper midline incision. This leads to severe pain and sometimes even negative outcomes [6]. Minimally Invasive Surgery (MIS) has become the norm in several specialties, including pancreatic resection, because of reduced pain, improved cosmesis, and smaller incisions. According to certain findings, older people can have Laparoscopic Pancreaticoduodenectomy (LPD) with good results [7-9]. However, pancreaticoduodenectomy entails precise identification of the vital vascular anatomy, considerable dissection and removal of visceral organs, and technically challenging repair. As a result, minimally invasive pancreaticoduodenectomy is not as widely used [10]. Recently, robotic surgery has emerged to overcome the limitations of laparoscopic surgery, following the release of the Intelligent Surgical®, Sunnyvale, California, USA, da Vinci Robotic Surgical Machine. This technology can offer tremor-free movements for both cams and tools, high-quality 3-Dimensional view of the surgical field, and end wrist devices to enhance the spectrum of flexibility emulating open procedures.

These developments help lessen surgeon fatigue, enhance ergonomics, and increase dexterity, but less used as its high patients cost and less surgeon experiences [10,11]. Although the robotic method of pancreaticoduodenectomy has been adopted slowly, a number of studies have demonstrated that RPD is a safe and viable technique compared with laparotomy [6,10,12,13].

The majority of the information on surgical outcomes and treatment choices that is currently accessible comes from studies conducted on older populations, as there is little research on pancreaticoduodenectomy in younger individuals. Therefore, it is unclear how younger and older groups differ in terms of tumor biology and surgical results. To date, there have we been no studies on RPD in younger groups. To better understand the clinicopathological characteristics, surgical outcomes, and survival outcomes of young patients (less than 50 years old) undergoing RPD, our study compared them with an older patient cohort (>50 years old) undergoing RPD at our institute.

Patients and methods

Patient choice

The study comprised patients who underwent RPD at five surgical institutes between Jan 2012 - Oct 2023 and data collected at our institute, 37 cases later, the learning curve for the RPD was surmounted. The first RPD was completed on Jan. 2012.

Division of the patients into two categories based on the age, RPD: young (less than 50 years) and old (>50 years). Any patient had history of operation with marked adhesion >2 cm specially upper part of the abdomen were excluded from our work.

Data gathering

All data related to patients character and tumor features were collected, patients classified physically by the American Society of Anesthesiologists (ASA). All Preoperative , intraoperative and post operative morbidity were detected and gathered. The likhookvarible associated with surgery, such as fatality and different postoperative difficulties, were also evaluated. Periampullary adenocarcinoma death incidence have also been reported.

Aim of study outcomes

Primary aim of the study to contrast the safety and risks of our cases categories. The secondary study goal is survival comparison between both.

Method procedures

A brief internal stent was inserted for a small pancreatic duct measuring less than 3 mm, although pancreatic duct stents are not commonly employed. The same jejunal limb was then used for hepaticojejunostomy without stenting, either with continuous (for dilated) or interrupted (for non dilated ducts) sutures. By carefully lowering the stomach, an extracorporeal technique was used to execute hand-sewn gastrojejunostomy. The gastrojejunostomy was placed in framesocolic, antecolic, and antiperistaltic positions close to the umbilical region. When feasible, a restricted antrectomy was received following right gastric artery bifercation in patients with an ischemic pylorus instead of attempting pylorus-preserving pancreaticoduodenectomy. Oral liquid after 24 h and soft diet after 3 days, no need for NGT feeding.

The Clavien-Dindo classification was used to categorize surgical complications [14]. According to the 2016 International Study Group for Pancreatic Fistula revised grading system [15], clinically meaningful grade B or C pancreatic leakage constitutes the definition of Postoperative Pancreatic Fistula (POPF). The International Study Group of Pancreatic Surgery (ISGPS) established classification criteria for Delayed Gastric Emptying (DGE), Post-Pancreatectomy Hemorrhage (PPH), and chyle leak [16-18].

Based on the state of the resection margin, compelete radical resection was we had three degree: If there was no microscopic evidence of cancer at a resection margin of less than 1 mm, the resection was classified as R0; if there was microscopic evidence of cancer at a resection margin of less than 1 mm, it was classified as R1; and if there was strong positive margin, it was classified as R2. Mortality that occurs through three months following surgery, involving hospitalization period after surgery, is referred to as surgical mortality.

Data statistics

The statistical product and service solutions version 26 pro-

gram was used to perform the statistical analysis. Continuous variables were compared using a two-tailed student's t-test and expressed as mean ± standard deviation. The Wilcoxon rank-sum test was used for continuous variables that were not normally distributed. Categorical variables are represented as numbers (percentages), and Pearson's χ^2 test or Fisher's exact test contingency tables were used to compare them. The overall survival between the young and old groups was compared using Kaplan-Meier survival curves, and significance was assessed using the log-rank test. Cox proportional hazards regression and binary logistic regression were used for the multivariate analysis. Statistical significance was set at P <0.05.

Table 1: Shows the demographics of the patients who underwent robotic pancreaticoduodenectomy with periampullary lesions.

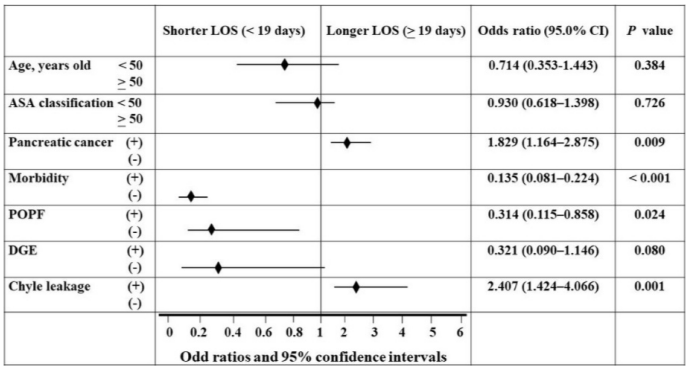
	Total	Age <50 y/o	Age ≥50 y/o	*P* value
Patients, n(%)	555	53(9.5%)	502(90.5%)	
Age, year old				<0.001
Median (range)	67(13-97)	42(13-49)	68(50-97)	
Mean ± SD[a]	66±12	40±9	69 ± 9	
Sex				0.512
female	259(46.7%)	27(50.9%)	232(46.2%)	
male	296(53.3%)	26(49.1%)	270(53.8%)	
BMI[b], kg/m^2				0.628
Median (range)	23.5(15.4–36.2)	23.1(16.7-34.1)	23.5(15.4-36.2)	
Mean ± SD	23.7±3.5	23.9±4.1	23.7±3.4	
ASA[c] physical status classification				<0.001
<3	359(64.7%)	48(90.6%)	311(62.0%)	
≥3	196(35.3%)	5(9.4%)	191(38.0%)	
Periampullary lesions				<0.001
Pancreatic head adenocarcinoma	193(34.8%)	7(13.2%)	186(37.1%)	
Ampullary adenocarcinoma	139(25.0%)	6(11.3%)	133(25.5%)	
Distal CBD[d] adenocarcinoma	43(7.7%)	0(0.0%)	43(8.6%)	
Duodenal adenocarcinoma	26(4.7%)	4(7.5%)	22(4.4%)	
IPMN[e]	43(7.7%)	4(7.5%)	39(7.8%)	
Neuroendocrine tumor	26(4.7%)	8(15.1%)	18(3.6%)	
Solid and pseudopapillary tumor	10(1.8%)	5(9.4%)	5(1.0%)	
Chronic pancreatitis	16(2.9%)	5(9.4%)	11(2.2%)	
Other malignant tumor	33(5.9%)	7(13.2%)	26(5.2%)	
Other benign tumor	26 (4.7%)	7(13.2%)	19(3.8%)	
Periampullary adenocarcinomas				<0.001
Yes	401(72.3%)	17(32.1%)	384(76.5%)	
No	154(27.7%)	36(57.9%)	118(23.5%)	
Periampullary adenocarcinomas				0.626
Pancreatic head adenocarcinomas	193(48.1%)	7(41.2%)	186(48.4%)	
Other periampullary adenocarcinoma	208(51.9%)	10(58.8%)	198(51.6%)	
Pancreatic parenchyma				0.033
soft	355(64.0%)	41(77.4%)	314(62.5%)	
hard	200(36.0%)	12(22.6%)	188(37.5%)	
Pancreatic duct				< 0.001
non-dilated ≤3 mm	270(49.3%)	41(77.4%)	229(46.3%)	
dilated >3 mm	278(50.7%)	12(22.6%)	266(53.7%)	
Tumor size, cm				0.263
Median (range)	3.0(0.5-11.0)	3.0(1.0-8.5)	3.0(0.5-11.0)	
Mean ± SD	3.1±1.4	3.3±1.7	3.1±1.4	

[a]SD: standard deviation; [b]BMI: body mass index; [c]ASA: American Society of Anesthesiologists; [d]CBD: common bile duct; [e]IPMN: intraductal papillary mucinous neoplasm

Results

This study included 555 patients; 53(9.5%) belonged to the younger group (age <50 years), whereas 502(90.5%) belonged to the older group (age ≥50 years) (Table 1). Regarding the demographics of the two groups, there were no notable differences in terms of sex, BMI, or tumor size. Nonetheless, a greater percentage of patients in the younger cohort were classified as having an ASA physical status ≥3 (9.4% vs. 38.0%, p<0.001). Periampullary adenocarcinomas were less common in the younger group than in the older group (32.1% vs 76.5%, p<0.001). However, solid and pseudopapillary tumors (9.4% vs. 1.0%) and neuroendocrine tumors (15.1% vs. 3.6%) were more common in the younger patients. Two types of periampullary adenocarcinoma were found in the same number of young and old people (p=0.626): Periampullary adenocarcinoma in the pancreatic head (41.2% vs. 48.4%) and other types (58.8% vs. 51.6%). Some pancreatic ducts were not dilated (≤3 mm) more often in the younger group (77.4% vs. 46.3%, p < 0.001), and the pancreatic parenchyma was softer (77.4% vs. 62.5%, p=0.033).

In terms of surgical outcomes (Table 2), there were no statistically significant differences between the young and old groups in terms of operation time (median, 7.8 vs. 8.3 h; p=0.508), intraoperative blood loss (median, 100 vs. 160 mL; p=0.681), surgical radicality (R0 resection, 92.5% vs. 85.1%; p=0.217), lymph node yield (median, 17 vs. 18; p=0.681), lymph node involvement (50.0% vs. 56.1%, p=0.798), stage 1 + 2 (58.8% vs. 70.6%, p = 0.292), conversion rate (5.7 vs. 8.4%, p = 0.492), and vascular resection rate (3.8% vs. 3.8%, p = 0.997). In the younger group, the majority of the surgical outcomes were positive. Compared to the senior group (median of 20 days), the LOS of the young group was shorter (median of 16 days; p = 0.033). Age by itself was not an independent predictor of longer length of stay (LOS) following RPD, although pancreatic head adenocarcinoma (+), morbidity (+), POPF (+), and chyle leakage (+) were observed on multivariate analysis using binary logistic regression (Figure 1).



The Length of Stay (LOS) following robotic pancreaticoduodenectomy was predicted by the independent components, as shown in Figure 1's forest plot of multivariate analysis using binary logistic regression. US Society of Anesthesiologists (ASA); Reliability interval (CI); Postoperative Pancreatic Fistula (POPF); Delayed Gastric Emptying (DGE).

Table 2: Surgical results following pancreaticoduodenectomy using robotics.

	Total	Age <50 y/o	Age ≥50 y/o	*P* value
Patients, n	555	53(9.5%)	502(90.5%)	
Operation time, hour				0.508
Median (range)	8.0(3.3-16.3)	7.8(4.0-13.5)	8.3(3.3-16.3)	
Mean ± SD[a]	8.4±2.3	7.9±2.3	8.4±2.3	
Blood loss, c.c.				0.681
Median (range)	160(0-6000)	100(0-4600)	160(0-6000)	
Mean ± SD	239±396	261±666	237±357	
Surgical radicality				0.217
R0	476(85.8%)	49(92.5%)	427(85.1%)	
R1	57(10.3%)	4(7.5%)	53(10.6%)	
R2	22(4.0%)	0	22(4.4%)	
Lymph node yield				0.351
Median (range)	18(12-49)	17(12-37)	18(12-49)	
Mean ± SD	19±6	18±6	19±5	
Lymph node involvement	218(55.9%)	8(50.0%)	210(56.1%)	0.798
Stage				0.292
1 + 2	281(70.1%	10(58.8%)	271(70.6%)	
3 + 4	120(29.9%)	7(41.2%)	113(29.4%)	
Conversion to open, n (%)	45(8.1%)	3(5.7%)	42(8.4%)	0.492
Vascular resection, n (%)	21(3.8%)	2(3.8%)	19(3.8%)	0.997
LOS[b], day				0.033
Median (range)	19(6-118)	16(6-46)	20(6-118)	
Mean ± SD	23±14	19±9	23±14	

[a]SD: standard deviation; [b]LOS: length of stay

Table 3: Risks associated with surgery following robotic pancreaticoduodenectomy.

	Total	Age <50 y/o	Age ≥50 y/o	*P* value
Patients, n	555	53(9.5%)	502(90.5%)	
Surgical mortality	8(1.5%)	0	8(1.6%)	0.352
Surgical morbidity	312(56.2%)	28(52.8%)	284(56.6%)	0.601
Surgical complication				0.888
Clavien–Dindo 0	236(42.5%)	23(43.4%)	213(42.4%)	
Clavien–Dindo I	191(34.4%)	18(34.0%)	173(34.5%)	
Clavien–Dindo II	52(9.4%)	5(9.4%)	47(9.4%)	
Clavien–Dindo III	62(11.2%)	7(13.2%)	55(11.0%)	
Clavien–Dindo IV	5(0.9%)	0	5(1.0%)	
Clavien–Dindo V (death)	9(1.6%)	0	9(1.8%)	
Severity of complication, n = 319				0.947
Minor (Clavien–Dindo I-II)	243(76.2%)	23(76.7%)	220(76.1%)	
Major (Clavien–Dindo ≥ III)	76(23.8%)	7(23.3%)	69(23.9%)	
POPF[a] (ISGPF[b] grade B and C)				
Overall	44(7.9%)	4(7.5%)	40(8.0%)	0.914
Parenchyma of pancreas				
soft	37(10.4%)	4(9.8%)	33(10.5%)	0.882
hard	7(3.5%)	0	7(3.7%)	0.496
Diameter of pancreatic duct				
non-dilated ≤3 mm	30(11.1%)	4(9.8%)	26(11.4%)	0.746
dilated >3 mm	14(5.0%)	0	14(5.3%)	0.415
DGE[c] (ISGPS[d] grade B and C)	24(4.3%)	1(1.9%)	23(4.6%)	0.359
PPH[e] (ISGPS[d] grade B and C)	32(5.8%)	4(7.5%)	28(5.6%)	0.559
Chyle leakage	140(25.2%)	14(26.4%)	126(25.1%)	0.834
Bile leakage	10(1.8%)	1(1.9%)	9(1.8%)	0.961
Wound infection	28(5.0%)	1(1.9%)	27(5.4%)	0.269

[a]POPF: Postoperative Pancreatic Fistula, [b]ISGPF: International Study Group of Pancreatic Fistula; [c]DGE: Delayed Gastric Emptying; [d]ISGPS: International Study Group of Pancreatic Surgery; [e]PPH: Postpancreatectomy Hemorrhage.

With no surgical mortality in the young group and 1.6% in the old group (p=0.352), the cohort's overall surgical mortality rate was 1.5%. All patients had a DGE rate of 4.3%:1.9% in the young group and 4.6% in the old group (P=0.359). With 7.5% in the young group and 8.0% in the old group, the overall POPF rate was 7.9% (P=0.914). Additionally, there were no appreciable differences between the younger and older groups in terms of surgical morbidity, Clavien-Dindo surgical complications, severity of problems, PPH, chyle leakage, bile leakage, or wound infection (Table 3).

Regarding survival results, 48.1% of the total cohort with periampullary adenocarcinomas survived for five years (Table 4). In terms of overall periampullary adenocarcinoma, the 5-year survival rate of the younger group was considerably higher than that of the older group (76.4% vs. 46.7%, p=0.047) (Figure 2). The 5-year survival rates for ampullary adenocarcinoma and pancreatic head adenocarcinoma were 100% vs. 61.4% (p=0.159) and 62.5% vs. 31.4% (p=0.171), respectively. However, there was no clear difference between the two groups in terms of survival rates. The Cox proportional hazards regression model (Figure 3) showed that age was not a reliable predictor of poor survival after robotic pancreaticoduodenectomy. However, pancreatic head cancer (+), Lymph Node (LN) involvement (+), and late stage 3+4 (+) were observed.

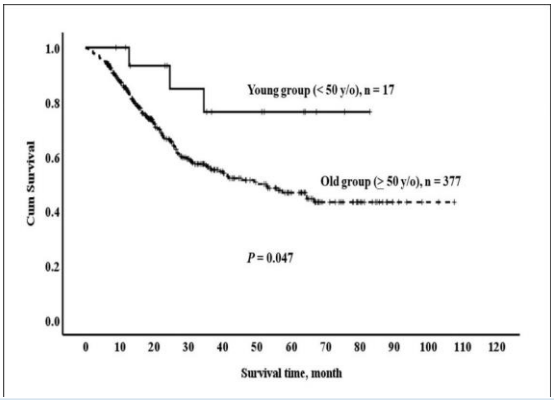


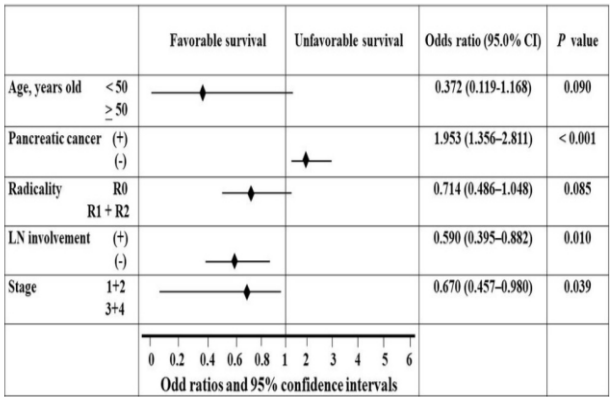
Figure 2: Actuarial survival curves following robotic pancreaticoduodenectomy for the young (age <50 years) and old (age ≥50 years) groups with periampullary cancer.

To estimate how long someone will live after a robotic pancreaticoduodenectomy, we used the Cox proportional hazards regression model and the forest plot in Figure 3 to identify independent prognostic factors.

Table 4: Survival rates following robotic pancreaticoduodenectomy for periampullary adenocarcinomas.

Periampullary adenocarcinoma	Median, (mon.)	Range, (mon.)	Mean ± SD[a], (mon.)	1-year survival	3-year survival	5-year survival	*P* value
Overall periampullary							
Total, n=394	20.4	0.2-107.6	28.7+23.3	85.4%	57.1%	48.1%	0.047
Age <50 y/o, n=17	35.3	8.9-82.9	40.1±24.2	100%	76.4%	76.4%	
Age ≥50 y/o, n=377	20.2	0.2-107.6	28.2±23.2	84.7%	56.2%	46.7%	
Pancreatic head							
Total, n=191	16.6	0.8-98.1	23.0±19.8	77.8%	40.4%	32.9%	0.171
Age <50 y/o, n=7	24.6	8.9-67.3	34.4±22.4	100%	62.5%	62.5%	
Age ≥50 y/o, n=184	16.5	0.8-98.1	22.6±19.6	76.9%	39.4%	31.4%	
Ampullary							
Total, n=136	28.1	0.2-107.6	35.7±26.3	91.3%	73.9%	63.1%	0.159
Age <50 y/o, n=6	43.4	11.7-75.6	41.9±29.0	100%	100%	100%	
Age ≥50 y/o, n=130	28.1	0.2-107.6	35.7±26.3	90.9%	72.8%	61.4%	

[a]SD: standard deviation.



Discussion

Given that less than 30% of tumors are projected to arise in young people, pancreatic cancer and other periampullary malignancies are uncommon among younger patients compared to older patients [19]. This is particularly true for pancreatic cancer and other periampullary malignancies. Malignancies in young people may differ from those in the elderly in terms of their molecular characteristics and tumor biology. Although there is debate about whether young patients have a worse prognosis than older patients, our present understanding of cancer in this population is inadequate [2]. Furthermore, the implementation of MIS occurs more frequently. Nevertheless, little research has been conducted on how early age affects surgery and survival after RPD.

Periampullary adenocarcinomas were less common in the younger group (32.1% vs. 76.5%) than in the older group. In contrast, the younger group had higher rates of solid and pseudopapillary tumors (9.4% vs. 1.0%) and neuroendocrine tumors (15.1% vs. 3.6%). In a study of pancreaticoduodenectomy in a young population (≤30 years old), Mansfield et al. [20] discovered that chronic pancreatitis (6, 27.3%) was the most common postoperative histologic diagnosis, followed by solid pseudopapillary tumors (22.7%) and adenocarcinomas (18.2%). A case series of young adults (less than 35 years) who underwent pancreaticoduodenectomy was described by El Nakeeb et al. [1]. The results showed that adenocarcinoma (41.4%) was the most common pathological diagnosis in this cohort, followed by solid pseudopapillary tumors (29.3%). Although the most common diagnosis reported in the literature is inconsistent, solid pseudopapillary tumors have become a common histological diagnosis in young individuals.

Younger people may be more susceptible to pancreatic leakage because they often have a smaller pancreatic duct, a less fibrotic pancreas, and a more normal pancreatic parenchyma. As predicted, the prevalence of non-dilated (<3 mm) pancreatic ducts and soft pancreatic parenchyma was higher in the younger group (77.4% vs. 62.5% and 77.4% vs. 46.3%, respectively). Despite these variations, the younger group did not have an increase in POPF or surgical complications compared with the older group. Furthermore, there was no surgical mortality in the younger group, supporting the findings of other studies [1,5,20] that RPD are safe for young patients. Although the youth group in this study had a shorter LOS (median: 16 vs. 20 days), age by itself was not an independent predictor of LOS following multivariate analysis. Most likely, reduced morbidity, lower POPF, and fewer cases of pancreatic head adenocarcinoma contributed to the shorter LOS in younger patients.

There is ongoing discussion regarding the relative aggressiveness of younger versus older patients with pancreatic duct adenocarcinomas [2-5]. Meng et al. [5] found no significant correlation between age and long-term survival in patients with pancreatic and periampullary adenocarcinomas after LPD. Additionally, Yeh et al. [21] showed that, following pancreaticoduodenectomy, actuarial survival was comparable between older and younger patients. According to several experts, cancer in older adults might be less aggressive biologically [22,23]. Consequently, it is believed that younger cancer patients have a poorer prognosis than older ones [24-27]. After radical resection of pancreatic ductal adenocarcinoma, Tang et al. [2] compared adolescents and young adults using propensity score matching and concluded that the disease may be more aggressive in these age groups. Additionally, Mansfield et al. [20] found that the median survival for juvenile adenocarcinoma patients was 10.2 months, compared to 57.8 months for adult patients. However, El Nakeeb et al. [1] demonstrated that the median survival of young adult patients with pancreatic adenocarcinoma was much better than that of older patients, in contrast to the findings of Tang and Mansfield [2,20]. In this investigation, the younger group outperformed the older group by five years for total periampullary adenocarcinoma (76.4% vs. 46.7%). In both

the ampullary and pancreatic head adenocarcinoma groups, there was a trend toward improved survival outcomes in the younger group, although the difference was not statistically significant. Age was not an independent predictive factor for periampullary adenocarcinoma after multivariate analysis. This may be because our study included fewer cases of pancreatic head cancer and lymph node involvement. Nevertheless, the small sample size of the young group made it difficult to reach firm conclusions. Larger sample sizes and additional research are required to validate these results and to explore the underlying mechanisms.

This study had certain shortcomings. Initially, all adult patients were included in the older cohort regardless of their comorbidities or overall health. Second, the small sample size of the young group makes statistical errors more likely and restricts our ability to properly grasp biological aggression.

Conclusions

Individuals under 50 years of age can safely undergo RPD, and their surgical results will be similar to those of older individuals. Additionally, although the results were not independent, younger patients with periampullary adenocarcinoma showed considerably better survival outcomes than older patients. These results lend credence to the viability and possible advantages of RPD in the pediatric population. Further investigation with a larger sample size is required to verify these results and to investigate the underlying mechanisms.

Declarations

Acknowledgment: Not applicable.

Declaration and ethical clearance: Ethical clearance was obtained from Zagagic University, Faculty of Medicine, Institutional Health Research Ethics (IHRERC), and written informed consent was obtained from the Review IHRERC under No. (ethical protocol number ZU-IRB#99902792023). Written informed consent was obtained from the Zagazig University Hospital database in accordance with the Declaration of Helsinki.

Consent for publication: Not applicable.

Availability of data and materials: A database is available to the corresponding author. This database is available upon review and request. All authors shared the database.

Competing interests: The authors declare that they have no competing interests or financial disclosures.

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