J Gastrointest Surg (2011) 15:1026–1034
DOI 10.1007/s11605-011-1493-y

ORIGINAL ARTICLE

Improvement in Treatment and Outcome of Pancreatic Ductal Adenocarcinoma in North China

Yong Chen · JiHui Hao · WeiDong Ma · Yong Tang · ChunTao Gao · XiShan Hao

Received: 20 January 2011 / Accepted: 21 March 2011 / Published online: 12 April 2011

Abstract
Background The incidence of pancreatic cancer has increased in China in the last decade, though efforts have been made in early detection and multimodality treatment. The aim of this study is to describe the decade-based development in early diagnosis and treatment modalities, as well as outcome for patients with pancreatic ductal adenocarcinoma (PDAC) in a high-volume facility.
Methods All the PDAC patients underwent surgery between 1991 and 2009 and were selected from the database of TianJin Cancer Institute and Hospital. Decade-based changes in early diagnosis, treatment modalities, and outcome of the patients were retrospectively analyzed.
Results Of the 565 patients with PDAC, patients in this decade (n=460) had better overall survival than those in the last decade (n=105), median survival was 10 months and 3 months, respectively. Patients in this decade had significantly improved in (P<0.001) 2-year (14.7%) and 5-year survival rates (3.5%) as compared to those in the last decade (6.7% and 3.4%, respectively). Patients with metastasis at diagnosis in the last decade and this decade were 54% and 26% (P<0.001), respectively. More patients in this decade had underwent R0/R1 resection (33% vs 20%, P=0.010), chemotherapy (37% vs 12%, P<0.001), and radical resection (34% vs 21%, P=0.014) than those in the last decade.
Conclusion Patients operated on for PDAC in this decade had a better outcome than those in the last decade. Early detection, improved resection margin, and development in multimodality treatment contribute to this improvement.

Keywords PDAC · Decade · Surgery type · Outcome

Introduction

Pancreatic cancer ranked 13th in the list of most commonly diagnosed cancers and was the fifth most common cause of cancer death in China in 2006.[1] The 5-year survival rate for all pancreatic cancer patients is below 5%.[2] Among the various subtypes of pancreatic cancer, pancreatic ductal adenocarcinoma (PDAC) is by far the most common and most important tumor type, accounting for more than 85% of pancreatic tumors.[3] Surgical removal of the tumor with negative resection margins remains to be the most potentially curative therapy.[3,4] Late presentation and fear of perioperative mortality[5] have left only a minority of patients amenable to curative resection[6] in the last decade. Efforts have been made towards early detection with biomarkers and advanced imaging techniques such that perioperative outcome has been markedly improved within the past two decades due to advances in both surgical technique and perioperative care.[7,8] Today, pancreas resection can be performed in more than 20% of pancreas cancer patients with localized disease resulting in a very low mortality rate (below 5%)[7–9] and producing a 5-year survival rate that exceeds 20% with adjuvant therapy.[10,11]

JiHui Hao contributed equally with Yong Chen.

Grant support National Natural Science Foundation of China (30701013, 30900596, 30973490, 30901448).

Y. Chen · X. Hao (✉)
Key Laboratory of Cancer Prevention and Therapy,
Huanhu Xi road, Hexi district, Tianjin 300060, China
e-mail: Haoxishan1950@gmail.com

J. Hao · W. Ma · Y. Tang · C. Gao
Department of Pancreatic Cancer,
Tianjin Medical University Cancer Institute and Hospital,
Tianjin 300060, China

With the development of diagnostic capacity and environmental influence, the incidence of PDAC in China has increased in the past several decades.[1,12] Though highly specialized centers for pancreatic cancers were built up with skilled surgical oncologists and experienced multimodality physicians, the improvement in treatment modalities and patients' outcomes have not yet been delineated. The purpose of this study is to investigate the decade-based improvement in diagnosis modalities and surgical treatment, and to compare the different outcomes in the same cancer center between two decades.

Materials and Methods

Retrospectively collected patient data from Tianjin Medical University Cancer Institute and Hospital was used to identify all patients with PDAC that underwent surgical treatment (n=565). Clinical variables include age at diagnosis, gender, serum CA-199, preoperative bilirium, site, American Joint Committee on Cancer (AJCC) stage,[13] perioperative blood transfusion, and hospital stay. Pathologic characteristics included tumor size, French Federation of Cancer Centres (FNCLCC) grade,[14] Union Internationale Contre Cancer (UICC) margin,[15] lymph nodes invasiveness (LNI), vascular involvement (VI), and perineural involvement (PNI).

Treatment modalities included the surgical procedures, radiation therapy, and neoadjuvant/adjuvant chemotherapy. All patients underwent surgical treatment, the surgical type included radical resection (n=179) and palliative surgery (n=386). Radical resection is an intraoperative evaluation which refers to an extensive en bloc resection of the tumor and surrounding tissues, as well as lymph drainage and vascular structures. Patients with operable diseases (n=132) were assigned to radical resection, patients with inoperable lesions were assigned either to neoadjuvant chemotherapy (n=156) or palliative surgery (n=277). Neoadjuvant chemotherapy was based on 5-Fu in the last decade and gemcitabine in this decade, including CF, CDDP, and paclitaxel, single dose or combined for 2 to 4 cycles. After neoadjuvant chemotherapy, the lesions were reassessed for resectability by surgical oncologists (JH H and XS H) with comparable pre- and post-neoadjuvant chemotherapy, computed tomography, or magnetic resonance imaging. After the reassessment, patients with operable lesions were assigned to radical resection (n=47) with postoperative chemotherapy of same regimen; patients with inoperable lesions (n=109) were treated with palliative procedures. All the pre- and post-adjuvant chemotherapy images were reviewed to identify borderline resectable lesions; their actual treatments depending on patients' preference were recorded.

SPSS 13.0 statistical software (SPSS, Chicago, IL, USA) was used for statistical analysis, the following variables were considered for their prognostic value: age at diagnosis, sex, tumor site, tumor size, AJCC stage, surgical type, blood transfusion, hospital stay, UICC margin, FNCLCC grade, chemotherapy, PNI, and vascular involvement. Univariate and multivariate analyses were carried out for overall survival (OS). Survival curves were computed by the Kaplan–Meier[16] method and compared by the log-rank test. Multivariate analyses based on the stepwise Cox[17] proportional hazards model were used to identify the most significant factors related to outcome. A stepwise forward selection procedure was used and a significance level of 5% was chosen as the criterion for entering factors in the multivariate model.

Results

Clinical, Pathologic, and Treatment Variable

All 565 patients underwent surgical treatment for radical or palliative purpose, clinical, pathologic, and treatment variables and their distribution for decades are listed in Table 1. The median follow-up for survivors was 6 months (range, 0–156 months). There were 359 (63.5%) males and 206 (36.5%) females with a median age of 61.0 years (range, 24–88 years). The median tumor size was 4.0 cm (range, 0.8–18 cm). At the time of diagnosis, the tumor stages according to AJCC staging system were as follows: I, 77 patients; II, 172 patients; III, 136 patients, and IV, 176 patients. Local invasiveness of tumor were confirmed by intraoperative exploration or postoperative pathological examination, 166 patients had vascular involvement, either in the artery or vein or both. Ninety-three patients had lymph node involvement and 34 patients had PNI.

Carbohydrate cantigen 19-9 (CA19-9) was investigated with a cutoff level of 30 U/L in 463 patients. Two hundred sixty-four patients had a positive CA19-9 with a sensitivity of 57.0%. In those with both CA19-9 and tumor size records (n=289), CA19-9 was positive in 170 patients, and most of them (163/170, 95.9%) had a primary tumor of over 2 cm. Of 552 patients that had a preoperative bilirium test, patients with preoperative bilirium of less than 200 U/L, between 200 and 300 U/L, and over 300 U/L were 372 (372/552, 67.4%), 85 (85/552, 15.4%), and 95 (95/552, 17.2%), respectively.

Palliative resection and exploratory laparotomy were assigned to be R2 resections. Of the 179 patients submitted to radical resection, resection was grossly complete (R0/R1) in 171 patients (94.4%), seven patients (10%) had a tumor rupture intraoperatively (R2), and one patient had missing data. Forty-eight of the 179 patients had undergone a

Table 1 Relationship between decades and clinical, pathologic, treatment parameters

Issues	Categories	All	Between 1990 and 2000	Between 2000 and 2009	χ^2	*P*
N		565	105	460		
Age (*n*=565)	≥50	458	70	388	17.409	<0.001
	<50	107	35	72		
Sex (*n*=565)	Male	359	70	289	0.544	0.461
	Female	206	35	171		
Site (*n*=565)	Head	502	97	405	1.623	0.203
	Body or tail	63	8	55		
Size (cm) (*n*=399)	≥2	387	77	310	2.959	0.085
	<2	12	0	12		
FNCLCC grade (*n*=30,918)	G1	54	19	35	0.147	0.701
	G2	68	3	65		
	G3	67	14	53		
	Gx	129	23	97		
UICC margin (*n*=5,567)	R0+R1	171	21	150	6.637	0.010
	R2	386	83	303		
Radiotherapy (*n*=565)	Yes	14	1	13	1.242	0.265
	No	551	104	447		
Chemotherapy (*n*=565)	Yes	184	13	171	23.928	<0.001
	No	381	92	289		
AJCC stage (*n*=565)	I–II	252	44	208	0.322	0.570
	III–IV	313	61	252		
Surgery type (*n*=565)	Radical	179	22	157	10.679	0.014
	Palliative	303	61	242		
	Exploratory	83	22	61		
PB (*n*=552)	<200	372	79	293	4.288	0.117
	200–300	85	12	73		
	>300	95	13	82		
CA199 (*n*=436)	Positive	264	4	260	113.465	<0.001
	Negative	172	70	102		
PNI (*n*=358)	Yes	34	6	28	0.247	0.619
	No	324	69	255		
VI (*n*=400)	Yes	166	31	135	0.207	0.649
	No	234	48	186		
LNI (*n*=398)	Yes	93	22	71	0.955	0.328
	No	305	58	247		
MAD (*n*=561)	Yes	176	57	119	31.500	<0.001
	No	385	48	337		
Blood tranfusion	Mean[a]	1.4 U	2.4 U	1.2 U	11.740	0.001
	Yes	164	46	118	13.657	<0.001
	No	401	59	342		
Hospital stay	Mean[b]	29.6	32.5	29.0	9.909	0.002
	<4 weeks	287	41	246	7.110	0.008
	>4 weeks	278	64	214		

FNCLCC Fédération Nationale des Centres de Lutte Contre le Cancer, *UICC* International Union Against Cancer, *AJCC* American Joint Committee on Cancer, *PB* preoperative bilirium, *PNI* perineural involvement, *VI* vascular involvement, *LNI* lymph node involvement, *MAD* metastasis at diagnosis

[a] Blood transfusion expressed as mean, F=11.740, P=0.001

[b] Hospital stay expressed as mean, F=9.909, P=0.002 (ANOVA test)

vascular resection and reconstruction; 28 patients had extended lymphadenectomy.

Neoadjuvant chemotherapy was performed in 156 patients with locally advanced or disseminated diseases,

after neoadjuvant treatment, 30.1% (47/156) of them underwent radical resection. One hundred eight-four (184/565, 32.6%) patients were treated with adjuvant chemotherapy. Adjuvant chemotherapy was administered after radical resection, palliative resection, and exploratory laparotomy in 82, 73, and 29 patients, respectively. Chemotherapy agents included 5-Fu, CF, CDDP, gemcitabine, and HCPT, single or combined for at least 2 cycles. Fourteen patients underwent postoperative radiotherapy.

Of the 565 patients, 164 underwent perioperative blood transfusion of a mean amount of 1.4 U. Blood transfusion was required in 45.3% (81/179) of patients who underwent radical resection, while this number decreased to 31.5% in patients with other procedures. All the 565 patients had a mean hospital stay of 29.6 days, and expectantly, patients with radical resections had a significantly longer hospital stay than those with non-radical resection (P=0.002, mean 31.6 days vs 28.7 days).

A Decade-Based Analysis of Early Diagnosis and its Impact on Outcomes

Of all 565 patients, 2-year and 5-year overall survival was 13.5% and 3.6%, respectively. AJCC stage was associated with OS, 2-year and 5-year OS was 38.0% and 8.8% for stage I, 13.2% and 2.6% for stage II, 8.1% and 1.6% for stage III, and 6.7% and 0% for stage IV, respectively (P< 0.001). More patients (208/460, 45.2%) operated on for PDAC in this decade had a stage I/II disease at diagnosis than those (44/105, 40.3%) in the last decade. Furthermore, fewer patients (119/460, 26.1%) operated on for PDAC in this decade were at their terminal stage compared to those (57/105, 54.3%) in the last decade (P<0.001) (Table 1). Patients with stage I/II PDAC in this decade had a significantly longer median survival of 14 months compared to those of 4 months in last decade (P<0.001). Accordingly, patients with stage III/IV PDAC in this decade had a significantly longer median survival of 6 months compared to those of 3 months in last decade (P<0.001) (Fig. 1a).

A Decade-Based Analysis of Clinical and Pathological Variables Predictive of Outcome

Patients of the two decades had similar tumor sites (P= 0.203), sizes (P=0.085), grades (P=0.701), stages (P= 0.570), PNIs (P=0.619), VIs (P=0.649), and LNIs (P= 0.328). Tumor site was an important prognostic factor (Fig. 1b). The 2-year and 5-year OS was 31.4% and 12.6% in patients with a tumor in pancreas body and tail, which was significantly different from 11.2% and 2.0% in those with a tumor in the pancreas head (P<0.001) (Table 2). Of all 565 patients, FNCLCC grade was a strong prognostic factor for OS (Fig. 1c), 2-year and 5-year OS was 24.3% and 4.0% for grade 1, 19.4% and 0% for grade 2, and 10.8% and 3.6% for grade 3, respectively (P=0.003) (Table 2). PDAC patients with normal CA19-9 had a poorer prognosis. Two-year and 5-year OS was 18.5% and 4.4% in patients with positive CA19-9 (n=264) compared to 9.7% and 2.2% in those with normal CA19-9 (n=172), respectively (P=0.001). But in this decade, CA19-9 did not seem to be significantly associated with prognosis. Median survival in 260 patients with positive CA19-9 was 10 months, which was similar (P=0.694) to 11 months in 102 patients with normal CA19-9, indicating that a more sensitive cutoff value should be investigated for prognostic purpose.

More patients underwent operation for PDAC in this decade (150/453, 33.1%) had a R0/R1 resection than those in the last decade (21/104, 20.2%, P=0.010). R0/R1 resection was significantly associated with improved OS compared to R2 resection, 2-year and 5-year OS in patients with R0/R1 margin was 29.6% and 6.1%, while in patients with R2 resection, they were 6.7% and 2.6%, respectively (P<0.001) (Fig. 1d).

We further identified that LNI was also associated with poorer prognosis in PDAC patients (Fig. 1e), as patients without LNI had a median survival of 11 months, which was significantly longer than LNI patients of 5 months (P= 0.005). PNI was not associated with OS (P=0.803) as indicated in Table 2, but VI was significantly associated with poor prognosis in PDAC patients (Fig. 1f). In 400 patients who had detailed information of vascular status, median OS in patients with VI (n=166) was 9 months, compared to 12 months in those without (n=234, P=0.013).

Blood transfusion was recognized as a prognostic factor for PDAC,[18] though not universally accepted.[19,20] We next investigated blood transfusion in the 565 patients. For all surgical procedures, blood transfusion was required in 43.8% (46/105) of patients in the last decade with a mean amount of 2.4 U, but it fell to 25.7% (118/420) and 1.2 U in this decade (Table 1). Though blood transfusion was not prognostic for survival in all patients (Table 2), it was of prognostic value in the subset of patients who underwent radical resection (P=0.032). Decade-based analysis indicated that requirement of blood transfusion for radical resection was significantly higher (P=0.001) in the last decade (77.3%, 17/22) than that in this decade (40.7%, 64/157).

Hospital stay reflects the capacity of multidisciplinary care in specialized high-volume centers. The mean hospital stay in the last decade was significantly longer than that in this decade (mean 32.5 days vs 29.0 days, P=0.002). Patients with radical resection had a significantly longer hospital stay than those with other procedures, indicating reasonably that more aggressive surgeries necessitate longer postoperative recovery.

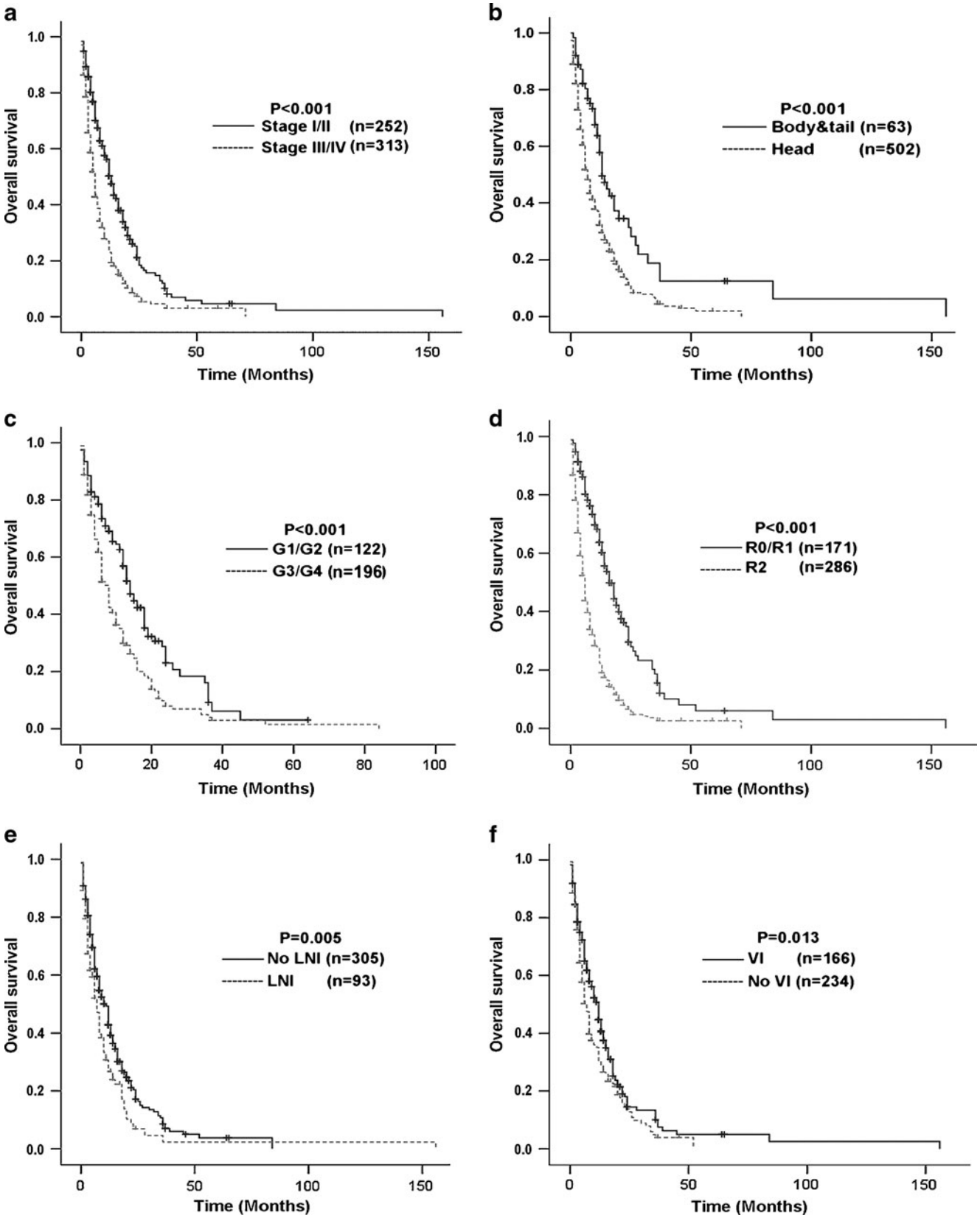

Fig. 1 The curves of overall survival in patients according to clinical and pathological parameters. **a** tumor site; **b** AJCC stage; **c** FNCLCC grade; **d** UICC margin; **e** lymph node involvement; **f** vascular involvement

Table 2 Univariate and multivariate analysis of variable factors for OS

Factors		Survival rate		Univariate analysis			Multivariate analysis		
		2 years	5 years	HR	95% CI	*P*	HR	95% CI	*P*
Age	≥50 (*n*=458)	12.9	1.8	1.252	0.981–1.597	0.059			
	<50 (*n*=107)	15.5	9.8	1					
Sex	Male (*n*=359)	10.6	3.1	1		0.197			
	Female (*n*=206)	18.2	4.7	0.884	0.726–1.075				
Site	Head (*n*=502)	11.2	2.0	1.915	1.384–2.649	<0.001	1.501	1.057–2.134	0.023
	Body/tail (*n*=63)	31.4	12.6	1			1		
FNCLCC grade	G1/G2 (*n*=122)	23.0	3.1	1		0.001	1		0.012
	G3/Gx (*n*=18,796)	9.7	1.5	1.723	1.318–2.252		1.414	1.081–1.851	
UICC margin	R0+R1 (*n*=171)	29.6	6.1	1		<0.001	1		<0.001
	R2 (*n*=386)	6.7	2.6	1.604	1.432–1.795		1.555	1.322–1.828	
Chemotherapy	Yes (*n*=184)	24.8	4.7	1		<0.001	1		<0.001
	No (*n*=381)	7.7	3.1	2.116	1.715–2.610		2.176	1.700–2.786	
AJCC stage	I–II (*n*=252)	21.2	4.6	1		<0.001	1		<0.001
	III–IV (*n*=313)	7.4	3.1	1.907	1.572–2.314		1.810	1.407–2.329	
Surgery type	Radical (*n*=179)	29.8	5.5	1		<0.001	1		<0.001
	Nonradical (*n*=386)	6.4	2.7	2.512	2.016–3.129		2.674	2.101–3.403	
VI	Yes (*n*=166)	13.8	0	1.315	1.049–1.648	0.013	1.002	0.777–1.292	0.988
	No (*n*=234)	14.5	5.0	1			1		
VR	Yes (*n*=48)	34.9	0	1		<0.001	1		<0.001
	No (*n*=118)	6.6	2.6	2.710	1.786–4.114		2.788	1.811–4.292	
LNI	Yes (*n*=93)	6.9	2.3	1.425	1.099–1.847	0.005	1.325	1.015–1.731	0.038
	No (*n*=305)	17.1	3.7	1			1		
EL	Yes (*n*=28)	20.9	10.4	1		<0.001	1		<0.001
	No (*n*=65)	1.9	0	2.926	1.690–5.066		2.868	1.648–4.991	
MAD	Yes (*n*=176)	6.7	0	1.827	1.500–2.226	<0.001	1.448	1.097–1.912	0.009
	No (*n*=389)	16.6	3.5	1			1		
Blood transfusion	Yes (*n*=164)	13.8	2.6	0.977	0.797–1.198				
	No (*n*=401)	13.4	4.5	1					

FNCLCC Fédération Nationale des Centres de Lutte Contre le Cancer, *UICC* International Union Against Cancer, *AJCC* American Joint Committee on Cancer, *PB* preoperative bilirium, *PNI* peri-neural involvement, *VI* vascular involvement, *VR* vascular reconstruction, *LNI* lymph node involvement, *EL* extended lymphadenectomy, *MAD* metastasis at diagnosis

A Decade-Based Analysis of Treatment Variables Predictive of Outcome

Of the 565 patients, more patients (157/460, 34.1%) operated for PDAC in this decade underwent a radical resection than those in last decade (22/105, 21.0%, $P=0.014$). Surgery type was significantly associated with OS (Fig. 2a); 2-year and 5-year OS in patients with radical resection was 29.8% and 5.5%, while in patients with non-radical resection, they were 6.4% and 2.7%, respectively ($P<0.001$). Neoadjuvant chemotherapy increased the rate of radical resection in patients with inoperable diseases (47/156 vs 8/277, $P<0.001$), and this increase was even more dominant in this decade, 36.2% (46/127) of the patients who underwent neoadjuvant chemotherapy for their inoperable diseases were able to have radical resection, indicating that the emergency of first-line gemcitabine for PDAC might have contributed to this improvement.

Similarly, of all 565 patients, more patients in this decade (171/460, 37.2%) underwent adjuvant chemotherapy than those in the last decade (13/105, 12.4%, $P<0.001$). Adjuvant chemotherapy was significantly associated with improved OS in PDAC patients; 2-year and 5-year OS in patients with chemotherapy was 24.8% and 4.7%, while in those without, they were 7.7% and 3.1%, respectively ($P<0.001$, Fig. 2b). Vascular resection and reconstruction performed for the purpose of radical resection mostly occurred in this decade (1/31 vs 47/135, $P<0.001$), with a single artery reconstruction in five, single venous reconstruction in 17, and both in 26. Of the 176 patients with radical resection who had a record of VI status, vascular reconstruction had no significant impact on survival; 2-year

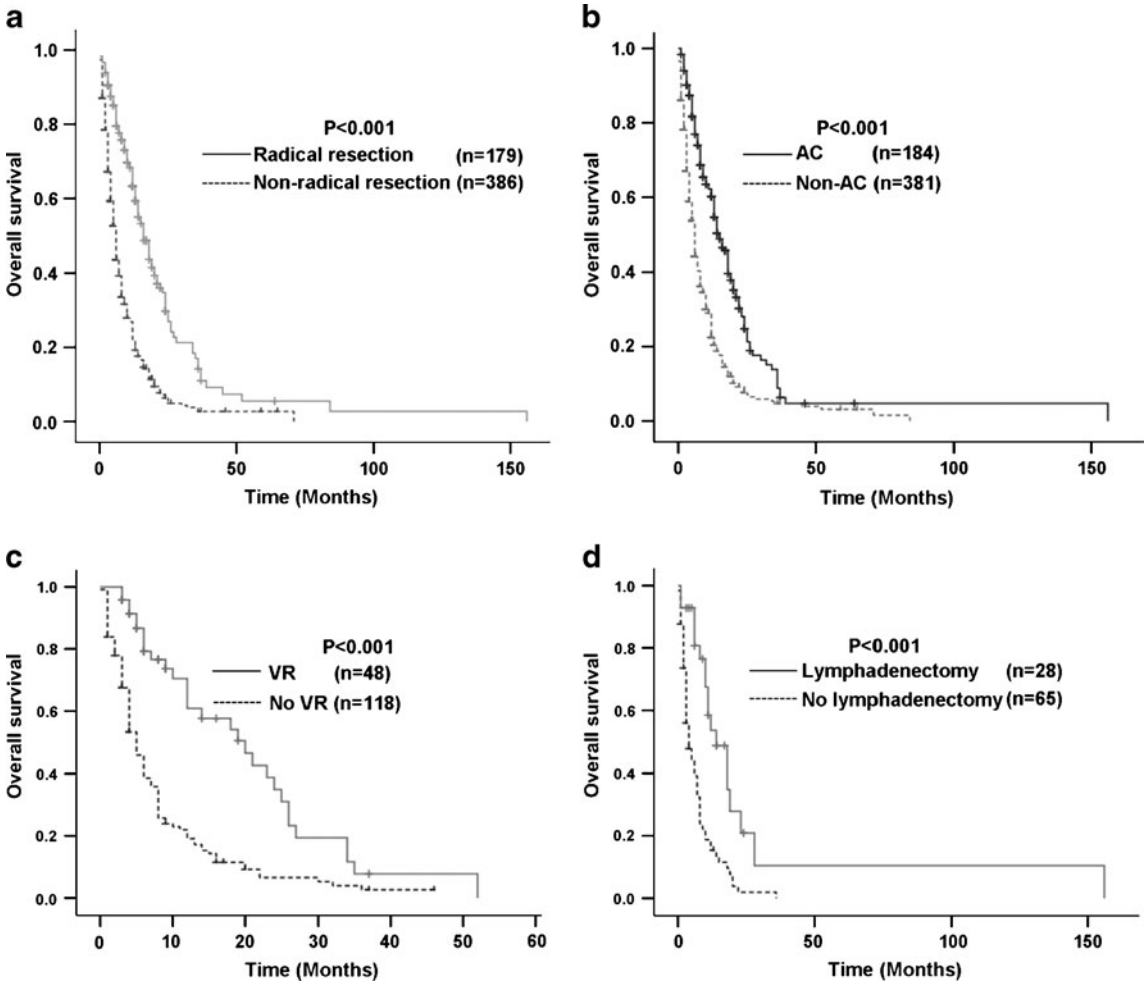

Fig. 2 The curves of overall survival in patients according to treatment variables. **a** surgery type; **b** adjuvant chemotherapy; **c** vascular reconstruction; **d** extended lymphadenectomy

and 5-year OS was 34.9% and 7.8% in patient with vascular reconstruction, which was similar to 27.0% and 8.4% in those without (P=0.686). But in all patients with VI, vascular reconstruction was significantly associated with improved OS, as patients with vascular reconstruction had a 2.7-fold decreased risk of death compared to those without (95% CI: 1.786–4.114, P<0.001, Fig. 2c). Twenty-eight patients underwent extended lymphadenectomy because of LNI, this was performed more in this decade (24/71, 33.8%) than in last decade (4/22, 18.2%). Of all 93 patients who had an LNI, extended lymphadenectomy was significantly associated with improved OS (Fig. 2d) and patients with extended lymphadenectomy had a 2.9-fold (95% CI: 1.690–5.066, P<0.001) of decreased risk of death compared to those without.

Discussion

Pancreatic adenocarcinoma is one of the leading causes of death due to cancer, with the lowest survival rate.[21] Difficulty in diagnosing the disease at an early stage is the major obstacle for improving the outcome in PDAC patients.[22] Current methods for early diagnosis are often ineffective and/or inaccurate, especially in identifying smaller, potentially curable lesions.[23] In our study, we detected that in patients with tumor size no more than 3 cm, the sensitivity of CA19-9 was only 57.0%, and its positive accuracy was also limited (63/93, 67.7%). Though it was a little higher than Steinberg's reports of 55% 20 years ago,[24] these unsatisfactory results indicated the limited predictive value of CA19-9 in detecting PDAC at early stage cancer, and necessitated other biomarkers and genetic markers to be used as a panel in combination with other modalities for early detection with high sensitivity and specificity in PDAC patients.[25]

Postoperative margin status in PDAC patients has been reported by various authors to be a prognostic factor associated with survival.[26–29] In our study, patients with R2 resection had a 1.60-fold of increased risk of death compared to those with R0/R1 resection (P<0.001). We

concluded here that the grossly total resection of tumor should be the primary goal in attempting a resection. R0/R1 resection was more common in this decade, indicating that more patients were resectable at diagnosis and that surgical techniques have improved in this high-volume center. Furthermore, patients with vascular involvement in our study benefited from vascular reconstruction, which was performed for the purpose of radical resection without extra morbidity. Some outcomes were satisfactorily extended, as vascular reconstruction had improved radical resection rate in patients with vascular involvement and subsequently improved survival. This is in accordance with previous reports that vascular reconstruction might provide a negative surgical margin and better survival in patients with locally advanced pancreatic cancer.[30,31] Similarly, more vascular reconstruction was performed in this decade, indicating that the procedures are complicated challenges to surgical oncologists, who should be surgically skilled in high-volume center with experience in perioperative care.

With awareness of surgical techniques and their impact on survival, surgical oncologists have improved survival in PDAC patients significantly in recent years,[32,33] but inoperable diseases remain to be the main cause of mortality. In our study, 47 patients were downstaged from inoperable PDAC to radical resections, and most of the downstage occurred to gemcitabine-based neoadjuvant chemotherapy in this decade. With increasing data supporting neoadjuvant chemotherapy in borderline resectable PDAC patients,[34,35] we now routinely recommend gemcitabine-based regimen for patients with inoperable PDACs.

Unfortunately, even an R0 resection will not guarantee long-term survival, and many patients will eventually have local and/or system failure and ultimately die of disease progression.[36,37] Therefore, the use of adjuvant therapy is a logical strategy for systemic disease and survival. Gemcitabine has proven to be essential in the management of advanced pancreatic cancer for clinical benefit and OS improvement in 1997.[38] Updated data from the CONKO-001 trial definitively ascertain the value of adjuvant chemotherapy and provide level 1 evidence supporting the use of adjuvant chemotherapy for patients with resected PDA.[11] In our study, median survival in patients with adjuvant chemotherapy was significantly longer than that in patients without (15 months vs 6 months, $P<0.001$). More patients underwent chemotherapy in this decade, reflecting that adjuvant chemotherapy has been recognized as an important component in treatment of PDA in this high-volume center.

The late presentation and poor response to chemotherapy has been the main obstacle in improving the outcome of PDAC patients. Sensitive and specific tumor markers are needed for patients to be diagnosed at an early, operable disease stage. To this point, CA glycoproteins are less satisfactory because of limited sensitivity and false-positives. Newly investigated genetic markers are still undergoing evaluation. Efficient evaluation of new markers of pancreatic neoplasia will benefit from recently completed pancreatic cancer genome[39] and require greater enrollment of patients with suspected pancreatic disease into clinical trials. These developments in early diagnosis of PDAC in this decade will undoubtedly increase the proportion of early disease and result in improved outcome in the coming decades. Also, with multiple genetic mutations being identified as the precursor to the development of pancreatic cancers and recognized as the target for therapeutic interventions,[40] with multiple immunotherapy and targeted therapy being investigated with encouraging results in different clinical trials,[41–44] and with high-volume centers being built worldwide, we believe that the results of treatment and outcome in PDAC patients in the next decade will be even more encouraging.

Acknowledgments We thank Dr. FengJu Song from the Department of Epidemiology for statistical assistance.

References

1. Song F, He M, Hao XS et al. (2008) A cancer incidence survey in Tianjin: the third largest city in China-between 1981 and 2000. Cancer Causes Control 19(5): 443–450.
2. Carpelan-Holmstrom M, Nordling S, Pukkala E, Sankila R, Lüttges J, Klöppel G, Haglund C. Does anyone survive pancreatic ductal adenocarcinoma? A nationwide study re-evaluating the data of the Finnish Cancer Registry. Gut 2005;54(3):385–387.
3. Parkin DM: International variation. Oncogene 2004;23:6329–6340.
4. Kleeff J, Michalski C, Friess H, Büchler MW. Pancreatic cancer: from bench to 5-year survival. Pancreas 2006;33(2):111–118.
5. Bramhall SR, Allum WH, Jones AG, Allwood A, Cummins C and Neoptolemos JP. Treatment and survival in 13,560 patients with pancreatic cancer, and incidence of the disease, in the West Midlands: an epidemiological study. Br J Surg 1995;82(1):111–115.
6. Niederhuber JE, Brennan MF, Menck HR. The national cancer data base report on pancreatic cancer. Cancer 1995;76(9):1671–1677.
7. Buchler MW, Wagner M, Schmied BM, Uhl W, Friess H and Z'graggen K. Changes in morbidity after pancreatic resection: toward the end of completion pancreatectomy. Arch Surg 2003;138(12): 1310–1314.
8. Cameron JL, Taylor SR, Coleman JA, Belcheret KA. One thousand consecutive pancreaticoduodenectomies. Ann Surg 2006;244(1): 10–15.
9. Winter JM, Cameron JL, Campbell KA et al. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. J Gastrointest Surg 2006;10(9):1199–1210.
10. Neoptolemos J, Stocken D, Freiss H et al. A randomised trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004;350:1200–1210.
11. Neuhaus P, Riess H, Post S et al. (2008) CONKO-001: final results of the randomized, prospective, multicenter phase III trial of adjuvant chemotherapy with gemcitabine versus observation in patients with resected pancreatic cancer (PC). J Clin Oncol 26 (May 20 suppl) (abstr LBA4504).
12. Li Q, Gao C, Li H, Juzi JT, Chen H, Hao X. Factors Associated with Survival after Surgical Resection in Chinese Patients with

Ductal Adenocarcinoma of the Pancreatic Head. Dig Surg 2008;25:87–92.
13. Greene FL, Compton CC, Fritz AG, Shan JP, Winchester DP (2002) American Joint Committee on Cancer, American Cancer Society. AJCC Cancer staging handbook: from the AJCC cancer staging manual 6th edition. Springer, New York
14. Kloppel G, Hruban RH, Longnecker DS. Ductal adenocarcinoma of the pancreas. In SR Hamilton, LA Aaltonen, (eds.) WHO Classification of Tumors: Pathology and Genetics of Tumors of the Digestive System. Lyon: IARC Press, 2000, pp221–230.
15. Sobin LH, Gospodarowicz MK, Wittekind C. Digestive system tumors. TNM Classification of malignant tumours. Wiley-Liss, New York, 2009, pp132–135.
16. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481.
17. Cox DR: Regression models and life-tables. J R Stat Soc B 1972; 34:187–220.
18. Millikan KW, Deziel DJ, Silverstein JC, Kanjo TM, Christein JD, Doolas A, Prinz RA. Prognostic factors associated with resectable adenocarcinoma of the head of the pancreas. Am Surg 1999;65:618–623.
19. Park SJ, Kim SW, Jang JY, Lee KU, Park YH. Intraoperative transfusion: is it a real prognostic factor of periampullary cancer following pancreatoduodenectomy? World J Surg 2002; 26:487–492.
20. Yeh JJ, Gonen M, Tomlinson JS, Idrees K, Brennan MF, Fong Y. Effect of blood transfusion on outcome after pancreaticoduodenectomy for exocrine tumour of the pancreas. Br J Surg 2007;94:466–472.
21. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E and Michael JT. Cancer statistics, 2003. CA Cancer J Clin 2003;53(1):5–26.
22. Esteller M, Hamilton SR, Burger PC, Baylin SB and Herman JG. Inactivation of the DNA repair gene O6-methylguanine-DNA methyltransferase by promoter hypermethylation is a common event in primary human neoplasia. Cancer Res 1999;59 (4):793–797.
23. Rosty C, Goggins M. Early detection of pancreatic carcinoma. Hematol Oncol Clin North Am 2002;16(1):37–52.
24. Tumour markers in gastrointestinal cancers—EGTM recommendations. European Group on Tumour Markers. Anticancer Res 1999;19 (4A):2811–2815.
25. AM Lennon, M Goggins (2010) Diagnostic and Therapeutic Response Markers. In: JP Neoptolemos, R Urrutia, JL Abbruzzese, MW Büchler. Pancreatic Cancer. Springer, New York; 676–691.
26. Kuhlmann KF, de Castro SM, Wesseling JG, et al. Surgical treatment of pancreatic adenocarcinoma; actual survival and prognostic factors in 343 patients. Eur J Cancer 2004;40(4):549–558.
27. Neoptolemos JP, Stocken DD, Dunn JA, et al. Influence of resection margins on survival for patients with pancreatic cancer treated by adjuvant chemoradiation and/or chemotherapy in the ESPAC-1 randomized controlled trial. Ann Surg 2001;234(6):758–68.
28. Kato K, Yamada S, Sugimoto H, et al. Prognostic factors for survival after extended pancreatectomy for pancreatic head cancer: influence of resection margin status on survival. Pancreas 2009;38(6):605–12.
29. Fatima J, Schnelldorfer T, Barton J, et al. Pancreatoduodenectomy for ductal adenocarcinoma: implications of positive margin on survival. Arch Surg. 2010;145:167–72.
30. Amano H, Miura F, Toyota N, et al. Is pancreatectomy with arterial reconstruction a safe and useful procedure for locally advanced pancreatic cancer? J Hepatobiliary Pancreat Surg. 2009;16(6):850–7.
31. Shimada K, Sano T, Sakamoto Y, Kosuge T. Clinical implications of combined portal vein resection as a palliative procedure in patients undergoing pancreaticoduodenectomy for pancreatic head carcinoma. Ann Surg Oncol. 2006;13:1569–1578.
32. Shaib Y, Davila J, Naumann C, El-Serag H. The impact of curative intent surgery on the survival of pancreatic cancer patients: a U.S. Population-based study. Am J Gastroenterol. 2007;102:1377–1382.
33. Wagner M, Redaelli C, Lietz M, Seiler CA, Friess H, Büchler MW. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. Br J Surg 2004;91:586–594.
34. Varadhachary GR, Tamm EP, Abbruzzese JL, et al. Borderline resectable pancreatic cancer: Definitions, management, and role of preoperative therapy. Ann Surg Oncol 2006;13(8):1035–1046.
35. Katz MH, Pisters PW, Evans DB, et al. Borderline resectable pancreatic cancer: The importance of this emerging stage of disease. J Am Coll Surg 2008;206(5):833–846.
36. Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. Recurrence after resection for ductal adenocarcinoma of the pancreas. World J Surg 1997;21:195–200.
37. Hishinuma S, Ogata Y, Tomikawa M, Ozawa I, Hirabayashi K, Igarashi S. Patterns of recurrence after curative resection of pancreatic cancer, based on autopsy findings. J Gastrointest Surg 2006;10: 511–518.
38. Burris HA, 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;15 (6):2403–2413.
39. Jones S, Zhang X, Parsons DW, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science 2008;321(5897):1801–1806.
40. Wong HH, Lemoine NR. Biological approaches to therapy of pancreatic cancer. Pancreatology 2008; 8:431–461.
41. Gjertsen MK, Buanes T, Rosseland AR, et al. Intradermal ras peptide vaccination with granulocytemacrophage colony-stimulating factor as adjuvant: Clinical and immunological responses in patients with pancreatic adenocarcinoma. Int J Cancer 2001;92:441–450.
42. Toubaji A, Achtar M, Provenzano M, et al. Pilot study of mutant ras peptide-based vaccine as an adjuvant treatment in pancreatic and colorectal cancers. Cancer Immunol Immunother 2008;57:1413–1420.
43. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007;25:1960–1966.
44. Melisi D, Ishiyama S, Sclabas GM, et al. LY2109761, a novel transforming growth factor b receptor type I and type II dual inhibitor, as a therapeutic approach to suppressing pancreatic cancer metastasis. Mol Cancer Ther 2008;7:829–840.