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Safety and oncologic efficacy of robotic compared to open pancreaticoduodenectomy after neoadjuvant chemotherapy for pancreatic cancer

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Abstract

Background Emerging data from multi-institutional and national databases suggest that robotic pancreaticoduodenectomy is safe and feasible for pancreatic adenocarcinoma. Nevertheless, there are limited reports evaluating its safety and oncologic efficacy following neoadjuvant chemotherapy.

Method This is a retrospective study from the 2010–2016 National Cancer Database comparing the postoperative, pathological and long-term oncologic outcomes between robotic pancreaticoduodenectomy (RPD) and open pancreaticoduodenectomy (OPD) for pancreatic adenocarcinoma following neoadjuvant chemotherapy.

Results We identified 155 (5%) RPD and 3329 (95%) OPD following neoadjuvant chemotherapy. The use of the robot increased from 3 cases in 2010 to 50 cases in 2016. RPD patients were more likely to receive adjuvant chemotherapy and to be treated at academic centers. After adjustment, RPD was associated with a higher proportion of adequate lymphadenectomy, receipt of adjuvant chemotherapy, decreased rate of prolonged length of stay, and similar 90-day mortality. There was no difference in median overall survival between RPD and OPD (25.6 months vs. 27.5 months, Log Rank $p=0.879$). The 1-, 3- and 5-year overall survival rates for RPD were 83%, 36% and 22% and for OPD were 86%, 38% and 22%. After adjustment, the use of robotic surgery was associated with similar overall survival compared to the open approach (HR 1.011, 95% confidence interval (CI) 0.776–1.316).

Conclusions Following neoadjuvant chemotherapy, RPD is associated with similar short- and long-term mortality with the advantage of shorter length of stay, higher proportion of adequate lymphadenectomy and receipt of adjuvant chemotherapy.

Keywords Pancreaticoduodenectomy · Robotic · Oncologic outcome · Neoadjuvant therapy

Introduction

Robotic surgery for pancreatic pathologies has been increasing over the last decade. Early adopters from high-volume centers developed the technique, established the safety of the procedure, determined the learning curve and then created educational curricula [1–9]. As more institutions joined this practice, multi-institutional and national studies were published documenting the feasibility, safety, reproducibility and oncologic efficacy of this platform [10–17]. Recently, the Miami international evidence-based guidelines on minimally invasive pancreas resection (IG-MIPR) were published [18]. The authors concluded that there is insufficient data to recommend robotic surgery over open approach and encouraged the centers performing this procedure to enroll their data into national and international registries.

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In addition, they acknowledged that there are no comparative data between both approaches following neoadjuvant chemotherapy.

The use of neoadjuvant therapy in pancreas cancer has been slowly adopted. This has been used for borderline resectable, locally advanced and even resectable disease [19–21]. The aim is to select favorable tumor biology which may benefit from resection, to downstage the disease and to potentially eradicate any micrometastatic disease. This practice is mainly supported by retrospective studies, with variability in implementation across institutions. Due to lack of phase 3 randomized trials, many surgeons still favor upfront resection for resectable disease. With limited numbers of patients undergoing neoadjuvant therapy and even smaller cohorts undergoing robotic surgery, it's challenging to analyze the safety and long-term oncologic efficacy of robotic pancreaticoduodenectomy (RPD) following neoadjuvant therapy especially using institutional databases.

The aim of this study is to compare RPD to open pancreaticoduodenectomy (OPD) in the National Cancer Database (NCDB) between 2010 and 2016 focusing on postoperative, pathological and long-term oncologic outcomes following neoadjuvant chemotherapy.

Methods

Data source and patient population

This is a retrospective study using the National Cancer Database (NCDB) from 2010 to 2016. Earlier years were excluded as the variable robotic surgery was not recorded before 2010. The NCDB is a national cancer registry that receives information from over 1500 Commission-on-Cancer–accredited cancer programs in the United States and captures approximately 70% of incident cancer cases in the United States. The study was approved by the University of Pittsburgh Medical Center IRB.

We included patients with pancreatic adenocarcinoma who underwent neoadjuvant therapy followed by pancreaticoduodenectomy (PD) for pathologic stage I-III pancreatic adenocarcinoma. We excluded patients who had neuroendocrine tumor or other histologies and those who had local excision, or total pancreatectomy, or laparoscopic surgery.

Variables and outcomes

The following variables were abstracted: patient gender, age, ethnicity, insurance status, median household income of each patient's area of residence (First quartile [Q1] was defined as < $38,000/year, Q2 was $38,000 to $47,999/year, Q3 was $48,000 to $62,999/year, and Q4 was > $63,000/year), Charlson/Deyo score, year of diagnosis, pathologic stage, tumor grade, facility type. We created mutually exclusive treatment groups (surgery alone, surgery with chemotherapy, surgery with radiation therapy, surgery with chemoradiation therapy, and surgery with unknown chemotherapy or radiation therapy).

Pathological outcomes (examined lymph node number and margin status), perioperative outcomes (length of stay, 30-day mortality, 90-day mortality, and 30-day readmission rates) and 5-year overall survival for adenocarcinoma were compared between RPD and OPD.

Statistical analysis

Data are presented as means with standard variations for continuous variables and counts with proportions for categorical ones, *t* test was used to compare continuous variables and the chi-squared test for categorical variable. Kaplan–Meier curves were used to estimate overall survival and compared using the log-rank test.

Data were adjusted for patient, tumor and treatment characteristics using multivariable logistic regression to determine the association of robotic surgery with examined lymph node number, length of stay, and postoperative mortality. Finally, we developed a Cox proportional hazard model to determine if robotic surgery is independently associated with survival. In this study, two-sided p values of ≤ 0.05 were considered statistically significant. Analyses were conducted using SPSS version 20.

Results

There were 3484 pancreaticoduodenectomies following neoadjuvant chemotherapy between 2010 and 2016. The number of cases increased from 291 cases (8%) in 2010 to 759 cases (22%) in 2016. Among these, 155 (5%) were performed robotically. Robotic assisted surgery increased over the years from three cases in 2010 to 50 cases in 2016 (Table 1 and supplementary Table 1).

Table 1 Distribution of cases between 2010 and 2016

Year	Total *N* (column%)	RPD *N* (column% /row %)	OPD *N* (column% /row %)
2010	291 (8%)	3 (2%/1%)	288 (9%/99%)
2011	332 (10%)	14 (9%/4%)	318 (10%/96%)
2012	402 (12%)	9 (6%/2%)	393 (12%/98%)
2013	474 (14%)	12 (8%/3%)	462 (14%/97%)
2014	56,316(%)	24 (16%/4%)	539 (16%/96%)
2015	663 (19%)	43 (28%/6%)	620 (19%/94%)
2016	759 (22%)	50 (32%/7%)	709 (21%/93%)

Baseline characteristics of RPD and OPD

There was no difference in gender, ethnicity and comorbidities between RPD and OPD groups, nevertheless RPD patients were more likely to be older, have Medicare insurance and have lower median income compared to OPD patients (Table 2).

OPD were more commonly performed for early stage disease and for well to moderately differentiated histologies compared to RPD and were more likely to receive radiation therapy (Tables 2, 3 and supplementary Table 2).

RPD patients were more likely to receive adjuvant chemotherapy and to be treated at academic/research programs (Table 2).

Postoperative and oncologic outcomes

The mean number of examined lymph nodes and the proportion of examined lymph nodes ≥ 12 were higher in RPD; furthermore, the mean length of stay and the proportion of prolonged length of stay (> 12 days) were lower in RPD. There was no difference in positive margin status, 30-day readmission, 30-day and 90-day mortality between both groups. (Table 3).

After adjustment for patient, tumor and treatment related characteristics, RPD was associated with higher proportion of adequate lymphadenectomy, receipt of adjuvant therapy, decreased rate of prolonged length of stay and similar 90-day mortality (Table 4).

Long-term oncologic outcomes

The median overall survival for pancreatic cancer was similar between RPD (25.6 months) and OPD (27.5 months, Log Rank $p = 0.879$; Fig. 1). The 1-, 3- and 5-year overall survival rates for RPD were 83%, 36% and 22% and for OPD were 86%, 38% and 22%.

Table 2 Patient and treatment related characteristics

	RPD	OPD	*p*
Number of patients	155	3329	
Male	75 (48%)	1710 (51%)	0.468
Mean age (SD)	66 (9)	64 (9)	0.006
Ethnicity (Non-Hispanic)	150 (97%)	3158 (95%)	0.280
Insurance status			0.042
Not insured	0 (0%)	54 (1.6%)	
Private	62 (40%)	149 (45%)	
Medicaid	8 (5%)	153 (5%)	
Medicare	85 (55%)	1531 (46%)	
Others/unknown	0 (0%)	91 (2.7%)	
Median income			< 0.001
Q1	23 (15%)	462 (14%)	
Q2	57 (37%)	761 (23%)	
Q3	41 (27%)	930 (28%)	
Q4	33 (21%)	1169 (35%)	
Charlson/Deyo score			0.309
0	92 (59%)	2206 (66%)	
1	47 (30%)	871 (26%)	
2	11 (7%)	181 (5%)	
3	5 (3%)	71 (2%)	
Facility type			0.001
Community CP	0 (0%)	22 (1%)	
Comprehensive community CP	6 (4%)	469 (14%)	
Academic/research program	135 (87%)	2432 (73%)	
Integrated network CP	13 (8%)	379 (12%)	
Radiation	55 (35%)	1882 (56%)	< 0.001
Adjuvant chemotherapy	87 (56%)	1124 (34%)	< 0.001

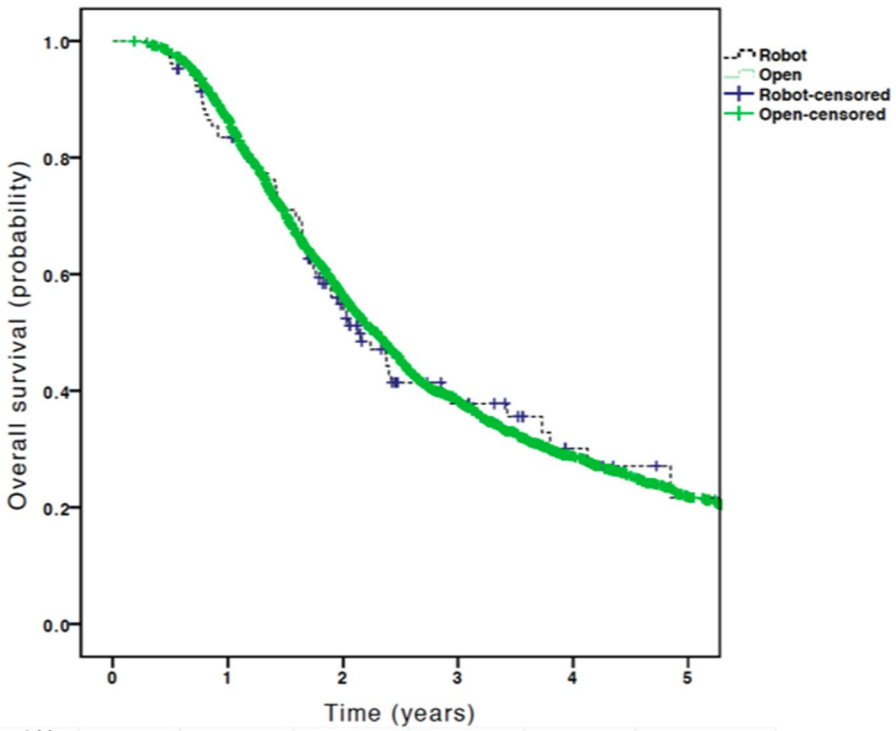
CP cancer program

Table 3 Pathologic and postoperative outcomes

	RPD	OPD	*p*
Number of patients	155	3329	
Stage			0.009
I	13 (8%)	596 (18%)	
II	136 (88%)	2594 (78%)	
III	6 (4%)	139 (4%)	
Grade			< 0.001
Well/moderately differentiated	39 (25%)	1417 (43%)	
Poorly/undifferentiated	20 (13%)	645 (19%)	
Unknown	96 (62%)	1267 (38%)	
Conversion	17 (11%)		
Mean examined lymph node (SD)	30 (15)	18 (11)	< 0.001
Examined lymph node ≥ 12	142 (92%)	471 (74%)	< 0.001
Positive margin status	33 (21%)	538 (16%)	0.132
Mean Length of stay (SD)	8 (5)	10 (7)	< 0.001
Length of stay > 12	16 (10%)	807 (24%)	< 0.001
30-day mortality	2 (1.3%)	48 (1.4%)	0.877
90-day mortality	4 (2.6%)	114 (3.4%)	0.570
30-day readmission	14 (9%)	204 (6.1%)	0.144

Table 4 Adjusted odds ratio

	RPD vs OPD Odds ratio	*p*	95% CI
Examined lymph node ≥ 12	3.055	< 0.001	1.704–5.477
Length of stay > 12	0.366	< 0.001	0.212–0.634
30-day mortality	0.975	0.973	0.226–4.213
90-day mortality	0.756	0.597	0.268–2.134
Receipt of adjuvant therapy	2.454	< 0.001	1.755–3.433



Numbers at risk						
RPD	104	83	44	21	11	3
OPD	2618	2182	1205	633	329	157

	Median OS	1-year OS	3-year OS	5-year OS
RPD	25.6 months	83%	36%	22%
OPD	27.5 months	86%	38%	22%

Fig. 1 Overall survival of RPD and OPD

On Cox regression model, the use of robotic surgery was not associated with overall survival (HR 1.011, 95% confidence interval (CI) 0.776–1.316). The predictors of improved survival were lower AJCC stage, well/moderately differentiated grade, and the receipt of adjuvant chemotherapy (Table 5).

Discussion

This is the first national study to compare RPD to OPD after neoadjuvant chemotherapy and to report the long-term oncologic outcomes of RPD. This work provides initial—but not exhaustive—data aimed to decrease a void in the literature that was recognized by the Miami (IG-MIPR). While a prospective trial is the optimal method to answer this question, this is currently not feasible. The rationale behind this lack of data is multifold, first and foremost one must acknowledge that it has been challenging to perform separate phase III randomized trial to address the efficacy of neoadjuvant therapy compared to upfront surgery in PDAC. Moreover, a trial comparing robotic surgery to open surgery—in the setting of pancreatic adenocarcinoma—has never been attempted. On the base of these premises, it is highly unlikely that a trial designed to address the safety and efficacy of robotic surgery following neoadjuvant therapy for pancreatic cancer will be performed, at least in the immediate future. Hence, using large national database is the one currently feasible strategy to answer this question.

In the current work, RPD had similar postoperative safety profile and long-term overall survival compared to OPD, with the advantage of shorter length of stay, higher proportion of adequate lymphadenectomy and receipt of adjuvant therapy.

The use of the robot for pancreaticoduodenectomy has been reluctantly adopted across the nation due to the

Table 5 Cox model determining predictors of mortality in PD and DP (Adjusted for year of diagnosis and income)

	HR (PD)	*p*	95% CI
Sex			
Male	1		
Female	0.937	0.188	0.850–1.032
Age*	1.006	0.096	0.999–1.013
Ethnicity			
Non-Hispanic	1		
Hispanic	0.966	0.808	0.731–1.276
Charlson comorbidity index			
0	1		
1	1.097	0.098	0.983–1.223
2	1.138	0.253	0.912–1.419
3	0.9	0.579	0.620–1.306
Insurance			
No insurance	1		
Private	1.08	0.693	0.737–1.583
Medicaid	1.08	0.731	0.697–1.674
Medicare	1.254	0.257	0.848–1.854
Facility type			
Community CP	1		
Comprehensive community CP	0.834	0.579	0.440–1.583
Academic/research program	0.64	0.166	0.341–1.203
Integrated network CP	0.863	0.652	0.455–1.638
Surgical approach			
Open	1		
Robotic	1.011	0.936	0.776–1.316
Stage			
I	1		
II	1.503	< 0.001	1.309–1.725
III	1.646	< 0.001	1.285–2.109
Differentiation			
Well/moderately differentiated	1		
Poorly/undifferentiated	1.289	< 0.001	1.136–1.462
Radiation			
No	1		
Yes	1.043	0.417	0.942–1.154
Adjuvant chemotherapy			
No	1		
Yes	0.842	0.001	0.758–0.934

complexity of the operation and the concern of increased morbidity and mortality. A multi-institutional comparison of robotic to open surgery has showed that RPD was associated with longer operative times, reduced blood loss and fewer major complications. There was no association between operative approach and 90-day mortality, clinically relevant postoperative pancreatic fistula and 90-day readmission [1]. Analysis from the National Surgical Quality Improvement Program (NSQIP) showed that minimally invasive pancreaticoduodenectomy was associated with longer operative time, higher readmission rate and lower prolonged length of stay compared to open approach. There was no difference in 30-day mortality, and overall complications [12]. A systematic review and meta-analysis of RPD versus OPD showed no difference in mortality and a decrease in overall complication rate and length of stay [22]. Collectively, all these studies—among many others—have shown that RPD is safe and feasible, especially when performed in high-volume centers and by surgeons with experience both in pancreatic procedure and in robotic surgery. Our study adds to this body of literature, showing that even after neoadjuvant therapy, RPD is associated with safe postoperative outcomes, mainly 90-day mortality and readmission rate. Unfortunately, the NCDB does not provide data on complication rates which is best analyzed by using institutional databases or national ones such as the NSQIP database.

The other major concern regarding robotic-assisted surgery for pancreatic cancer is its oncologic efficacy both in the short and long term. In a recent study at our institution, Girgis et al. compared 226 RPD to 230 OPD for pancreatic adenocarcinoma and demonstrated that the robotic platform was associated with similar rates of positive resection margin and receipt of adjuvant therapy. Moreover, the authors showed a higher number of harvested lymph nodes and improved overall survival (HR 0.77, $p = 0.041$) [6]. The Mayo Clinic compared total laparoscopic pancreaticoduodenectomy (TLPD) to OPD and showed no difference in overall survival or the receipt of adjuvant therapy, but there was an advantage for TLPD with lower disease-free survival and early initiation of adjuvant therapy [23]. In the current study, we demonstrate that the robotic approach has similar short- and long-term oncologic outcomes when compared to a conventional laparotomy approach. RPD was associated with a similar rate of positive resection margin, an increased number of examined lymph nodes and receipt of adjuvant therapy. In addition, we demonstrated no significant difference in long-term overall survival between RPD and OPD. These findings, albeit limited by a small sample size, support the use of robotic surgery in pancreaticoduodenectomy following neoadjuvant therapy as an effective oncologic alternative to the open approach.

Our study has several limitations mainly by the virtue of its retrospective design. First, we could not determine the type of chemotherapy and the number of cycles given, both in the neoadjuvant and adjuvant setting. Second, the number of robotic cases was relatively low, mostly performed at few high-volume centers which makes the external validity of study limited. Surgeons should offer patients the approach with which they have the most experience. Finally, the absence of postoperative complication data limits the ability to compare both approaches although surrogate

measures such as prolonged length of stay, readmission and 90-day mortality may mitigate this gap in the database.

Conclusions

After neoadjuvant chemotherapy, RPD is a feasible operation both from a safety and oncologic perspective. PRD was associated with similar rate of 90-day mortality, 30-day readmission, positive resection margin, and 5-year overall survival with the advantage of shorter length of stay, higher proportion of adequate lymphadenectomy and receipt of adjuvant therapy.

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Compliance with ethical standards

Disclosures Ibrahim Nassour MD MSCS, Samer Tohme MD, Richard Hoehn MD, Mohamed Abdelgadir Adam MD, Amer H Zureikat MD, and Paniccia Alessandro MD have no conflicts of interest or financial ties to disclose.

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