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DATABASE ANALYSIS

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The Main Bottleneck for Non-Metastatic Pancreatic Adenocarcinoma in Past Decades: A Population-Based Analysis

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Background: Despite recent advancements in surgical techniques, chemotherapy, and radiotherapy, the 5-year survival rate of patients with pancreatic ductal adenocarcinoma (PDAC) remains an unsatisfactory ~8%.

Material/Methods: Data were extracted to identify patients with non-metastatic pancreatic adenocarcinoma diagnosed in the periods 1988–1996 and 2010–2014 in the Surveillance, Epidemiology, and End Results (SEER) database. The statistical analyses were performed with the log-rank test, Pearson's chi-square test, propensity score matching, and Cox regression model.

Results: The hazard ratio (HR) of surgery was reduced from 0.454 to 0.302 in Cox regression modeling, and there was no overlapping about the 95% confidence intervals (CI) of surgery between the 2 periods. The HR values of radiotherapy, which were new prognostic factor for resectable PDAC in 2010–2014, were reduced in both the resectable and unresectable groups. The upgraded chemotherapy regimen reduced the HR values from 0.738 to 0.689 in all PADC patients, and from 0.656 to 0.588 in unresectable PDAC. The log-rank test results showed that advances in surgery significantly improved the median survival from 13 months to 32 months. Radiotherapeutic and chemotherapeutic advancements extended median survival by 12 months and 11 months, respectively, in resectable PDAC. The median survivals were extended by 3 months for both of radiotherapy and chemotherapy in unresectable PDAC.

Conclusions: The development of chemotherapy and radiotherapy has been slow, especially for unresectable PDAC. Although advances in surgery contributed significantly to improved survival for resectable PDAC, lack of early diagnostic tools, which lead to low resection rates, remain a barrier for all PDAC patients.

MeSH Keywords: Carcinoma, Pancreatic Ductal • Chemotherapy, Adjuvant • General Surgery • Radiotherapy

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Background

Pancreatic cancer is one of the leading causes of cancer mortality in developed countries and one of the most lethal malignant neoplasms worldwide [1]. The main histological type of pancreatic tumor is pancreatic ductal adenocarcinoma (PDAC), which accounts for about 85% of cases [2,3]. Early locoregional metastasis, unusual aggressiveness, and distant spread of pancreatic cancer cells are the basis of the urgent need for new therapeutic options for patients with PDAC, as its incidence is still nearly equal to its mortality in Western countries [4].

Treatment for PDAC involves surgical resection, chemotherapy, and/or radiotherapy. The development of surgical resection has involved perfection of surgical concepts and equipment. Several techniques, including total mesopancreatic excision (TMpE) and accurate assessment of the resection margins, which have been learned from experience treating colorectal cancer, are used by pancreatic surgeons [5,6]. Additionally, application of robot-assisted laparoscopy contributes to the refinement of surgery [7]. Adjuvant chemotherapy for patients with PDAC was converted from 5-FU-based regimens in the early 1990s to gemcitabine-based regimens in the 2000s [8,9] and FOLFIRINOX in the 2010s. Intensity-modulated radiation therapy (IMRT), which can not only adjust the dose of radiotherapy and increase the radiation dose of tumor but also reduce the radiation damage of normal tissues, emerged due to the development of CT technology and three-dimensional conformal radiotherapy (3D-CRT) [10,11].

Despite recent advances in surgical techniques, chemotherapy, and radiation therapy, the 5-year survival rate of patients with PDAC remains a dismal 8.2% [12]. The present study explored whether improved surgical resection, chemotherapy, and radiotherapy regimens have helped patients with PDAC obtain a longer survival, as well as to identify the main barriers to improved survival in non-metastatic PDAC, in recent decades. Thus, the purpose of the present study was to determine the impact of therapeutic advancements by comparing the overall survival (OS) of patients with PDAC between the periods 1988–1996 and 2010–2014.

Material and Methods

Materials

Patient data were extracted from the Surveillance, Epidemiology, and End Results (SEER) linked database in this retrospective analysis. The SEER Program of the National Cancer Institute is an authoritative source of information on cancer incidence and survival in the United States (U.S.) that is updated annually. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximate 34.6% of the U.S. population. according to SEER historic stage A (localized PDAC is limited to the pancreas; regional PDAC is confined to nearby lymph nodes or other organs and distant disease involves systemic metastasis). The target population in our study was limited to patients with localized and regional pancreatic adenocarcinoma diagnosed in the periods of 1988–1996 and 2010–2014, with a total of 20 589 patients. Follow-up times of all patients were more than 2 years. We excluded patients with missing data regarding race, tumor size, extension, lymph nodes, regional nodes examined, and treatment programs. The final study sample embodied consisted of 15 077 patients.

We chose the period 1988–1996 as a baseline because partial data, which included tumor size, regional nodes examined, and lymph nodes, were available since 1988 and gemcitabine was recommended as first-line chemotherapy for pancreatic cancer in 1997. We chose patients from the period 2010–2014, which was the latest for the 2-year follow-up, since the FOLFIRINOX regimen emerged as a new treatment options for metastatic pancreatic cancer in 2010 [13,14]. According to the code of CS extension and EOD 10-extent, we classified patients who were equivalent to the T0-2 staging in the seventh edition of AJCC as mild extension, and those who matched with T3-4 staging as grievous extension. The codes of negative node were 0 in CS lymph nodes (2004–2015) and EOD 10 – nodes (1988–2003). The codes of positive nodes were 100, 110, 200, 210, 250, and 800 in CS lymph nodes (2004–2015) and 1 and 8 in EOD 10-nodes (1988–2003). Patients with codes of 10–90 in RX Summ – Surg Prim Site (1998+) and Site-specific surgery (1973–1997, with varying details by year and site) were classified to the resectable group.

Methods

Pearson's chi-square test was applied for intergroup comparisons and the log-rank test was applied to compare overall survival (OS) between different cohorts. We evaluated 95% confidence interval (CI) and hazard ratio (HR) by multivariate Cox proportional hazards regression models. Propensity score matching (PSM) was conducted to eliminate the influence of other variables. The nearest neighbor matching with a caliper width of 0.0001 was employed. Statistical analyses were performed with IBM SPSS statistics trial ver. 25.0 (IBM, Armonk, NY, USA). All reported p-values lower than 0.05 were considered significant.

Results

Patient Characteristics

This study enrolled 15 077 patients, involving 2144 (14.22%) cases in 1988–1996 and 12 933 (85.78%) cases in 2010–2014.

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Patients with resectable pancreatic cancer accounted for 49.86% (1069/2144) in 1988–1996 and 38.34% (4958/12933) in 2010–2014. The ratio of qualified regional nodes examined (RNE), which was RNE more than 15, an available indicator that reflects the quality of surgery in SEER database [15], increased by 8.50%. The proportion of patients receiving chemotherapy increased significantly by 14.36%, whereas radiotherapy regimens decreased by 14.12%. In addition, differences in sex, age, primary tumor location, histologic grade, lymph nodes, tumor size, and extension were also compared between the 2 periods (Table 1).

Survival improvement of PDAC

Patients with non-metastatic PDAC had longer overall survival due to therapeutic advancements, including surgery and adjuvant therapy, during 1988–1996 and 2010–2014. Median survival improved from 10 months to 14 months in all patients ($p<0.001$, Figure 1A). Median survival significantly increased by 23 months in the resectable patients ($p<0.001$, Figure 1B). The proportion of resectable PDAC patients receiving chemotherapy increased from 34.89% (373/1069) to 50.18% (2488/4958), and those receiving radiotherapy decreased from 37.61% (402/1069) to 25.47% (1263/4958). Furthermore, the proportion of qualified RNE significantly improved from 16.28% (174/1069) to 43.49% (2156/4958).

However, median survival only slightly improved, from 7 months to 9 months, in the unresectable PDAC ($p<0.001$, Figure 1C). There were also significant differences in the ratio of radiotherapy (44.19%, 475/1075 *vs.* 27.72%, 2211/7975) and chemotherapy (42.70% 459/1075 *vs.* 55.15% 4398/7975) between the 2 periods.

Cox regression model

We used Cox regression modeling to analyze prognostic factors in all, unresectable, and resectable patients (Table 2). Age, histologic grade, tumor size, extension, and lymph nodes were always prognostic factors in all groups. Importantly, surgery was associated with survival in the 2 periods. Moreover, the hazard ratio (HR) of surgery decreased from 0.454 to 0.302, and there was no overlapping about the 95% confidence intervals (CI) of surgery between the 2 periods. In addition, although not for all PDAC patients, RNE can be used as a prognostic factor for resectable pancreatic cancer.

The HR values of radiotherapy, which was a new prognostic factor for resectable PDAC in 2010–2014, were reduced in both the resectable and unresectable groups. Advances in radiotherapeutic technology not only made radiotherapy a prognostic factor, but also reduced HR values for all PDAC patients. In addition, the 95% CIs of radiotherapy in 1988–1996 were wider than those in 2010–2014.

Use of the upgraded chemotherapy regimen reduced the HR values from 0.738 to 0.689 in all PADC patients, and from 0.656 to 0.588 in unresectable PDAC, but it did not improve the survival of resectable patients in 2010–2014 ($p=0.366$). Similarly, the 95% CIs of chemotherapy in 1988–1996 were wider than those in 2010–2014, except for the resectable group (Figure 2).

The impact of therapeutic advancement on survival

We conducted a propensity score matching (PSM) to eliminate the influence of the other variables such as sex, race, age, and grade, which better show the effects of therapeutic advances on the survival of PDAC patients. First, we screened resectable PDAC patients without adjuvant therapy (Supplementary Table 1). The number of RNEs, an available indicator that reports the quality of surgery in the SEER database, did not match between the 2 groups. Log-rank testing showed that advances in surgery significantly improved the median survival, from 13 months to 32 months ($p<0.001$, Figure 3A). Radiotherapeutic and chemotherapeutic advances extended median survival by 12 months ($p<0.001$, Figure 3B) and 11 months, respectively ($p<0.001$, Figure 3C), after PSM (Supplementary Tables 2, 3) in resectable PDAC.

PSM then was performed to explore the impact of radiotherapeutic and chemotherapeutic advancements in the unresectable group (Supplementary Tables 4, 5). Log-rank testing showed that the median survivals were extended by 3 months for radiotherapy ($p=0.005$, Figure 4A) and chemotherapy ($p= 0.003$, Figure 4B). Finally, we performed PSM for those who missed all treatments in the unresectable group (Supplementary Table 6). The log-rank test indicated that selective bias was effectively eliminated by PSM ($p=0.875$, Figure 4C).

Discussion

To the best of our knowledge, this is the first study to assess barriers to improvement of survival in patients with PDAC in recent decades. We selected PDAC patients from the periods 1988–1996 and 2010–2014, determined the influences of prognostic factors by HR value and 95% CI in Cox regression modeling, and explored the significance of therapeutic advances involving surgery and adjuvant therapy for survival following PSM. Researches focusing on the progress of treatment can be a basis for guiding improvement of current therapeutic modalities.

The cornerstones for treating pancreatic cancer undoubtedly include surgery, chemotherapy, and radiotherapy, which prolonged the survival of PDAC patients in the past few decades. Among them, surgery was always the preferred choice of treatment for PDAC, since HRs of surgery had the smallest value in

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Table 1. Characteristics of non-metastatic PDAC.

Characteristics	1988–1996 (n=2144)		2010–2014 (n=12933)		P value
Gender					0.014
Male	1013	(47.25%)	6481	(50.11%)	
Female	1131	(52.75%)	6452	(49.89%)	
Age (years)					<0.001
≤50	214	(9.98%)	979	(7.57%)	
51–70	1080	(50.37%)	6096	(47.14%)	
>70	850	(39.65%)	5858	(45.29%)	
Race					0.052
White	1768	(82.46%)	10413	(80.51%)	
Black	217	(10.12%)	1461	(11.30%)	
Other	159	(7.42%)	1059	(8.19%)	
Primary tumor location					<0.001
Head	1692	(78.92%)	8666	(67.01%)	
Body or tail	243	(11.33%)	2334	(18.05%)	
Other	209	(9.75%)	1933	(14.94%)	
Histologic grade					<0.001
I/II	942	(43.94%)	4295	(33.21%)	
III/IV	558	(26.02%)	1885	(14.57%)	
Unknown	644	(30.04%)	6753	(52.22%)	
Resectable					<0.001
No	1075	(50.14%)	7975	(61.66%)	
Yes	1069	(49.86%)	4958	(38.34%)	
Radiotherapy					<0.001
No	1265	(59.00%)	9457	(73.12%)	
Yes	879	(41.00%)	3476	(26.88%)	
Chemotherapy					<0.001
No	1310	(61.10%)	6045	(46.74%)	
Yes	834	(38.90%)	6888	(53.26%)	
Regional nodes examined					<0.001
<15	1968	(91.79%)	10772	(83.29%)	
≥15	176	(8.21%)	2161	(16.71%)	
Lymph nodes					<0.001
Negative	1224	(57.09%)	8751	(67.66%)	
Positive	920	(42.91%)	4182	(32.34%)	
Tumor size (cm)					<0.001
≤2	291	(13.57%)	2185	(16.89%)	
2–4	1006	(46.92%)	7091	(54.83%)	
>4	847	(39.51%)	3657	(28.28%)	
Extension					<0.001
Mild	665	(31.02%)	4253	(32.88%)	
Grievous	1479	(68.98%)	8680	(67.12%)	

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Table 2. Multivariate analysis of survival months in non-metastatic pancreatic adenocarcinoma.

Variables	Whole				Resectable				Unresectable			
	1988–1996		2010–2014		1988–1996		2010–2014		1988–1996		2010–2014	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Gender												
Male	Reference		Reference		Reference		Reference		Reference		Reference	
Female	0.989 (0.907–1.079)	0.802	0.961 (0.924–1.000)	0.051	1.010 (0.892–1.144)	0.873	0.949 (0.880–1.024)	0.179	0.994 (0.878–1.125)	0.922	0.967 (0.924–1.013)	0.160
Age(years)												
≤50	Reference		Reference		Reference		Reference		Reference		Reference	
51–70	1.490 (1.272–1.746)	<0.001	1.527 (1.388–1.679)	<0.001	1.358 (1.103–1.673)	0.004	1.650 (1.408–1.934)	<0.001	1.442 (1.121–1.856)	0.004	1.315 (1.167–1.481)	<0.001
>70	1.844 (1.564–2.174)	<0.001	2.197 (1.997–2.418)	<0.001	1.647 (1.315–2.062)	<0.001	2.369 (2.012–2.789)	<0.001	1.722 (1.334–2.224)	<0.001	1.804 (1.603–2.031)	<0.001
Race												
White	Reference		Reference		Reference		Reference		Reference		Reference	
Black	1.134 (0.982–1.310)	0.086	1.013 (0.952–1.079)	0.677	1.140 (0.926–1.404)	0.218	1.157 (1.016–1.317)	0.027	1.050 (0.857–1.287)	0.637	0.975 (0.908–1.047)	0.484
Other	1.137 (0.962–1.343)	0.131	0.949 (0.881–1.022)	0.165	1.113 (0.878–1.411)	0.377	0.946 (0.814–1.099)	0.466	1.186 (0.937–1.502)	0.157	0.954 (0.875–1.039)	0.277
Primary tumor location												
Head	Reference		Reference		Reference		Reference		Reference		Reference	
Body or tail	0.751 (0.648–0.870)	<0.001	0.623 (0.585–0.663)	<0.001	0.675 (0.544–0.839)	<0.001	0.532 (0.460–0.615)	<0.001	1.075 (0.876–1.318)	0.489	0.709 (0.661–0.760)	<0.001
Other	0.912 (0.786–1.057)	0.221	0.799 (0.755–0.846)	<0.001	0.869 (0.683–1.106)	0.253	0.793 (0.699–0.900)	<0.001	1.052 (0.868–1.276)	0.604	0.847 (0.794–0.904)	<0.001
Histologic grade												
I/II	Reference		Reference		Reference		Reference		Reference		Reference	
III/IV	1.370 (1.232–1.524)	<0.001	1.821 (1.707–1.944)	<0.001	1.305 (1.135–1.501)	<0.001	1.700 (1.560–1.853)	<0.001	1.465 (1.237–1.735)	<0.001	1.648 (1.490–1.823)	<0.001
Unknown	0.909 (0.817–1.013)	0.083	1.352 (1.277–1.432)	<0.001	0.579 (0.466–0.721)	<0.001	1.164 (1.028–1.319)	0.017	1.169 (1.017–1.344)	0.028	1.335 (1.245–1.432)	<0.001
Surgery												
No	Reference		Reference		NA		NA		NA		NA	
Yes	0.454 (0.409–0.503)	<0.001	0.302 (0.282–0.324)	<0.001	NA		NA		NA		NA	
Radiotherapy												
No	Reference		Reference		Reference		Reference		Reference		Reference	
Yes	0.937 (0.826–1.063)	0.313	0.852 (0.812–0.893)	<0.001	0.933 (0.755–1.153)	0.521	0.886 (0.809–0.971)	0.009	0.843 (0.720–0.988)	0.035	0.813 (0.769–0.860)	<0.001
Chemotherapy												
No	Reference		Reference		Reference		Reference		Reference		Reference	
Yes	0.738 (0.649–0.838)	<0.001	0.689 (0.657–0.722)	<0.001	0.800 (0.647–0.990)	0.040	1.047 (0.948–1.155)	0.366	0.656 (0.558–0.771)	<0.001	0.588 (0.557–0.621)	<0.001

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Table 2 continued. Multivariate analysis of survival months in non-metastatic pancreatic adenocarcinoma.

Variables	Whole				Resectable				Unresectable			
	1988–1996		2010–2014		1988–1996		2010–2014		1988–1996		2010–2014	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Regional nodes examined												
<15	Reference		Reference		Reference		Reference		Reference		Reference	
≥15	0.846 (0.716–1.001)	0.051	1.000 (0.926–1.080)	0.998	0.777 (0.656–0.922)	0.004	0.832 (0.768–0.901)	<0.001	0.395 (0.055–2.833)	0.355	1.066 (0.399–2.845)	0.899
Lymph nodes												
Negative	Reference		Reference		Reference		Reference		Reference		Reference	
Positive	1.218 (1.114–1.332)	<0.001	1.243 (1.188–1.301)	<0.001	1.390 (1.221–1.584)	<0.001	1.558 (1.423–1.706)	<0.001	1.060 (0.931–1.206)	0.379	1.093 (1.035–1.154)	0.001
Tumor size (cm)												
≤2	Reference		Reference		Reference		Reference		Reference		Reference	
2–4	1.229 (1.073–1.407)	0.003	1.661 (1.550–1.781)	<0.001	1.241 (1.058–1.456)	0.008	1.470 (1.313–1.645)	<0.001	1.353 (1.033–1.771)	0.028	1.754 (1.606–1.914)	<0.001
>4	1.311 (1.136–1.512)	<0.001	1.883 (1.748–2.028)	<0.001	1.288 (1.072–1.547)	0.007	1.670 (1.471–1.896)	<0.001	1.542 (1.175–2.022)	0.002	2.032 (1.852–2.229)	<0.001
Extension												
Mild	Reference		Reference		Reference		Reference		Reference		Reference	
Grievous	1.213 (1.102–1.336)	<0.001	1.538 (1.463–1.618)	<0.001	1.439 (1.246–1.661)	<0.001	2.005 (1.787–2.250)	<0.001	0.999 (0.876–1.139)	0.982	1.394 (1.318–1.475)	<0.001

NA – not available.

Cox regression model of the 2 analyzed periods. Advancements in surgery were demonstrated by the increasing rate of qualified RNE and non-intersecting 95% CIs in Cox regression modeling between the 2 periods. Moreover, the maximum median survival extension proved that advances in surgery are the main contributor to improved survival in resectable PDAC patients. In fact, advances in pancreatic surgery involved refined equipment and new concepts. Although they contributed to the refinement of surgery, laparoscopic and robotic surgery have not improved the survival of patients with PDAC [16]. Several concepts may be used as milestones in the treatment of pancreatic cancers, including total mesopancreatic excision (TMpE) and accurate assessment of the resection margins, which have been learned from clinical experiences in colorectal cancer. The presence of mesopancreas and the feasibility and clinical value of TMpE are important topics among surgeons. Pancreatic surgeons were committed to the development of TMpE after the concept of "mesopancreas" was first proposed by Gockel et al. in 2007 [17]. Adham et al. reported a significant increase in the R0 resection rate of pancreatic cancer with TMpE compared with conventional pancreatic cancer radical surgery in 2012 [5]. In the same year, Kawabata et al. retrospectively compared TMpE with standard pancreatic cancer surgery, showing that the TMpE group had more lymph node dissections (26 *vs.* 18, p=0.027) and a higher R0 resection rate (93% *vs.* 60%, p=0.019) [18]. Due to almost symptomless progression, PDAC is still often diagnosed in advanced stages, at which point the best opportunity for surgical resection has been missed [4]. The surgical resection rate of pancreatic cancer was only 38.34% in 2010–2014 in the present study.

The surgical advancements were accompanied by an increase in RNE. This study selected 15 as the cutoff value of RNE because Schwarz et al. found that the number of lymph nodes detected had an important effect on lymph node ratio (LNR) and prognosis by retrospectively analyzing the SEER database [19]. The proportion of eligible RNE, which was refined as RNE ≥15 for PDAC in this study, increased from 16.28% to 43.49% in resectable PDAC patients. Meanwhile, qualified RNE was beneficial for the survival of resectable PDAC (p=0.004 in 1988–1996; p<0.001 in 2010–2014). Other retrospective database analyses also found that PDAC patients had a better prognosis with an increasing number of examined lymph nodes [20].

Additionally, this study showed some evidence that the chemotherapy regimens for PDAC in 2010–2014 were superior to that in 1988–1996. The median survival increased in PDAC patients with chemotherapy in 2010–2014. The HR value of chemotherapy

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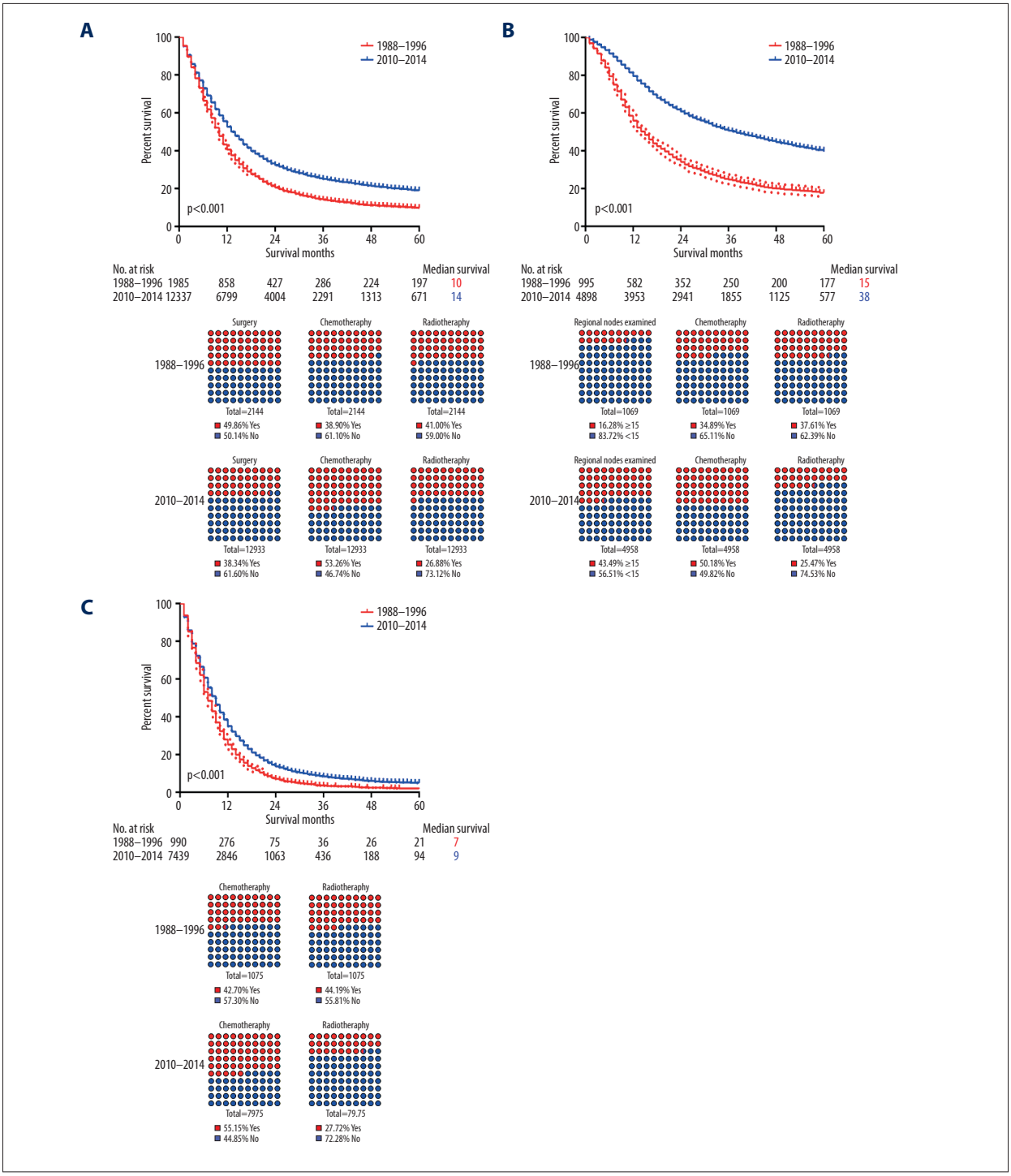

Figure 1. Log-rank test showed that PDAC patients had longer overall survival due to therapeutic advances. (**A**) Median survival improved from 10 months to 14 months in all patients with PDAC (p<0.001). The proportion of chemotherapy increased by 14.36% while the ratio of patients receiving radiotherapy and surgery decreased by 14.12% and 11.52%, respectively. (**B**) Median survival improved from 15 months to 38 months in patients with resectable PDAC (p<0.001). The ratio of qualified RNE, which was ≥15, and patients receiving chemotherapy, increased by 27.21% and 15.29%, respectively, while the proportion of radiotherapy decreased by 12.14%. (**C**) Median survival improved from 7 months to 9 months in patients with irresectable PDAC (p<0.001). The ratio of patients receiving chemotherapy increased by 12.45%, while the proportion of patients receiving radiotherapy decreased by 16.47%.

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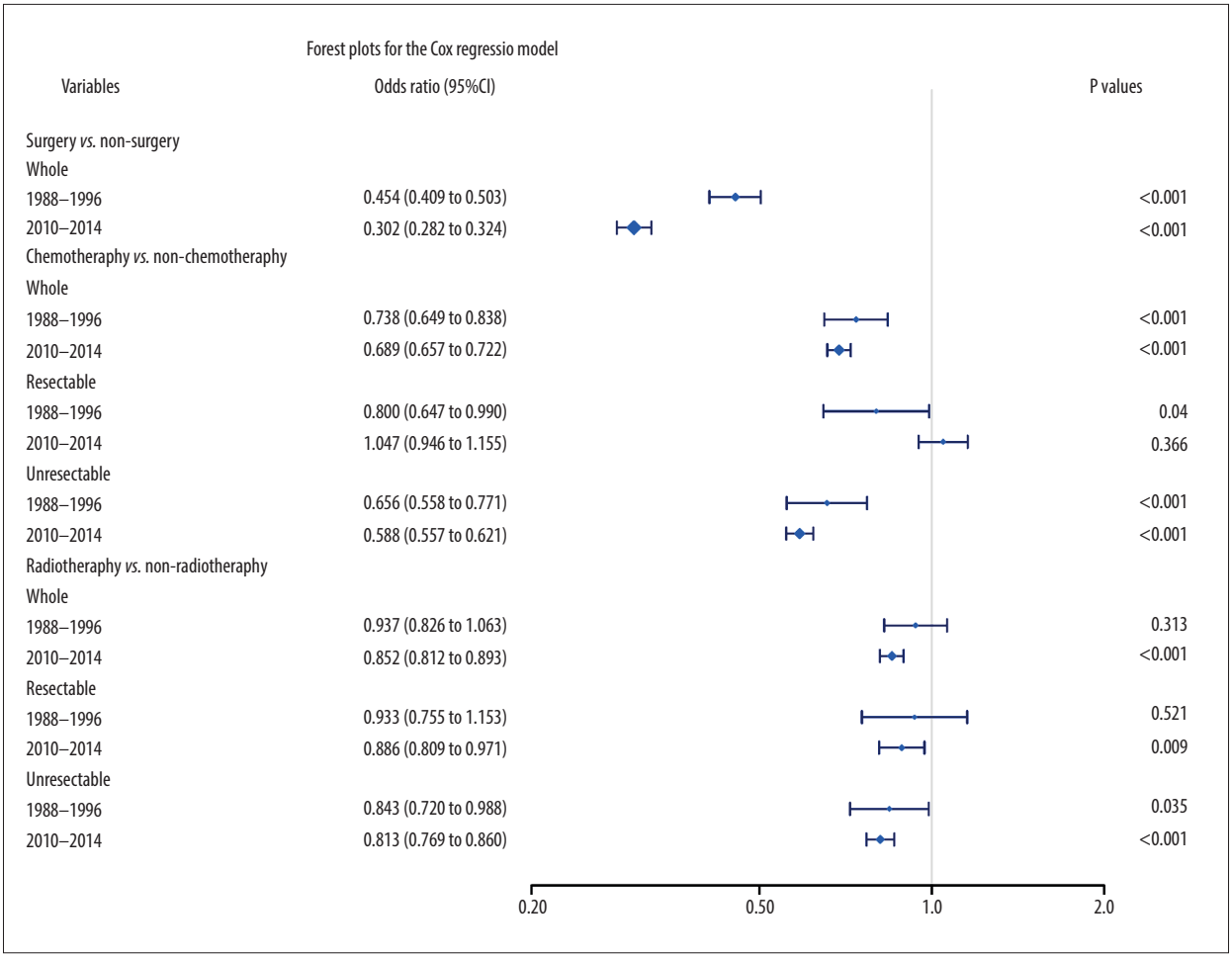

Figure 2. Forest plots for Cox regression model. The hazard ratio (HR) of surgery fell from 0.454 to 0.302, and there was no overlapping about the 95% confidence intervals (CI) of surgery between the 2 periods. The HR values of radiotherapy were reduced in both the resectable and unresectable groups. Meanwhile, the 95% CIs for radiotherapy in 2010–2014 were narrower than those in 1988–1996. The improvement in chemotherapy regimens reduced the HR values from 0.738 to 0.689 in all PADC patients, and from 0.656 to 0.588 in unresectable PDAC. However, there was no improved survival of resectable patients in 2010–2014 (p=0.366). Similarly, the 95% CIs for chemotherapy in 2010–2014 were narrower than those in 1988–1996, except for the resectable group.

was reduced from 1988–1996 to 2010–2014. However, the development of chemotherapy has been slow. In particular, the median survival of unresectable patients with updated chemotherapy was only extended by 3 months. Another study also reported that gemcitabine, which was the most important chemotherapy drug for PDAC in 2010–2014, provides clinical benefit and a modest survival advantage over treatment with bolus 5-FU, which was the main chemotherapy drug used in 1988–1996 [8]. Promising chemotherapy regimens, including nab-paclitaxel plus gemcitabine and FOLFIRINOX, also demonstrated superiority [21–23], but advances in chemotherapy regimens seemed to be unable to keep up with the pace of surgery, which cannot be used as a prognostic factor for resectable PDAC in 2010–2014. In addition, the updated chemotherapy regimen did not improve survival as much as surgical advancements after PSM.

The 95% CIs for radiotherapy in 1988–1996 nearly covered the Cox regression model of regional PDAC analyzed for 2010–2014, showing the accuracy and reliability of current radiotherapy technology. Precise radiotherapy can improve margin-negative resection, sterilize vessel margins, and/or improve local control [24]. Landry et al. reported a significant reduction in radiation dose to the small intestine during IMRT [25]. Ben-Josef and Milano also found that the efficacy of IMRT was satisfactory, with low secondary damage [10,26]. Regrettably, this study reported that advanced radiotherapy, which was similar to chemotherapy, slightly improved the median survival of PDAC patients. In fact, chemotherapy drugs could be used as sensitizers for radiotherapy. Therefore, the update of chemotherapy regimens may improve the effect of radiotherapy for pancreatic cancer. Moreover, advanced chemoradiotherapy can

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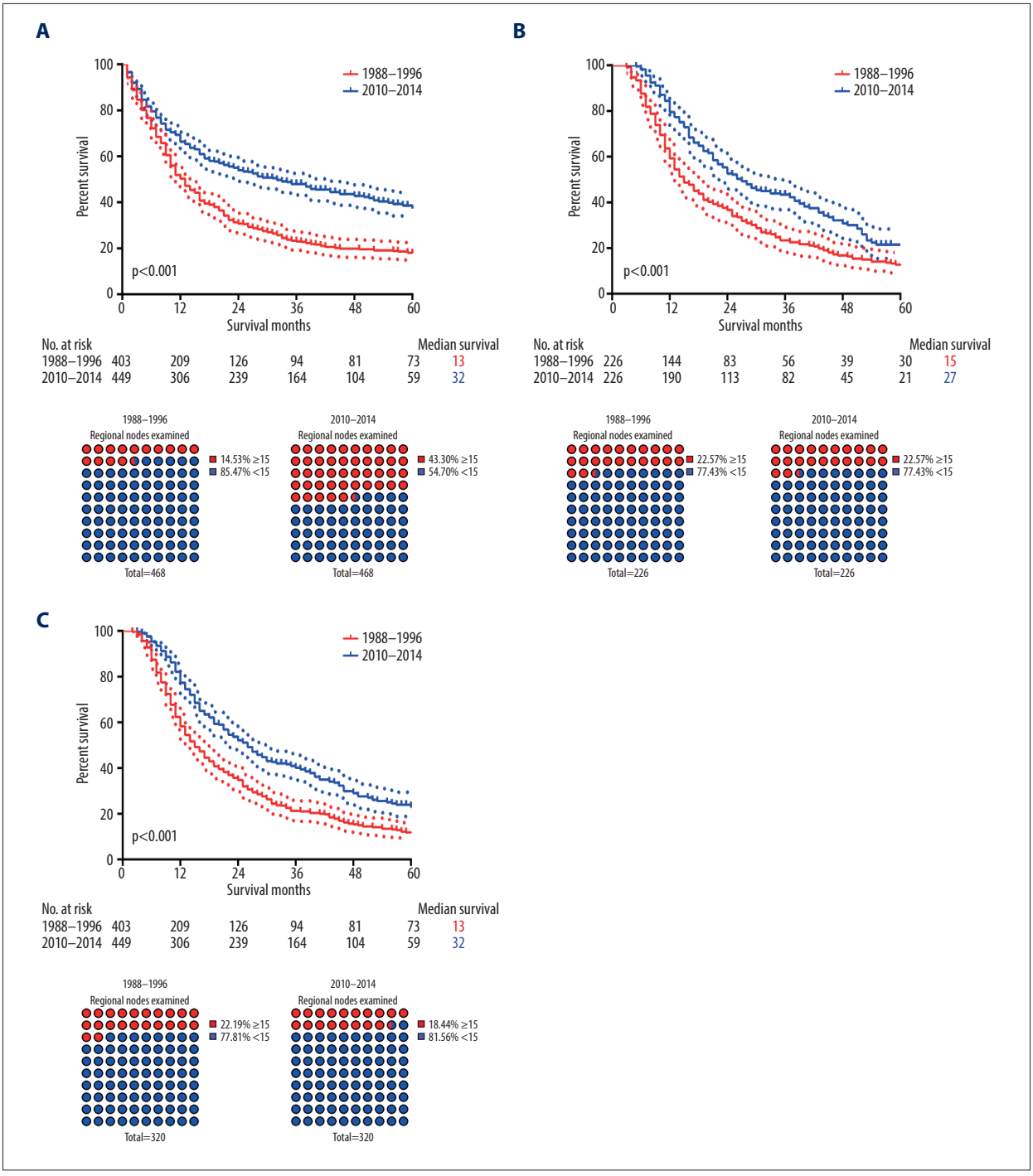

Figure 3. The impact of therapeutic advancement on survival of resectable PDAC. (**A**) Advances in surgery extended the median survival by 19 months and increased the qualified RNE rate by 30.77% in resectable PDAC patients (p<0.001). (**B**) Median survival increased by 12 months in resectable PDAC patients with radiotherapeutic advances (p<0.001). (**C**) Median survival increased by 11 months in resectable PDAC patients with chemotherapeutic advances (p<0.001).

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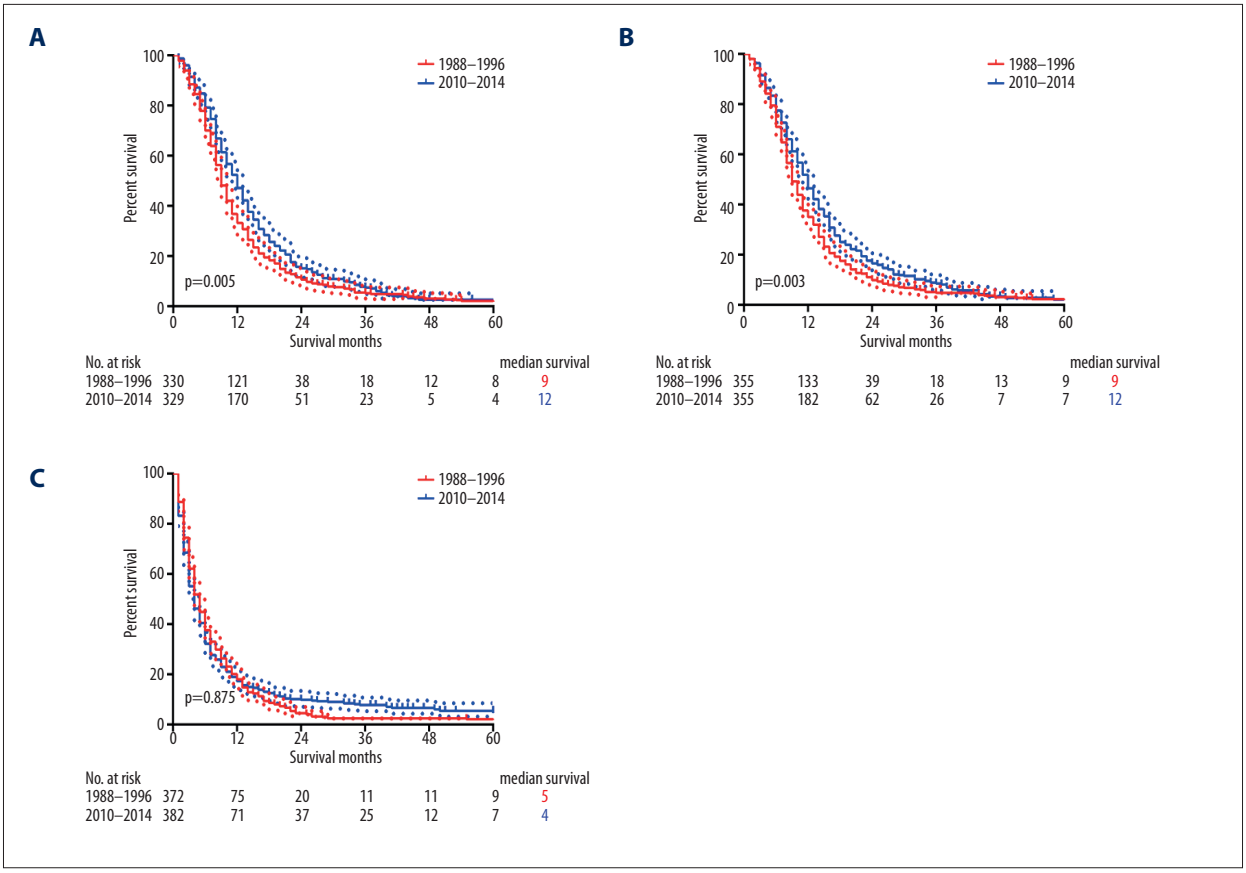

Figure 4. The impact of therapeutic advances on survival of irresectable PDAC patients. (**A**) Median survival increased by 3 months in irresectable PDAC patients with radiotherapeutic advances (p=0.005). (**B**) Median survival also increased by 3 months in irresectable PDAC patients with chemotherapeutic advances (p=0.003). (**C**) There was no difference in irresectable PDAC patients without adjuvant therapy (p=0.875).

promote surgical resection rates for locally advanced and borderline resectable PDAC, which may extend survival for those patients. However, this study cannot draw clear conclusions due to the limited information in the SEER database.

Advances in adjuvant therapy contributed markedly to the increased survival for locally advanced rectal cancer (LARC) after the emergence of total mesorectal excision (TME) [15]. However, disappointing adjuvant therapy limited the conversion therapy and survival improvement in patients with PDAC. Although it provided survival benefits for advanced pancreatic cancer [21], FOLFIRINOX cannot be recommended for all PDAC patients, especially those with poor performance status, due to its highly toxic combination and serious adverse effects [27]. Another promising regimen for PDAC, Nab-paclitaxel plus gemcitabine, has similar problems. It is believed that current chemotherapy and/or radiotherapy are still far from perfect for PDAC. Therefore, we still have a long and challenging journey ahead of us to establish a satisfactorily chemotherapy program.

The significance of this study was to find barriers to treating pancreatic cancer, which are the low rate of surgical resection and poor adjuvant therapy. This is why researchers are eagerly looking for new therapy targets and improving early diagnostic tools for pancreatic cancer, which could help to improve the outcome of PDAC in combination with surgery. Limitations of this study include: (1) the use of retrospective data; (2) detailed treatment information for included patients was not recorded in the SEER cohort, and we could not investigate specific options, including R0 or not, preoperative or postoperative chemotherapy in the survival of PDAC patients; (3) Cases in 1988–1996 lacked TNM staging data.

Conclusions

Development of chemotherapy and radiotherapy has been slow, especially for unresectable pancreatic cancer. Although advances in surgery were major contributors to the improvement of survival in resectable patients, lack of early diagnostic tools, which resulted in low resection rates, was still an obstacle for all PDAC patients.

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Conflict of interests

None.

Supplementary Data

Supplementary Table 1. Characteristics of localized PDAC patients underwent surgery without adjuvant therapy after PSM.

Characteristics	1992–1996 (n=86)	2010–2014 (n=86)	P value
Gender			0.879
Male	46 (53.49%)	45 (52.33%)	
Female	40 (46.51%)	41 (47.67%)	
Age (years)			1.000
≤50	7 (8.14%)	7 (8.14%)	
51–70	46 (53.49%)	46 (53.49%)	
>70	33 (38.37%)	33 (38.37%)	
Race			0.583
White	76 (88.37%)	72 (83.72%)	
Black	4 (4.65%)	8 (9.30%)	
Other	6 (6.98%)	6 (6.98%)	
Primary tumor location			0.824
Head	60 (69.77%)	59 (68.60%)	
Body or tail	17 (19.77%)	17 (19.77%)	
Other	9 (10.47%)	10 (11.63%)	
Histologic grade			0.923
Well/moderately differentiated	55 (63.95%)	56 (65.12%)	
Poor differentiated/uindifferentiated	15 (17.44%)	14 (16.28%)	
Unknown	16 (18.60%)	16 (18.60%)	
Regional nodes positive			0.532
Negative	74 (86.05%)	71 (82.56%)	
Not checked	12 (13.95%)	15 (17.44%)	
Tumor size (cm)			0.807
≤2	32 (37.21%)	31 (36.05%)	
2–4	34 (39.53%)	34 (39.53%)	
>4	13 (15.12%)	13 (15.12%)	
Unknown	7 (8.14%)	8 (9.30%)	

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Supplementary Table 2. Characteristics of regional PDAC patients underwent surgery without adjuvant therapy after PSM.

Characteristics	1992–1996 (n=283)	2010–2014 (n=283)	P value
Gender			0.801
Male	143 (50.53%)	146 (51.59%)	
Female	140 (49.47%)	137 (48.41%)	
Age (years)			0.776
≤50	15 (5.30%)	18 (6.36%)	
51–70	147 (51.94%)	145 (51.24%)	
>70	121 (42.76%)	120 (42.40%)	
Race			0.936
White	239 (84.45%)	240 (84.81%)	
Black	30 (10.60%)	27 (9.54%)	
Other	14 (4.95%)	16 (5.65%)	
Primary tumor location			0.937
Head	252 (89.05%)	252 (89.05%)	
Body or tail	12 (4.24%)	11 (3.89%)	
Other	19 (6.71%)	20 (7.07%)	
Histologic grade			0.890
Well/moderately differentiated	174 (61.48%)	175 (61.84%)	
Poor differentiated/undifferentiated	91 (32.16%)	91 (32.16%)	
Unknown	18 (6.36%)	17 (6.01%)	
Regional nodes positive			0.874
Negative	111 (39.22%)	112 (39.58%)	
Positive	165 (58.30%)	165 (58.30%)	
Not checked	7 (2.47%)	6 (2.12%)	
Tumor size (cm)			0.906
≤2	49 (17.31%)	47 (16.61%)	
2–4	160 (56.54%)	161 (56.89%)	
>4	65 (22.97%)	67 (23.67%)	
Unknown	9 (3.18%)	8 (2.83%)	
Extension			1.000
Mild	23 (8.13%)	23 (8.13%)	
Grievous	260 (91.87%)	260 (91.87%)	

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Supplementary Table 3. Characteristics of localized PDAC patients with chemotherapy after PSM.

Characteristics	1992–1996 (n=82)	2010–2014 (n=82)	P value
Gender			1.000
Male	46 (56.10%)	46 (56.10%)	
Female	36 (43.90%)	36 (43.90%)	
Age (years)			0.752
≤50	0 (0.00%)	0 (0.00%)	
51–70	32 (39.02%)	34 (41.46%)	
>70	50 (60.98%)	48 (58.54%)	
Race			0.860
White	70 (85.37%)	69 (84.15%)	
Black	10 (12.20%)	11 (13.41%)	
Other	2 (2.44%)	2 (2.44%)	
Primary tumor location			0.834
Head	59 (71.95%)	60 (73.17%)	
Body or tail	10 (12.20%)	10 (12.20%)	
Other	13 (15.85%)	12 (14.63%)	
Histologic grade			0.794
Well/moderately differentiated	25 (30.49%)	26 (31.71%)	
Poor differentiated/undifferentiated	13 (15.85%)	14 (17.07%)	
Unknown	44 (53.66%)	42 (51.22%)	
Surgery			0.823
Yes	11 (13.41%)	12 (14.63%)	
No	71 (86.59%)	70 (85.37%)	
Radiotherapy			1.000
Yes	56 (68.29%)	56 (68.29%)	
No	26 (31.71%)	26 (31.71%)	
Regional nodes examined			1.000
<15	81 (98.78%)	81 (98.78%)	
≥15	1 (1.22%)	1 (1.22%)	
Regional nodes positive			0.809
Negative	9 (10.98%)	10 (12.20%)	
Not checked	73 (89.02%)	72 (87.80%)	
Tumor size (cm)			0.864
≤2	6 (7.32%)	7 (8.54%)	
2–4	33 (40.24%)	33 (40.24%)	
>4	25 (30.49%)	24 (29.27%)	
Unknown	18 (21.95%)	18 (21.95%)	

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Supplementary Table 4. Characteristics of regional PDAC patients with chemotherapy after PSM.

Characteristics	1992–1996 (n=538)	2010–2014 (n=538)	P value
Gender			0.808
Male	270 (50.19%)	266 (49.44%)	
Female	268 (49.81%)	272 (50.56%)	
Age (years)			0.526
≤50	37 (6.88%)	46 (8.55%)	
51–70	334 (62.08%)	328 (60.97%)	
>70	167 (31.04%)	164 (30.48%)	
Race			0.413
White	472 (87.73%)	463 (86.06%)	
Black	44 (8.18%)	49 (9.11%)	
Other	22 (4.09%)	26 (4.83%)	
Primary tumor location			0.318
Head	428 (79.55%)	416 (77.32%)	
Body or tail	44 (8.18%)	45 (8.36%)	
Other	66 (12.27%)	77 (14.31%)	
Histologic grade			0.512
Well/moderately differentiated	207 (38.48%)	222 (41.26%)	
Poor differentiated/undifferentiated	125 (23.23%)	114 (21.19%)	
Unknown	206 (38.29%)	202 (37.55%)	
Surgery			0.608
Yes	182 (33.83%)	190 (35.32%)	
No	356 (66.17%)	348 (64.68%)	
Radiotherapy			0.823
Yes	426 (79.18%)	423 (78.62%)	
No	112 (20.82%)	115 (21.38%)	
Regional nodes examined			0.152
<15	492 (91.45%)	478 (88.85%)	
≥15	46 (8.55%)	60 (11.15%)	
Regional nodes positive			0.966
Negative	66 (12.27%)	67 (12.45%)	
Positive	152 (28.25%)	151 (28.07%)	
Not checked	320 (59.48%)	320 (59.48%)	
Tumor size (cm)			0.475
≤2	39 (7.25%)	30 (5.58%)	
2–4	217 (40.33%)	211 (39.22%)	
>4	179 (33.27%)	198 (36.80%)	
Unknown	103 (19.14%)	99 (18.40%)	
Extension			1.000
Mild	35 (6.51%)	35 (6.51%)	
Grievous	503 (93.49%)	503 (93.49%)	

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Supplementary Table 5. Characteristics of localized PDAC patients with radiotherapy after PSM.

Characteristics	1992–1996 (n=78)	2010–2014 (n=78)	P value
Gender			0.874
Male	39 (50.00%)	38 (48.72%)	
Female	39 (50.00%)	40 (51.28%)	
Age (years)			0.741
≤50	0 (0.00%)	0 (0.00%)	
51–70	29 (37.18%)	27 (34.62%)	
>70	49 (62.82%)	51 (65.38%)	
Race			0.849
White	68 (87.18%)	66 (84.62%)	
Black	8 (10.26%)	11 (14.10%)	
Other	2 (2.56%)	61 (1.28%)	
Primary tumor location			0.904
Head	62 (79.49%)	62 (79.49%)	
Body or tail	7 (8.97%)	8 (10.26%)	
Other	9 (11.54%)	8 (10.26%)	
Histologic grade			0.789
Well/moderately differentiated	23 (29.49%)	25 (32.05%)	
Poor differentiated/undifferentiated	13 (16.67%)	12 (15.38%)	
Unknown	42 (53.85%)	41 (52.56%)	
Surgery			1.000
Yes	10 (12.82%)	10 (12.82%)	
No	68 (87.18%)	68 (87.18%)	
Chemotherapy			0.852
Yes	59 (75.64%)	60 (76.92%)	
No	19 (24.36%)	18 (23.08%)	
Regional nodes examined			1.000
<15	77 (98.72%)	77 (98.72%)	
≥15	1 (1.28%)	1 (1.28%)	
Regional nodes positive			1.000
Negative	8 (10.26%)	8 (10.26%)	
Not checked	70 (89.74%)	70 (89.74%)	
Tumor size (cm)			0.856
≤2	8 (10.26%)	6 (7.69%)	
2–4	39 (50.00%)	43 (55.13%)	
>4	17 (21.79%)	17 (21.79%)	
Unknown	14 (17.95%)	12 (15.38%)	

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Supplementary Table 6. Characteristics of regional PDAC patients with radiotherapy after PSM.

Characteristics	1992–1996 (n=466)	2010–2014 (n=466)	P value
Gender			0.432
Male	225 (48.28%)	237 (50.86%)	
Female	241 (51.72%)	229 (49.14%)	
Age (years)			1.000
≤50	32 (6.87%)	30 (6.44%)	
51–70	288 (61.80%)	292 (62.66%)	
>70	146 (31.33%)	144 (30.90%)	
Race			0.203
White	416 (89.27%)	403 (86.48%)	
Black	34 (7.30%)	42 (9.01%)	
Other	16 (3.43%)	21 (4.51%)	
Primary tumor location			0.961
Head	372 (79.83%)	372 (79.83%)	
Body or tail	41 (8.80%)	40 (8.58%)	
Other	53 (11.37%)	54 (11.59%)	
Histologic grade			0.797
Well/moderately differentiated	179 (38.41%)	187 (40.13%)	
Poor differentiated/undifferentiated	103 (22.10%)	94 (20.17%)	
Unknown	184 (39.48%)	185 (39.70%)	
Surgery			0.891
Yes	162 (34.76%)	160 (34.33%)	
No	304 (65.24%)	306 (65.67%)	
Chemotherapy			0.306
Yes	419 (93.95%)	428 (91.85%)	
No	47 (6.05%)	38 (8.15%)	
Regional nodes examined			0.817
<15	424 (90.99%)	426 (91.42%)	
≥15	42 (9.01%)	40 (8.58%)	
Regional nodes positive			0.817
Negative	58 (12.45%)	59 (12.66%)	
Positive	136 (29.18%)	129 (27.68%)	
Not checked	272 (58.37%)	278 (59.66%)	
Tumor size (cm)			0.761
≤2	33 (7.08%)	31 (6.65%)	
2–4	192 (41.20%)	188 (40.34%)	
>4	154 (33.04%)	160 (34.33%)	
Unknown	87 (18.67%)	87 (18.67%)	
Extension			0.772
Mild	26 (5.58%)	24 (5.15%)	
Grievous	440 (94.42%)	442 (94.85%)	

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