Original Article

Primary tumor resection and lymph node dissection improve survival in *de novo* metastatic pancreatic ductal adenocarcinoma: an inverse probability of treatment weighting analysis

Chaorui Wu, Xiaojie Zhang, Tongbo Wang, Hong Zhou, Chunguang Guo, Yingtai Chen, Dongbing Zhao

Department of Pancreatic and Gastric Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Contributions: (I) Conception and design: C Wu, Y Chen, D Zhao; (II) Administrative support: C Guo, Y Chen, D Zhao; (III) Provision of study materials or patients: T Wang, H Zhou, X Zhang; (IV) Collection and assembly of data: T Wang, H Zhou, X Zhang; (V) Data analysis and interpretation: C Wu, C Guo; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yingtai Chen; Dongbing Zhao. Department of Pancreatic and Gastric Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China.
Email: yingtai.chen@hotmail.com; dbzhao@cicams.ac.cn.

Background: Primary tumor resection (PTR) and lymph node dissection (LND) may be performed occasionally in patients with *de novo* metastatic pancreatic ductal adenocarcinoma (mPDAC). However, the role of PTR and LND in such cases remains unclear. Thus, we aimed to test the effect of PTR and LND on overall survival (OS) and cancer-specific survival (CSS) in mPDAC patients.

Methods: Patients with *de novo* mPDAC were identified from the Surveillance Epidemiology and End Results (SEER) database (2010–2015). The inverse probability of treatment weighting (IPTW) method was used to minimize the selection bias. IPTW-adjusted Kaplan-Meier curves and Cox proportional hazards models were used to compare OS and CSS in different treatment groups.

Results: A total of 10,036 patients met the inclusion criteria. Of these patients, 275 (2.7%) underwent PTR, while 217 (2.2%) also underwent LND with a median of 16 nodes removed. In the IPTW-adjusted Kaplan-Meier analysis, the median OS was 13 versus 6 months (P<0.001) for the PTR and non-PTR groups, respectively, and 15 versus 5 months (P=0.007) for the LND and non-LND groups, respectively. In the IPTW-adjusted Cox regression analysis, PTR was independently associated with better OS [hazard ratio (HR) 0.483, 95% confidence interval (CI): 0.468–0.498, P<0.001], as was LND (HR 0.286, 95% CI: 0.228–0.358, P<0.001). Similar results were observed in the analysis of CSS. In the LND group, the extent of LND was not associated with either OS or CSS.

Conclusions: PTR and LND were independent prognostic factors that prolonged OS and CSS in de novo mPDAC patients. These findings must be validated in prospective randomized studies.

Keywords: Metastatic pancreatic ductal adenocarcinoma (mPDAC); SEER program; primary tumor resection (PTR); lymph node dissection (LND); prognosis; inverse probability of treatment weighting (IPTW)

Submitted Oct 11, 2019. Accepted for publication Feb 08, 2020.
doi: 10.21037/tcr.2020.04.02
View this article at: http://dx.doi.org/10.21037/tcr.2020.04.02

Introduction

Pancreatic ductal carcinoma (PDAC) represents the fourth leading cause of cancer-related mortality worldwide (1). Surgery remains the only treatment option with the potential of cure for PDAC, and only a subset (20–30%) of patients have diseases at a locally resectable stage (2). Once distant metastases have occurred, only palliative chemotherapy or chemoradiation therapy is recommended by the guidelines (3). Despite progress in the treatment of metastatic PDAC (mPDAC), the prognosis remains dismal, with a median survival of only 8–11 months, even for patients receiving intensive chemotherapy with nab-paclitaxel/gemcitabine or FOLFIRINOX (4).

With the improved morbidity profile of pancreatic resection and metastasectomy and the potential for surgery to enhance survival, symptom control, and quality of life, primary tumor resection (PTR) with or without metastasectomy is gradually being attempted in select patients with mPDAC at some medical centers (5-7). For several other malignancies, such as gastrointestinal cancer and sarcoma, surgery and/or locoregional treatment within a multidisciplinary approach was considered to benefit select cases in terms of long-term disease control and survival (8,9). However, the beneficial role of PTR versus palliative chemotherapy for mPDAC in terms of long-term survival remains controversial. Moreover, the role of lymph node dissection (LND), which also contributes to the oncologic outcomes associated with the curative resection of non-metastatic PDAC, remains unclear (10).

Given that previous studies concerning this topic were primarily case series (5,6,11-15), this study aimed to analyze the impact of PTR and LND on OS and CSS in *de novo* mPDAC using a population-based database. Inverse probability of treatment weighting (IPTW) was applied to minimize the selection bias between the groups.

Methods

Database and population

This cohort study retrospectively analyzed data from the Surveillance Epidemiology and End Results (SEER) database (2010–2015), which sampled 26% of new cancers in the US. Ethics approval and informed consent were waived by the Chinese National Cancer Center Institutional Review Board, as no patient, physician, or hospital identifiers were examined.

Patients with *de novo* mPDAC diagnosed between 2010 and 2015 and treated with palliative chemotherapy or PTR plus chemotherapy were identified from the SEER database. Patients with PDAC were identified based on the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) morphological codes 8140, 8150, 8210, 8211, 8251, 8260, 8261, 8263, 8480, 8481, 8490, 8500, 8503, and topographical codes C25.0–C25.9. Only patients diagnosed between 2010 and 2015 were eligible because details regarding the specific locations of metastases (liver, lung, bone, and brain) have only been provided in the SEER database since 2010. The following patients were excluded: patients with any previous cancer diagnosis; patients with incomplete follow-up data; patients with an unknown cause of death; and patients with incomplete information regarding their PTR and LND status.

Study variables

Patient-related information included age at diagnosis, race, sex, and marital status. Tumor data included primary tumor location, clinical T stage, clinical nodal status, the number of positive lymph nodes, and the specific location of metastases. The T stage was restaged according to the American Joint Commission on Cancer 8th edition for pancreatic cancer (16). Specifically, T1 was defined as a tumor ≤2 cm in size; T2 was defined as a tumor 2–4 cm in size; T3 was defined as a tumor >4 cm in size; and T4 was defined as a tumor invading the celiac axis, the superior mesenteric artery, and/or common hepatic artery, regardless of size. Treatment-related factors included the number of examined lymph nodes, receipt of PTR, receipt of metastasectomy, and receipt of LND. LND was defined according to the combination of two variables: the scope of regional lymph node surgery and the number of lymph nodes retrieved. The primary endpoint in this study was overall survival (OS), and the secondary endpoint was cancer-specific survival (CSS).

Statistical analysis

We compared the baseline characteristics between patients who underwent PTR (PTR group) and those who received palliative chemotherapy (non-PTR group) among the entire cohort and between patients who underwent LND (LND group) and those who did not undergo LND (non-LND group) among the patients treated with PTR. Binary logistic regression analysis was used to identify independent predictive factors for PTR or LND. To minimize the

treatment selection bias, significant differences in patient characteristics were adjusted using the IPTW method. Specifically, we first calculated the propensity score, i.e., the odds of receiving PTR, using a logistic regression model that included variables affecting treatment allocation and survival (age at diagnosis, sex, marital status, race, primary tumor location, clinical T stage, clinical nodal status, and location of metastases). The propensity score of receiving LND was calculated in a similar way.

We used the IPTW-adjusted Kaplan-Meier curves and log-rank test to compare OS and CSS between groups. IPTW-adjusted univariate and multivariate Cox regression models were used to estimate the effects of PTR and LND on survival. Covariates with univariate P<0.1 were selected for the logistic and Cox regression multivariable analyses. In this study, R version 3.5.1 (R Core Team 2018, Vienna, Austria) and SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) were used to perform all statistical analyses. Statistical significance was set at 2-sided P<0.05.

Results

Baseline characteristics

Overall, 10,036 patients with *de novo* mPDAC diagnosed between 2010 and 2015 met the inclusion criteria; 275 (2.7%) of these patients underwent PTR. The baseline features of the eligible patients before and after IPTW adjustment, stratified by receipt of PTR, are listed in *Table 1*. In a multivariable logistic regression analysis based on unadjusted patients, age at diagnosis, marital status, primary tumor location, clinical T category, clinical nodal status, bone metastasis, lung metastasis, and liver metastasis were independently associated with the odds of receiving PTR (*Table 2*). After IPTW adjustment, except for bone metastasis, the covariates did not differ significantly between the PTR group and the non-PTR group.

Among the 275 patients who underwent PTR, 217 (78.9%) also underwent LND. The baseline features of the patients treated with PTR before and after IPTW adjustment, stratified by receipt of LND, are presented in *Table 3*. The unweighted patient-based multivariable logistic regression analysis suggested that marital status, clinical T category, and clinical nodal status were independently associated with the odds of receiving LND (*Table 2*). After IPTW adjustment, except for bone metastasis, no residual significant imbalance was observed between the LND group and the non-LND group. Among patients who underwent LND, the median number of examined lymph nodes was 16 [interquartile range (IQR), 9–23]. Metastatic nodal disease was documented in a total of 245 patients (75.4%).

Survival outcomes

Overall, 9,447 patients (94.1%) died during the study period, and 9,213 (91.8% of all deaths) died of mPDAC. The median follow-up time was 41.0 [95% confidence interval (CI), 38.2–43.7] months.

PTR and survival in mPDAC

In the IPTW-adjusted Kaplan-Meier analysis, PTR was associated with a significant OS benefit [hazard ratio (HR), 0.456; 95% CI, 0.442–0.470; P<0.001] and CSS benefit (HR, 0.457; 95% CI, 0.444–0.472; P<0.001). The IPTW-adjusted median OS was 13 (IQR, 13–14) versus 6 (IQR, 6–7) months, and the median CSS was 13 (IQR, 13–14) versus 7 (IQR, 6–7) months for the PTR group and non-PTR group, respectively (*Figure 1A*,*B*). In the IPTW-adjusted multivariate Cox proportional hazards regression analysis, PTR was independently associated with an OS benefit (HR, 0.504; 95% CI, 0.441–0.576; P<0.001) and a CSS benefit (HR, 0.505; 95% CI, 0.441–0.579; P<0.001) (*Table 4*).

LND and survival in mPDAC

In the IPTW-adjusted Kaplan-Meier analysis, LND was associated with a significant OS benefit (HR, 0.526; 95% CI, 0.439–0.631; P=0.007) and CSS benefit (HR, 0.509; 95% CI, 0.424–0.611; P=0.005). The IPTW-adjusted median OS was 15 (IQR, 14–17) versus 5 (IQR, 5–7) months, and the median CSS was 15 (IQR, 14–18) versus 5 (IQR, 5–7) months for the LND group and non-LND group, respectively (*Figure 1C*,*D*). In IPTW-adjusted multivariate Cox proportional hazards regression analysis, LND was independently associated with an OS benefit (HR, 0.286; 95% CI, 0.228–0.358; P<0.001) and a CSS benefit (HR, 0.264; 95% CI, 0.209–0.333; P<0.001) (*Table 5*).

Lymph node status and survival in mPDAC

The multivariate analysis results suggested that nodal status was an independent prognostic factor of OS and CSS (*Table 4*). However, the number of examined lymph nodes was not associated with OS (HR 1.000; 95% CI, 0.991–

Table 1 Baseline characteristics between the PTR and non-PTR groups, before and after IPTW adjustment

Variables	Before IPTW, n (%)			After IPTW (%)		
	PTR (n=9,761) (97.3%)	Non-PTR (n=275) (2.7%)	P value	PTR	Non-PTR	P value
Age, years						
>65	4,917 (50.4)	115 (41.8)	0.006	50.1	52.0	0.726
≤65	4,844 (49.6)	160 (58.2)		49.9	48.0	
Gender						
Female	4,398 (45.1)	120 (43.6)	0.685	45.0	49.0	0.454
Male	5,363 (54.9)	155 (56.4)		55.0	51.0	
Race						
Black	1,210 (12.4)	30 (10.9)	0.691	12.4	16.2	0.613
White	7,816 (80.1)	222 (80.7)		80.1	75.4	
Other	735 (7.5)	23 (11.6)		7.5	8.4	
Marital status						
Never married	1,370 (14.0)	31 (11.3)	0.021	14.0	17.6	0.248
Married	6,063 (62.1)	196 (71.3)		62.4	63.7	
Previously married	1,925 (19.7)	39 (14.2)		19.6	12.5	
Unknown	403 (4.1)	9 (3.3)		4.1	6.1	
Primary tumor location						
Head	3,446 (35.3)	147 (53.5)	<0.001	35.8	37.4	0.935
Body and tail	3,790 (38.8)	94 (34.2)		38.7	37.0	
Other	2,525 (25.9)	34 (12.4)		25.5	25.6	
Clinical nodal status						
Negative	4,880 (50.0)	94 (34.2)	<0.001	49.6	57.2	0.388
Positive	3,424 (35.1)	174 (63.3)		35.8	28.7	
Unknown	1,457 (14.9)	7 (2.5)		14.6	14.1	
Clinical T category						
T1	311 (3.2)	3 (1.1)	<0.001	3.1	5.2	0.794
T2	2,626 (26.9)	128 (46.5)		27.4	25.2	
T3	2,375 (24.3)	88 (32.0)		24.5	26.9	
T4	2,085 (21.4)	37 (13.5)		21.1	18.4	
Tx	2,364 (24.2)	19 (6.9)		23.7	24.4	
Bone metastasis						
No	8,756 (89.7)	263 (95.6)	0.005	89.9	92.3	0.018
Yes	699 (7.2)	7 (2.5)		7.0	1.3	
Unknown	306 (3.1)	5 (1.8)		3.1	6.4	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Before IPTW, n (%)			After IPTW (%)		
	PTR (n=9,761) (97.3%)	Non-PTR (n=275) (2.7%)	P value	PTR	Non-PTR	P value
Lung metastasis						
No	7,404 (75.9)	238 (86.5)	<0.001	76.2	79.3	0.366
Yes	1,999 (20.5)	34 (12.4)		20.3	14.5	
Unknown	358 (3.7)	3 (1.1)		3.6	6.1	
Brain metastasis						
No	9,388 (96.2)	270 (98.2)	0.213	96.2	93.6	0.547
Yes	46 (0.5)	1 (0.4)		0.5	1.3	
Unknown	327 (3.4)	4 (1.5)		3.3	5.0	
Liver metastasis						
No	2,189 (22.4)	124 (45.1)	<0.001	23.1	20.9	0.749
Yes	7,415 (76.0)	149 (54.2)		75.4	76.8	
Unknown	157 (1.6)	2 (0.7)		1.6	2.3	

IPTW, inverse probability of treatment weighting; PTR, primary tumor resection.

1.009, P=0.960) or CSS (HR 0.953; 95% CI, 0.991–1.009, P=0.953). There was no significant difference between patients with <16 and ≥16 examined lymph nodes in terms of OS (P=0.728) or CSS (P=0.733).

Discussion

This SEER-based study represents one of the latest attempts to investigate the survival benefit of PTR and the first study to investigate LND among *de novo* mPDAC patients. Our results suggested that PTR and LND were independently associated with a significant survival benefit compared to palliative chemotherapy in patients with *de novo* mPDAC.

With the decreasing surgery-related morbidity over the past decades, mortality rates lower than 5%, and the emergence of potent chemotherapy regimens such as nab-paclitaxel and FOLFIRINOX, PTR with or without preoperative chemotherapy has been gradually adopted as a potential treatment option for mPDAC. Our findings suggested that PTR was associated with survival benefit compared to palliative chemotherapy. Similar to our results, Tao *et al.* identified 467 patients with mPDAC who had PTR from the SEER database. They concluded that local treatment has a primary benefit on both CSS and OS in patients with mPDAC (17). Bahra *et al.* suggested that the survival of 45 patients who had primary cytoreductive surgery followed by chemotherapy was superior to that of patients who received palliative chemotherapy if a tumor-free margin could be achieved (7). The potential mechanism underlying the beneficial role of PTR may be as follows. PDAC is a tumor with more than half of the tumor volume being stroma characterized by extensive fibrosis and extracellular matrix deposition (18,19). The dense stroma mediates the chemotherapy-resistant property of pancreatic cancers by blocking tumor cells from the effects of chemotherapeutic agents. Thus, stroma-mediated chemotherapy insensitivity is one of the important mechanisms underlying the poor prognosis of patients with PDAC (20,21). It was observed that unconformity existed in the response to chemotherapy between the primary lesion and the metastases. Dense stroma within the primary tumor versus the metastases may be the reason for this discrepancy in tumor response. Thus, PTR could theoretically improve the chemotherapy sensitivity of mPDAC by removing the primary tumor with dense stroma even when complete removal of all tumor lesions is not possible.

Relevant literature regarding the benefits of PTR for *de novo* mPDAC in terms of long-term survival is very limited, and suggestions on this issue remain controversial. Gleisner *et al.* retrospectively analyzed data from 22 patients who underwent upfront surgical resection for PDAC with

Table 2 Multivariate logistic regression model predicting receipt of PTR or LND in the unadjusted population

Variables	PTR*		LND§	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (>65) (years)	0.737 (0.572–0.949)	0.018		
Marital status				
Never married	Reference		Reference	
Married	1.536 (1.036–2.279)	0.033	0.980 (0.277–3.461)	0.975
Previously married	1.023 (0.626–1.672)	0.929	0.245 (0.057–1.050)	0.058
Unknown	1.084 (0.502–2.336)	0.838	0.125 (0.016–0.960)	0.046
Primary tumor location				
Head	Reference			
Body and tail	0.638 (0.485–0.838)	0.001		
Other	0.458 (0.309–0.678)	<0.001		
Clinical T category				
T1	Reference			
T2	4.035 (1.262–12.903)	0.019		
T3	3.336 (1.038–10.728)	0.043		
T4	1.361 (0.412–4.489)	0.613		
Tx	1.066 (0.310–3.663)	0.919		
Clinical nodal status				
Negative	Reference		Reference	
Positive	2.647 (2.037–3.440)	<0.001	16.706 (7.267–38.407)	<0.001
Unknown	0.401 (0.184–0.877)	0.022		
Bone metastasis				
No	Reference			
Yes	0.340 (0.158–0.732)	0.006		
Unknown	1.900 (0.621–5.811)	0.261		
Liver metastasis				
No	Reference			
Yes	0.286 (0.221–0.369)	<0.001		
Unknown	0.353 (0.069–1.801)	0.211		
Lung metastasis				
No	Reference			
Yes	0.390 (0.267–0.571)	<0.001		
Unknown	0.307 (0.073–1.282)	0.105		

*, adjusted for age at diagnosis, marital status, primary tumor location, clinical T category, clinical nodal status, bone metastasis, liver metastasis, and lung metastasis; §, adjusted for age at diagnosis, race, marital status, clinical T category, and clinical nodal status. LND, lymph node dissection; OR, odds ratio; CI, confidence interval; PTR, primary tumor resection.

Table 3 Baseline characteristics between the LND and non-LND groups, before and after IPTW adjustment

Variables	Before IPTW, n (%)			After IPTW (%)		
	LND (n=217) (78.9%)	Non-LND (n=58) (21.1%)	P value	LND	Non-LND	P value
Age, years						
>65	84 (38.7)	31 (53.4)	0.061	37.4	55.5	0.199
≤65	133 (61.3)	27 (46.6)		62.6	44.5	
Gender						
Female	89 (41.0)	31 (53.4)	0.122	42.4	42.9	0.972
Male	128 (59.0)	27 (46.6)		57.6	57.1	
Race						
Black	19 (8.8)	11 (19.0)	0.082	9.1	10.3	0.465
White	180 (82.9)	42 (72.4)		82.0	71.4	
Other	18 (8.3)	5 (8.6)		8.9	18.3	
Marital status						
Never married	25 (11.5)	6 (10.3)	0.009	11.1	10.1	0.971
Married	162 (74.7)	34 (58.6)		72.2	74.5	
Previously married	26 (12.0)	13 (22.4)		14.3	12.5	
Unknown	4 (1.8)	5 (8.6)		2.4	3.0	
Primary tumor location						
Head	113 (52.1)	34 (58.6)	0.491	51.0	46.6	0.780
Body and tail	78 (35.9)	16 (27.6)		36.8	33.6	
Other	26 (12.0)	8 (13.8)		12.1	19.8	
Clinical nodal status						
Negative	52 (24.0)	42 (72.4)	<0.001	34.4	32.1	0.430
Positive	165 (76.0)	9 (15.5)		65.6	65.5	
Unknown	0 (0)	7 (12.1)		0.0	2.4	
Clinical T category						
T1	2 (0.9)	1 (1.7)	0.005	1.1	0.7	0.624
T2	104 (47.9)	24 (41.4)		47.0	32.7	
T3	75 (34.6)	13 (22.4)		32.2	42.6	
T4	27 (12.4)	10 (17.2)		13.2	18.2	
Tx	9 (4.1)	10 (17.2)		6.5	5.8	
Bone metastasis						
No	207 (95.4)	56 (96.6)	0.229	96.1	99.3	0.029
Yes	7 (3.2)	0 (0.0)		2.7	0.0	
Unknown	3 (1.4)	2 (3.4)		1.2	0.7	
Lung metastasis						
No	190 (87.6)	48 (82.8)	0.136	88.5	90.7	0.728
Yes	26 (12.0)	8 (13.8)		11.1	8.6	
Unknown	1 (0.5)	2 (3.4)		0.4	0.7	

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Before IPTW, n (%)			After IPTW (%)		
	LND (n=217) (78.9%)	Non-LND (n=58) (21.1%)	P value	LND	Non-LND	P value
Brain metastasis						
No	214 (98.6)	56 (96.6)	0.317	98.8	99.3	0.586
Yes	1 (0.5)	0 (0.0)		11.1	0.0	
Unknown	2 (0.9)	2 (3.4)		0.4	0.7	
Liver metastasis						
No	104 (47.9)	20 (34.5)	0.129	46.3	45.0	0.956
Yes	112 (51.6)	37 (63.8)		53.3	54.6	
Unknown	1 (0.5)	1 (1.7)		0.4	0.4	
Metastasectomy	39 (18.0)	11 (19.0)	1.000	18.7	9.2	0.089

IPTW, inverse probability of treatment weighting; LND, lymph node dissection.

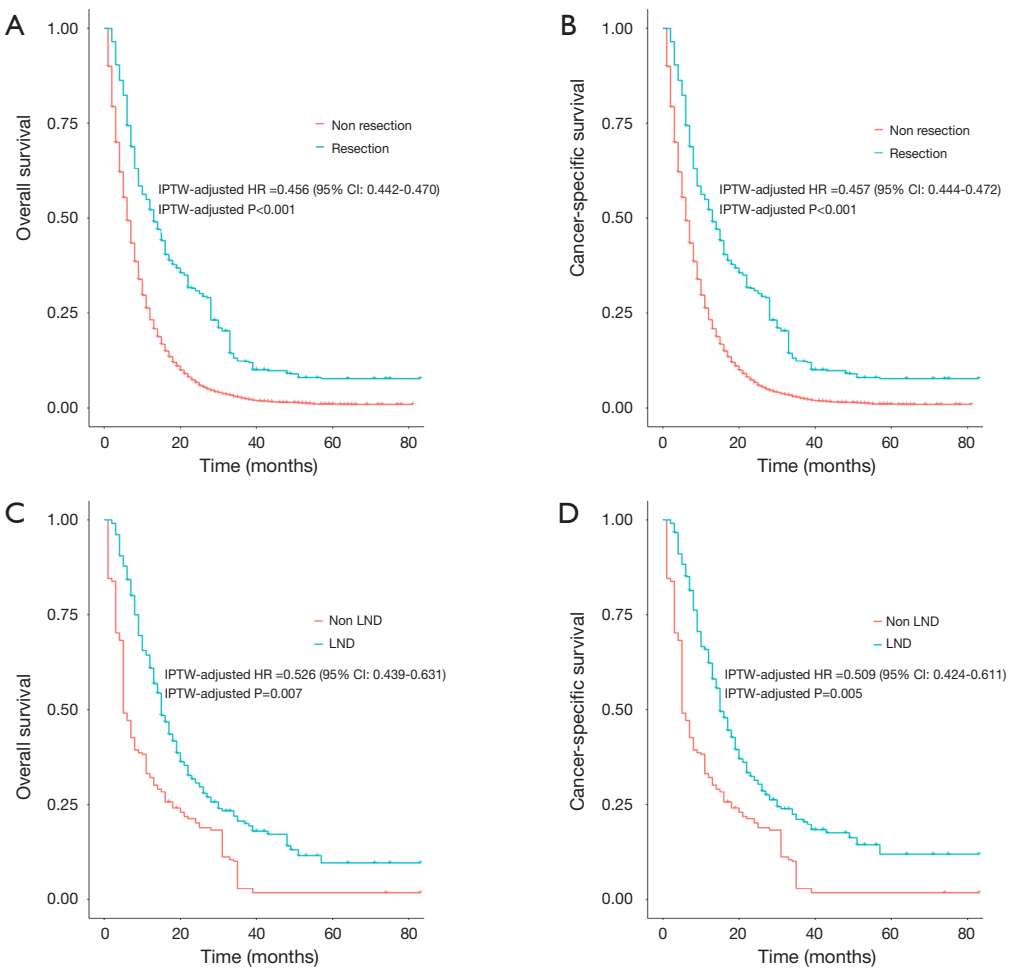

Figure 1 Survival curves depicting overall survival (A,C) or cancer-specific survival (B,D) of patients stratified according to presence or absence of primary tumor resection or lymph node dissection. LND, lymph node dissection; IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence interval.

Table 4 Multivariable Cox regression models predicting OS and CSS in patients who underwent or not PTR after IPTW adjustment

Variables	OS*		CSS*	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (>65) (years)	1.436 (1.393–1.480)	<0.001	1.460 (1.415–1.506)	<0.001
Gender (female)	0.894 (0.867–0.922)	<0.001	0.898 (0.870–0.926)	<0.001
Race				
Black	Reference		Reference	
White	1.061 (1.014–1.111)	0.011	1.067 (1.018–1.117)	0.005
Other	1.304 (1.217–1.396)	<0.001	1.331 (1.242–1.427)	<0.001
Marital status				
Never married	Reference		Reference	
Married	0.688 (0.659–0.718)	<0.001	0.683 (0.654–0.713)	<0.001
Previously married	0.907 (0.860–0.956)	<0.001	0.869 (0.824–0.918)	<0.001
Unknown	0.862 (0.793–0.938)	0.001	0.857 (0.788–0.933)	<0.001
Primary tumor location				
Head	Reference		Reference	
Body and tail	0.882 (0.850–0.915)	<0.001	0.871 (0.840–0.904)	<0.001
Other	0.927 (0.890–0.966)	<0.001	0.933 (0.896–0.973)	0.001
Clinical T category				
T1	Reference		Reference	
T2	0.844 (0.772–0.923)	<0.001	0.832 (0.761–0.910)	<0.001
T3	0.811 (0.741–0.887)	<0.001	0.793 (0.725–0.868)	<0.001
T4	0.716 (0.654–0.784)	<0.001	0.694 (0.634–0.761)	<0.001
Tx	1.138 (1.040–1.244)	<0.001	1.122 (1.026–1.227)	<0.001
Clinical nodal status				
Negative	Reference		Reference	
Positive	1.132 (1.094–1.172)	<0.001	1.121 (1.083–1.161)	<0.001
Unknown	1.295 (1.236–1.356)	<0.001	1.296 (1.237–1.358)	<0.001
Bone metastasis				
No	Reference		Reference	
Yes	1.110 (1.030–1.196)	0.006	1.114 (1.033-1.201)	0.005
Unknown	1.053 (0.871–1.274)	0.591	1.062 (0.876-1.288)	0.541
Liver metastasis				
No	Reference		Reference	
Yes	1.212 (1.167–1.259)	<0.001	1.205 (1.159–1.252)	<0.001
Unknown	0.852 (0.735–0.989)	0.035	0.848 (0.730-0.985)	0.030
Brain metastasis				
No	Reference		Reference	
Yes	1.110 (1.030–1.196)	0.037	1.233 (0.989–1.538)	0.063
Unknown	1.054 (0.871–1.274)	0.002	1.298 (1.091–1.543)	0.003

Table 4 (*continued*)

Table 4 (*continued*)

Variables	OS*		CSS*	
	HR (95% CI)	P value	HR (95% CI)	P value
Lung metastasis				
No	Reference		Reference	
Yes	1.108 (1.064–1.153)	<0.001	1.113 (1.069–1.160)	<0.001
Unknown	0.984 (0.866–1.119)	0.803	0.995 (0.874–1.132)	0.926
PTR	0.483 (0.468–0.498)	<0.001	0.485 (0.470–0.500)	<0.001

*, all variables collected in this study was with a univariate P value <0.1. IPTW, inverse probability of treatment weighting; OS, overall survival; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval, PTR, primary tumor resection.

Table 5 Multivariable Cox regression models predicting OS and CSS in patients who underwent or not LND after IPTW adjustment

Variables	OS*		CSS*	
	HR (95% CI)	P value	HR (95% CI)	P value
LND	0.286 (0.228–0.358)	<0.001	0.264 (0.209–0.333)	<0.001
Age (>65) (years)	1.540 (1.269–1.868)	<0.001	1.583 (1.301–1.926)	<0.001
Race				
Black	Reference		Reference	
White	1.112 (0.785–1.575)	0.552	1.112 (0.780–1.586)	0.558
Other	2.065 (1.353–3.151)	0.001	2.079 (1.354–3.192)	0.001
Clinical nodal status				
Negative	Reference		Reference	
Positive	2.034 (1.599–2.589)	<0.001	2.122 (1.656–2.718)	<0.001
Unknown	0.947 (0.425–2.111)	0.895	0.941 (0.421–2.102)	0.882
Marital status				
Never married	Reference		Reference	
Married	1.649 (1.197–2.273)	0.002	1.631 (1.181–2.252)	0.003
Previously married	0.999 (0.670–1.489)	0.996	0.886 (0.589–1.332)	0.560
Unknown	0.899 (0.430–1.878)	0.776	0.851 (0.406–1.782)	0.668
Clinical T category				
T1	Reference		Reference	
T2	0.624 (0.165–2.358)	0.487	0.600 (0.158–2.277)	0.453
T3	0.793 (0.209–3.007)	0.733	0.754 (0.198–2.869)	0.679
T4	0.173 (0.044–0.690)	0.013	0.153 (0.038–0.614)	0.008
Tx	0.740 (0.185–2.955)	0.669	0.717 (0.179–2.873)	0.638
Bone metastasis				
No	Reference		Reference	
Yes	0.434 (0.162–1.167)	0.098	0.431 (0.160–1.160)	0.096
Unknown	1.460 (0.590–3.610)	0.413	1.462 (0.590–3.623)	0.411
Metastasectomy	0.700 (0.516–0.950)	0.022	0.685 (0.502–0.935)	<0.001

*, all variables collected in this study was with a univariate P value <0.1. IPTW, inverse probability of treatment weighting; LND, lymph node dissection; OS, overall survival; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval.

synchronous liver disease (22). In their results, simultaneous resection of primary lesions and liver metastases did not result in a better prognosis, even for select patients with a low burden of liver metastasis. Tachezy *et al.* also identified 69 similar patients who underwent simultaneous resection of the pancreas and liver metastasis. The OS was improved in patients who underwent simultaneous resection (median 14 *vs.* 8 months, P<0.001) (14). Tumor resection was the only independent predictor of OS in the multivariate analysis. Based on these studies, surgery could be discreetly considered as a treatment strategy for super select patients with mPDAC.

To the best of our knowledge, this is the first study to investigate the beneficial role of LND in terms of long-term survival for patients with mPDAC. For patients treated with PTR, LND was significantly associated with better OS and CSS. The oncologic benefit of LND in non-metastatic PDAC could be justified by the complete removal of cancer. However, it was interesting to observe a beneficial prognostic role of LND in the resection of the primary tumor for mPDAC. LND usually did not bear prognostic benefits in patients with mPDAC whose metastatic lesions were largely left intact. A mechanism associated with cancer immunity may be responsible for the beneficial role of LND in mPDAC. It was reported that there was a balance between antitumor and protumor immunity inside the tumor-draining lymph nodes (TDLN). As the cancer advanced, the metastatic tumor cells inside the TDLN tipped the balance toward protumor immunity and converted the immunologic microenvironment of the TDLN to a tolerogenic milieu (23). Preclinical studies have suggested that the accumulation of Foxp3+ T regulatory cells in the TDLN inhibited the function of CD8+ T cells (24). Foxp3+ T cell-dependent dendritic cell death in the TDLN inhibited the onset of CD8+ T cell responses (25). Therefore, the removal of regional lymph nodes, even if they are negative, may also reverse protumor immunity, resulting in a better prognosis.

There are some limitations to our study. First, this study was retrospective and thus could not be free of selection bias. The selection criteria for surgery were unknown in the SEER database, although they must be related to the amount of tumor burden. Indeed, the SEER database lacks information regarding the number and distribution of metastatic lesions. Second, the SEER database did not contain information on comorbidities, performance status, and chemotherapeutic agents, which may confound the evaluation of the actual effects of surgery. Finally, the SEER database also lacks information about surgical margin status and complication rates, which are instrumental in the decision to perform a major operation.

Conclusions

Although this is a retrospective study, the results suggest that PTR and LND were independent prognostic factors that prolonged OS and CSS in *de novo* mPDAC patients. However, these findings must be validated in prospective randomized studies.

Acknowledgments

The authors appreciate the Surveillance, Epidemiology, and End Results database in providing high quality clinical data for our research.
Funding: This study was supported by a grant from National Key R&D Program of China (Grant No. 2017YFC0908300).

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2020.04.02). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The Institutional Review Board of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital has reviewed and approved this study, and has also agreed that individual patient consent was not required to report clinical outcomes alone (No. 17-156/1412).

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Cite this article as: Wu C, Zhang X, Wang T, Zhou H, Guo C, Chen Y, Zhao D. Primary tumor resection and lymph node dissection improve survival in *de novo* metastatic pancreatic ductal adenocarcinoma: an inverse probability of treatment weighting analysis. Transl Cancer Res 2020;9(5):3312-3323. doi: 10.21037/tcr.2020.04.02

