Intra-Ampullary Papillary-Tubular Neoplasm: A Population-Based Analysis

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Intra-ampullary papillary-tubular neoplasm (IAPN) is recognized as a precancerous lesion with a great tendency to evolve into pancreatic cancer. The Surveillance, Epidemiology, and End Results (SEER) database is now large enough to study unusual cancers. Based on pathologic and epidemiologic characteristics of IAPN available in SEER, important clinicopathological correlations can be made.

Material/Methods: Cases of IAPN and other intraductal papillary mucinous neoplasms of the bile duct (OBIPMN) diagnosed between 1973 and 2014 were searched in the SEER database. The analysis was carried out with respect to patient clinical characteristics, tumor characteristics, incidence, and survival.

Results: In total, 685 patients with IAPN were identified compared with 2465 patients with OBIPMN in the same period. The incidence rate of IAPN was decreased, with a 4.882% annual percent change. The patient characteristics of IAPN were quite different from OBIPMN in many characteristics, including age, gender, marital status, and survival. Compared with OBIPMN, the tumor characteristics of IAPN indicated that more patients were diagnosed at an earlier stage in multiple stage systems such as pathological grade ($P<0.001$), sixth American Joint Committee on Cancer stage ($P<0.001$), TNM stage ($P<0.001$), and SEER historic stage ($P<0.001$). In the survival analysis, the cancer-specific survival of IAPN was significantly better than OBIPMN ($P<0.001$) and the cancer-specific survival get worse at higher stages ($P<0.001$). Moreover, the 5-year cancer-specific survival rate of IAPN was also significantly better than that of OBIPMN (36.5% versus 25.4%, $P<0.001$). Finally, the multivariate analysis showed a correlation between cancer-specific survival and age of diagnosis and N stage ($P<0.001$).

Conclusions: Analysis of the SEER database clearly demonstrated that IAPN was a precancerous lesion tend to be diagnosed earlier compared with OBIPMN, which contributed to the better prognosis, and surgery was suggested if possible.

MeSH Keywords: Ampulla of Vater • SEER Program • Survival Analysis

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Background

Intraductal papillary mucinous neoplasms (IPMN) is recognized as a precancerous lesion with a great tendency to evolve into pancreatic cancer. Although Dalmas et al. reported on benign papilloma of Vater's ampulla as early as 1953 [1], IPMN was initially described as a "mucin-producing" pancreatic neoplasm in 1982 by Ohhashi et al. [2]. In addition, a study based on cases of pancreatic cancer diagnosed between 1960 and 1980 showed that IPMN existed in its current known form prior to 1982 [3]. Before the currently accepted name of intraductal papillary mucinous neoplasm (IPMN) [4], this "mucin-producing" neoplasm was reported in a number of small case series with a variety of names, including mucin-secreting carcinoma [5], villous adenoma of the duct of Wirsung [6], diffuse intraductal papillary adenocarcinoma [7], intraductal cystadenoma [8], and so on. The staple pathological characteristic of IPMN was mucin-filled dilated ducts with neoplastic cells grown on the inner surface, which could form papillae with a diverse range of morphologies and varying grades of atypia [9]. IPMN has been classified into 4 categories based upon the degree of epithelial dysplasia by the World Health Organization: adenoma, borderline, carcinoma *in situ*, and invasive carcinoma [10]. According to histological characteristics, IPMNs are classified into 4 subtypes: gastric, intestinal, pancreatobiliary, and oncocytic [11]. According to the definition of international consensus guidelines, IPMNs were grossly visible, noninvasive, mucin-producing, predominantly papillary or, rarely flat, epithelial neoplasm arising from the main pancreatic duct or branch ducts with varying degrees of ductal dilatation [4].

On the basis of macroscopic location in the pancreas, IPMN could be divided into 3 duct types: main duct (MD), branch duct (BD), and a mixed duct combined both MD and BD [12]. MD IPMNs, whether with or without symptomatic, had a higher rate of malignancy than BD IPMNs, which very often were incidentally discovered [13]. Apart from pancreatic duct, several studies had reported IPMN-B, intraductal papillary mucinous neoplasm of the bile duct, which was occasionally seen in the biliary tree, with predominantly papillary or tubular architectures similar to pancreatic IPMN or ITPN (intraductal tubulopapillary neoplasm) [14].

The ampulla of Vater, also known as the hepatopancreatic ampulla, is located at the major duodenal papilla and formed by the union of the pancreatic duct and the common bile duct. Therefore, the ampulla of Vater region represents a crossroad of 3 different epithelia: intestinal epithelia, ductal pancreatic epithelia, and biliary epithelia, which is a very peculiar histological aspect [15]. With the unique complexity and morphological heterogeneity, the pathological and clinical characteristics of IPMN in the ampulla of Vater must be quite different from those in other sites.

The existing literature describing intra-ampullary papillary-tubular neoplasm (IAPN) is limited to case reports or small case series; a comprehensive review at the population level is urgently needed to better inform pancreas surgeons. Initiated in 1973, the Surveillance, Epidemiology, and End Results (SEER) database has now reached a huge size with clinical and descriptive characteristics of uncommon tumors described at a population level. In our research, we want to analyze the epidemiological characteristics of IAPN, compared with IPMN of the bile duct (OBIPMN), by searching the SEER 18 database to examine the information, such as incidence, clinical characteristics, tumor characteristics, survival information, etc.

Material and Methods

The SEER 18 database was searched for frequency, incidence, and survival data for IPMN diagnosed between 1973 and 2014. Approval from the Institutional Review Board was not required because the data set, which is maintained by the National Cancer Institute, excluded sensitive patient information.

Patient and tumor characteristics

Similar to a study conducted by Tollefson et al. [3], pathologic specimens with the descriptors "mucinous", "cystic," or "papillary" in the pathology report were included in our study. Using the topography codes of the International Statistical Classification of Diseases for Oncology, Third Edition (ICD-O-3), we queried SEER for IPMN (8050, 8260/3, 8450/3, 8453/3, 8471/3, 8480/3, 8481/3, and 8503/3). The results were filtered to only include cases labeled with ICD-O-3 topography codes corresponding to an IAPN site: C24.1 (ampulla of Vater). Patient characteristics were stratified by year of diagnosis, gender, race, marital status, treatment, age, and survival, whereas tumor characteristics were stratified by pathological grade, American Joint Committee on Cancer (AJCC) sixth edition stage, SEER historic stage, and TNM stage.

Corresponding incidence and frequency data for OBIPMN were determined by searching for all cases within the database with ICD-O-3 topography codes corresponding to OBIPMN sites: C22.1 (intrahepatic bile duct), C23.9 (gallbladder), C24.0 (extrahepatic bile duct), C24.8 (overlapping lesion of biliary tract), and C24.9 (biliary tract, not otherwise specified [NOS]). Therefore, OBIPMN would refer to an average of all IPMN except IAPN and be used as a comparison against IAPN.

Incidence and survival

Adjusting for the 2000 standard United States (US) population as per census P25–1130, incidence data for IAPN were reported per 100 000 people for cases diagnosed between 2000

and 2014. Incidence data were analyzed for the annual percent change during the same 15-year period. The corresponding incidence for all OBIPMN was calculated for the same period.

Survival trends for case lists extracted from the SEER 18 database for IAPN and OBIPMN were analyzed using cancer-specific survival (CSS) and overall survival (OS). The 1-year, 3-year, and 5-year disease-specific survival (DSS) rates were calculated through Kaplan-Meier analysis. In the absence of other causes of death, CSS estimated the probability of surviving a specific cause of death specified by IPMN.

Statistical analysis

Frequency, incidence, and survival data were extracted from the SEER database via SEER*Stat 8.3.4 software (National Cancer Institute, Bethesda, MD, USA). Annual percent change was determined using weighted least squares and 1-year endpoints in the SEER*Stat 8.1.5 software. Differences in patient characteristics and tumor characteristics between IAPN and OBIPMN were compared using 2-proportion z tests of Power Analysis and Sample Software 13 (NCSS Statistical Software, Silver Spring, MD, USA). Survival data exported from SEER were reorganized in Microsoft Excel 2013 (Microsoft Corporation, Redmond, WA, USA). Then the data was analyzed for CSS using log-rank analysis in JMP Statistical Discovery 11 (SAS Institute, Cary, NC, USA). For all tests, probability values (P value) <0.05 were considered statistically significant.

Results

Patient and tumor characteristics

The SEER 18 database search for frequency yielded 685 cases of IAPN, compared to 2465 cases for OBIPMN (Table 1). Males constituted 42.5% of IAPN cases and 62.8% of OBIPMN, whereas females comprised 57.5% and 37.2%, respectively (P<0.001). Analysis of the data of race demonstrated a white preponderance for both IAPN (77.7%) and OBIPMN (76.8%), while blacks constituted 6.6% of IAPN cases and 9.2% of OBIPMN cases (P=0.129). The married patients constituted 65.4% of IAPN cases and 52.0% of OBIPMN cases (P<0.001). The patients who underwent surgical treatment accounted for 39.7% of IAPN cases and 36.7% of OBIPMN cases (P=0.076). Patient age ranged from 58 to 76 years for IAPN cases and 61 to 78 years for OBIPMN cases and the mean (median) age of diagnosis was 67 years for IAPN cases and 70 years for OBIPMN cases (P<0.001). The mean survival time was 23 years for IAPN cases and 9 years for OBIPMN cases (P<0.001).

Staging information was available for 216 of the 685 cases of IAPN and 860 of the 2465 cases of OBIPMN, who were

diagnosed between 2004 and 2014. Cases of IPMN were analyzed for the pathological grade, AJCC stage, TNM classification, and SEER historic stage (Table 2). In terms of pathological grade, cases of IAPN were most commonly in G2 (49.5%), followed by G3 (19.5%), G1 (15.3%), and G4 (0.9%), whereas cases of OBIPMN were most commonly in G2 (34.3%), followed by G1 (20.9%), G3 (15.6%), and G4 (0.7%) (P<0.001). According to sixth AJCC stage, most cases of IAPN were in stage II (32.9%), compared with most cases in stage I (39.5%) for OBIPMN (P<0.001). A majority of tumors were T3 for both IAPN and OBIPMN cases (25.5% versus 29.4%). Most IAPN cases had did not get involved in nodal metastasis (54.6%) or distant metastasis (86.1%). Similarly, cases of OBIPMN were also most common for no nodal metastasis (63.0%) and no distant metastasis (67.1%). In the SEER historic stage, the regional stage was the most common for IPMN, comprising 61.6% of cases, compared with 43.0% for OBIPMN.

Incidence analysis

The incidence of IAPN and OBIPMN in 2014 was 0.025 and 0.095 per 100 000 based on the age-adjusted population standard per US Census P25-1130 from the year 2000 (Table 1). The annual percent change for IAPN between 2000 and 2014 was -4.822%, compared with -2.939 for OBIPMN. The incidence trends are shown in Figure 1.

Survival analysis

In our survival analysis, the CSS and OS of IAPN cases were both significantly better than those of OBIPMN cases (Figure 2, P<0.001). The CSS for both IAPN and OBIPMN cases at an earlier stage was also significantly better compared with later stages (Figure 3, P<0.001). CSS at 1-year, 3-year, and 5-year for IAPN cases were significantly higher than those of OBIPMN cases during the same time period, which was also applied to OS and CSS for patients with or without surgery (Table 3, P<0.001). After adjusted potential confounders assessed with multivariate analysis for CSS of IAPN patients, including gender, age, age of diagnosis, race, grade, TNM stage, and SEER historic stage, only age of diagnosis and N stage showed a significant difference in CSS for IAPN cases (Table 4).

Discussion

IAPN is relatively uncommon and is known to have 4 subtypes: gastric type, intestinal type, pancreatobiliary type, and oncocytic type. From 1973 to 2014, 685 cases of IAPN were recorded in the SEER database, compared with 2465 cases of OBIPMN reported in the same period.

Table 1. Patients characteristics for IAPN and OBIPMN.

SEER patients (1973–2014) Patients characteristics	IAPN (n=685) (%)		OBIPMN (n=2465) (%)		P value
Year of diagnosis					0.621
1973–1984	150	(21.9%)	555	(22.5%)	
1985–1994	134	(19.6%)	464	(18.8%)	
1995–2004	202	(29.5%)	768	(31.2%)	
2005–2014	199	(29.0%)	768	(31.2%)	
Gender					<0.001
Male	291	(42.5%)	1547	(62.8%)	
Female	394	(57.5%)	918	(37.2%)	
Race					0.129
White	532	(77.7%)	1892	(76.8%)	
Black	45	(6.6%)	228	(9.2%)	
Other	107	(15.6%)	342	(13.9%)	
Unknown	1	(0.1%)	3	(0.1%)	
Marital status					<0.001
Unmarried	215	(31.4%)	1085	(44.0%)	
Married	448	(65.4%)	1282	(52.0%)	
Unknown	22	(3.2%)	98	(4.0%)	
Treatment					0.076
No surgery	82	(12.0%)	373	(15.1%)	
Surgical treatment	272	(39.7%)	901	(36.6%)	
Unknown	331	(48.3%)	1191	(48.3%)	
Age	67	(58–76)	70	(61–78)	<0.001
Survival	23	(8–65)	9	(2–30)	<0.001

IAPN – intra-ampullary papillary-tubular neoplasm; OBIPMN – other intraductal papillary mucinous neoplasms of the bile duct.

According to the SEER database, the incident rate of IAPN has been decreasing annually for the past 16 years (Figure 1A), which is similar to other malignant biliary tract tumors (Figure 1B). In contrast, cancers of the pancreas and extrahepatic bile ducts have not decreased, but have remained stable for at least 33 years (1973–2005), and given that the diagnostic criteria have not changed [15]. Additionally, the incidence rate of ampullary cancer for all racial groups has been increasing with an annual percent rate of 0.9% since 1973, which is statistically significant [16]. As shown in Figure 1, the incident rate of IPMN decreased more rapidly than that of other malignant biliary tract tumors, almost a 4.822% decreased for the annual percent change of IAPN versus 2.939% probably decreased for annual percent change of OBIPMN. The decreasing

incident rate of IPMN can be attributed to the improved diagnostic technology and the changed diagnostic criteria so that more cancerous IPMN cases had been diagnosed correctly [17].

As a result of the discrepancy in macroscopic location and histological types, the clinical characteristics and tumor characteristics of IAPNs were quite distinct in our study (Tables 1, 2). In contrast to OBIPMN, which occurred in much more elderly male patients, IAPNs involved more females and younger patients. Meanwhile, there was no significant difference in terms of year of diagnosis, race, or treatment.

It is worth noting that the survival rate for IAPN cases was much better than OBIPMN cases (Table 1, P<0.001). Without

Table 2. Tumor characteristics for IAPN and OBIPMN.

SEER patients (2004–2014)	IAPN (n=216)		OBIPMN (n=860)		P value
Tumor characteristics	**n (%)**				
Pathological grade					<0.001
G1	33	(15.3%)	180	(20.9%)	
G2	107	(49.5%)	295	(34.3%)	
G3	42	(19.5%)	134	(15.6%)	
G4	2	(0.9%)	6	(0.7%)	
Gx	32	(14.8%)	245	(28.5%)	
6th AJCC stage					<0.001
I	67	(31%)	340	(39.5%)	
II	71	(32.9%)	185	(21.5%)	
III	46	(21.3%)	30	(3.5%)	
IV	23	(10.6%)	252	(29.3%)	
Unknown	9	(4.1%)	53	(6.2%)	
T stage					<0.001
T0	0	(0%)	4	(0.5%)	
T1	51	(23.6%)	247	(28.7%)	
T2	46	(21.3%)	210	(24.4%)	
T3	55	(25.5%)	253	(29.4%)	
T4	55	(25.5%)	59	(6.9%)	
Tx	9	(4.1%)	87	(10.1%)	
N stage					<0.001
N0	118	(54.6%)	542	(63.0%)	
N1	86	(39.8%)	197	(22.9%)	
Nx	12	(5.6%)	121	(14.1%)	
M stage					<0.001
M0	186	(86.1%)	577	(67.1%)	
M1	23	(10.7%)	252	(29.3%)	
Mx	7	(3.2%)	31	(3.6%)	
SEER historic stage					<0.001
Localized	38	(17.6%)	370	(43.0%)	
Regional	133	(61.6%)	185	(21.5%)	
Distant	40	(18.5%)	291	(33.8%)	
Unstaged	5	(2.3%)	14	(1.6%)	
Size	30	(20–40)	30	(20–50)	0.021
Incidence (2014)	0.025		0.095		
Annual percent change	–4.822		–2.939		

IAPN – intra-ampullary papillary-tubular neoplasm; OBIPMN – other intraductal papillary mucinous neoplasms of the bile duct; AJCC – American Joint Committee on Cancer; SEER – Surveillance, Epidemiology, and End Results.
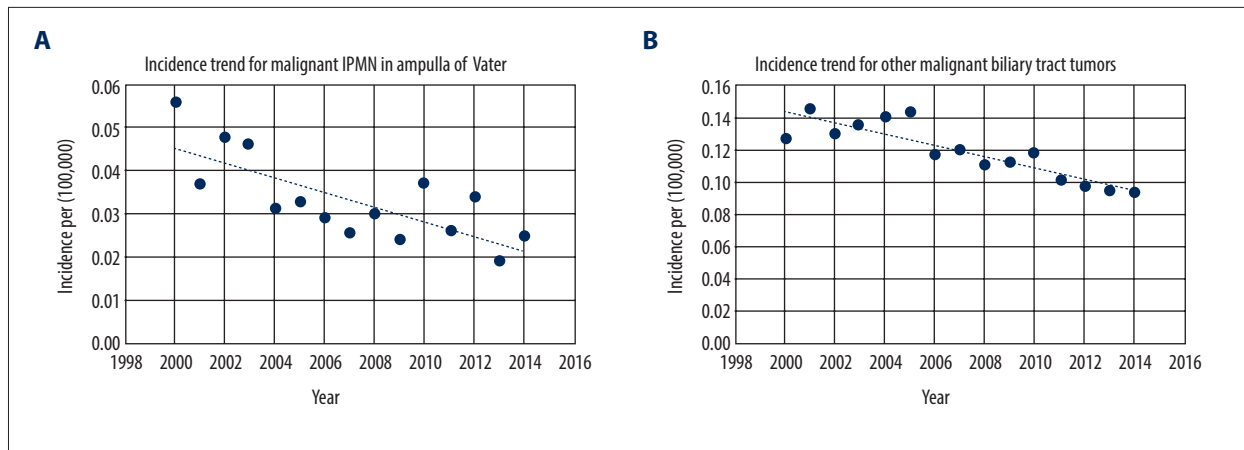
Figure 1. (**A**, **B**) Incidence trend for intra-ampullary papillary-tubular neoplasm (IAPN) and other intraductal papillary mucinous neoplasm (OBIPMN) between 2000 and 2014.
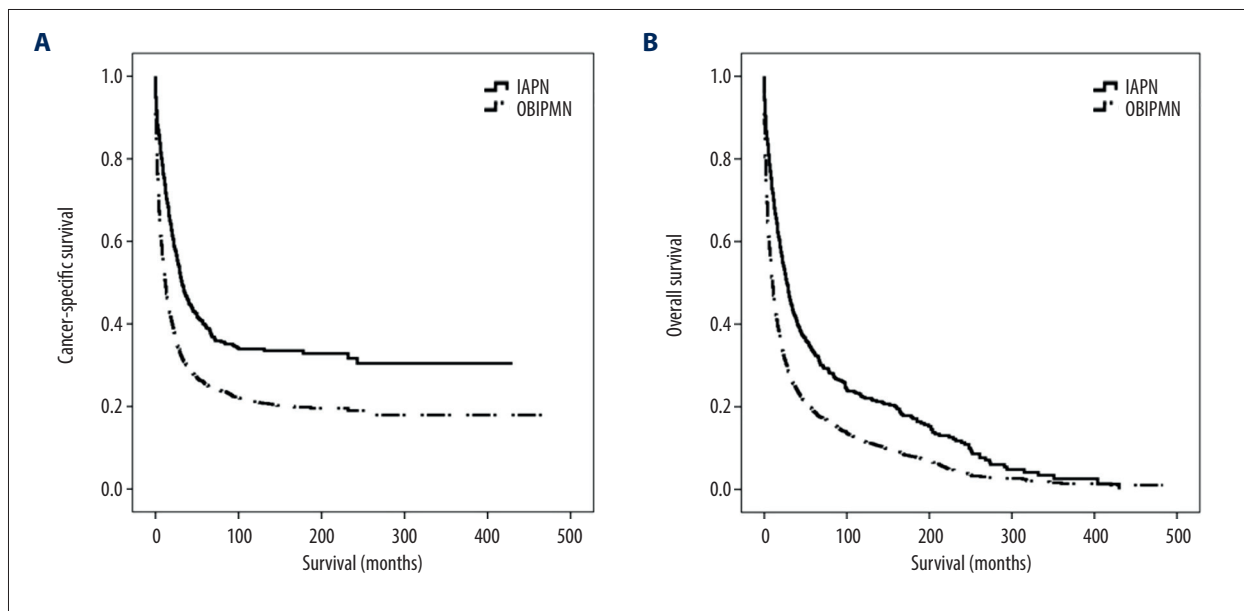

Figure 2. Cancer-specific survival (**A**) and overall survival (**B**) for intra-ampullary papillary-tubular neoplasm (IAPN) and other intraductal papillary mucinous neoplasm (OBIPMN).

specific clinical symptoms, early diagnosis IPMN is more diffi-cult; occasional symptoms are abdominal pain, nausea, vomit-ing, weight loss, jaundice, and diabetes. The ampulla of Vater is the major exit for pancreatic juice and bile, and thus it is nec-essary to keep it unobstructed. Consequently, patients would have specific clinical symptoms at the early stage of IAPN. Thus, it is more possible for early diagnose of IAPN compared to OBIPMN, which can result in a better prognosis in the long-term. Consistently in our study, the tumor characteristics of IAPN and OBIPMN indicated the diagnosis of IAPN at an earlier stage, not only at earlier pathological grade but also when the sixth AJCC stage, N stage, M stage, SEER historic stage were applied (Table 2, *P*<0.001). In total, IPMN patients generally are diagnosed with a better stage, which can contribute to a better prognosis. To determine the exact difference in survival, we an-alyze CSS and OS. Hereafter, we concluded that patients with IAPN had a significantly greater CSS than those with OBIPMN (Figure 2A). Consistently, the OS of IAPN patients also showed a significantly better difference than that of OBIPMN patients (Figure 2B). Additionally, the 1-year, 2-year, and 5-year surviv-al rates, in terms of OS and CSS, also revealed poor prognosis of OBIPMN in contrast to IAPN (Table 3). Overall, the IAPN cas-es had a better outcome owing to macroscopic location and histological types, which is the reason why IAPN cases tend-ed to be diagnosed at an earlier stage.

Similar to the well-defined adenoma-carcinoma sequence in colorectal cancer and pancreatic intraepithelial neoplasia
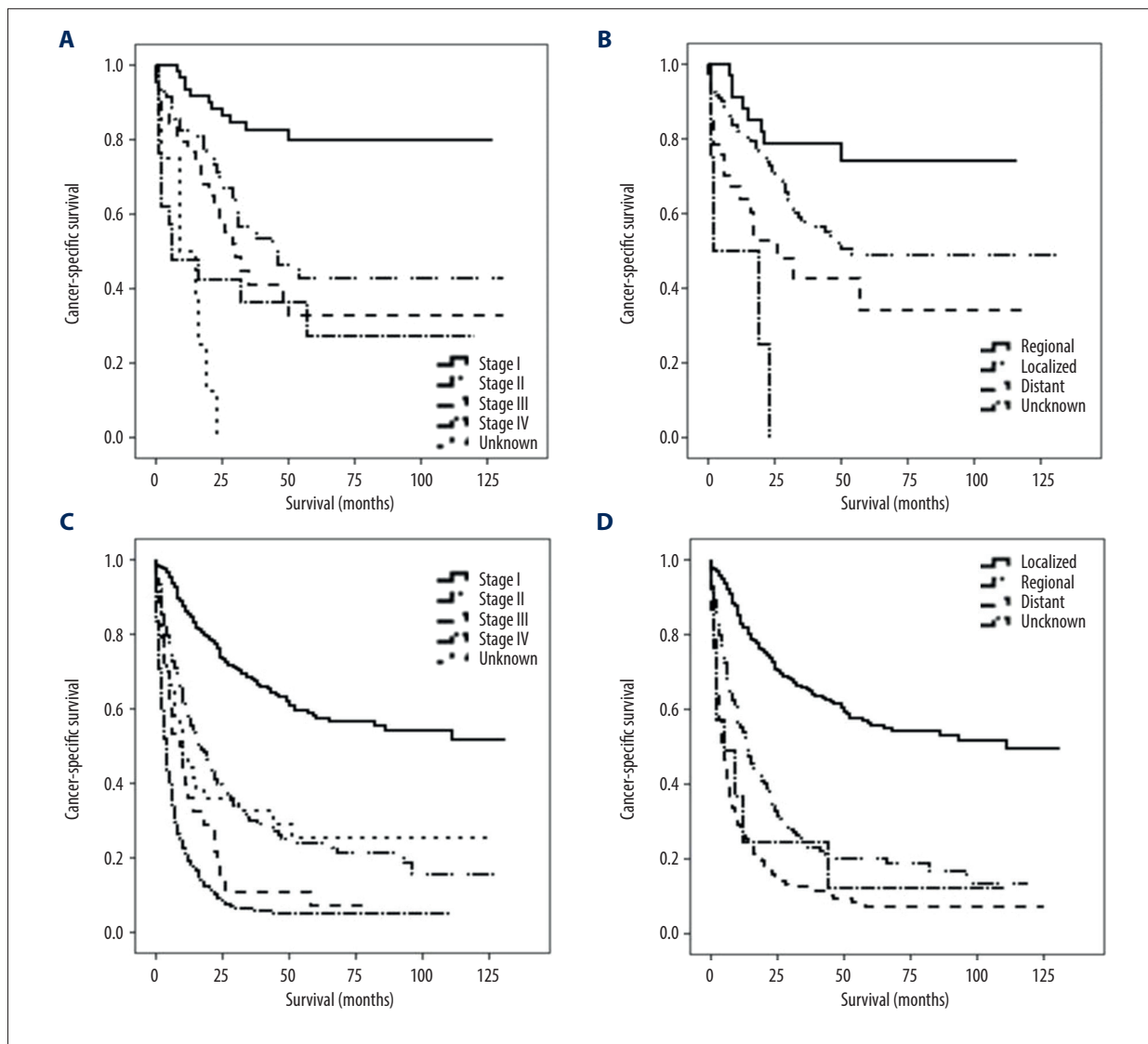
Figure 3. Cancer-specific survival for intra-ampullary papillary-tubular neoplasm (IAPN) (**A, B**) and other intraductal papillary mucinous neoplasm (OBIPMN) (**C, D**) based on different stage system (i.e., sixth AJCC stage was used for **A** and **C**; whereas the SEER historic stage was used for **B** and **D**). AJCC – American Joint Committee on Cancer; SEER – Surveillance, Epidemiology, and End Results.

Table 3. Survival rates analysis of IAPN and OBIPMN.

	IAPN					OBIPMN			
		Survival rates,%					Survival rates,%		
	n	1 year	3 years	5 years		n	1 year	3 years	5 years
CSS	681	71.7	46.9	39.6	CSS	2444	49.0	30.3	25.4
OS	681	68.1	42.3	33.1	OS	2444	45.2	25.3	18.9
CSS-no surgery	80	25.8	5.7	–	CSS-no surgery	368	14.6	3.4	2.3
CSS- surgery	272	83.8	58.4	46.7	CSS- surgery	1175	41.8	21.3	15.7

IAPN – intra-ampullary papillary-tubular neoplasm; OBIPMN – other intraductal papillary mucinous neoplasms of the bile duct; CSS – cancer-specific survival; OS – overall survival.

Table 4. Univariate and multivariate survival analysis of IAPN and OBIPMN.

	CSS for IAPN (2004-2014)			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Gender				
Female	Reference			
Male	1.00 (0.65–1.53)	0.998		
Year of diagnosis	1.00 (0.93–1.08)	0.948		
Age at diagnosis				
≤70 years	Reference		Reference	
>70 years	1.56 (1.01–2.39)	0.043	1.70 (1.05–2.75)	0.031
Race				
White	Reference			
Black	1.58 (0.78–3.18)	0.205		
Others	1.31 (0.75–2.29)	0.337		
Unknown	10.59 (1.42–79.25)	0.022		
Grade				
Well-differentiated	Reference		Reference	
Moderately differentiated	1.89 (0.84–4.23)	0.124	1.85 (0.78–4.35)	0.160
Poorly differentiated	2.76 (1.16–6.57)	0.022	1.98 (0.78–4.35)	0.148
Undifferentiated	4.60 (0.56–37.71)	0.156	4.35 (0.51–37.23)	0.180
Unknown	4.53 (1.91–10.74)	0.001	3.94 (1.57–9.87)	0.003
T stage				
T0	Reference		Reference	
T1	0.80 (0.38–1.72)	0.573	0.84 (0.28–2.48)	0.748
T2	1.43 (0.74–2.78)	0.287	1.09 (0.40–2.95)	0.868
T3	2.39 (1.28–4.47)	0.006	1.50 (0.58–3.91)	0.403
T4	8.83 (3.51–22.23)	<0.001	7.27 (1.56–33.80)	0.011
N stage				
N0	Reference		Reference	
N1	3.18 (1.98–5.12)	<0.001	2.68 (1.53–4.69)	0.001
Nx	8.21 (4.03–16.72)	<0.001	4.92 (1.26–19.22)	0.022
M stage				
M0	Reference		Reference	
M1	2.77 (1.55–4.95)	0.001	3.00 (0.93–9.72)	0.066
Unknown	5.32 (2.39–11.84)	<0.001	0.73 (0.12–4.45)	0.728
SEER historic stage				
Localized	Reference		Reference	
Regional	2.19 (1.04–4.62)	0.038	1.40 (0.41–4.81)	0.591
Distant	3.83 (1.67–8.78)	0.001	0.78 (0.16–3.82)	0.762
Unstaged	10.90 (3.23–36.73)	<0.001	0.67 (0.08–5.90)	0.721

IAPN – intra-ampullary papillary-tubular neoplasm; OBIPMN – other intraductal papillary mucinous neoplasms of the bile duct; CSS – cancer-specific survival; HR – hazard ratio; CI – confidence interval; SEER – Surveillance, Epidemiology, and End Results

(PanIN), IPMN seemed to progress from intraductal papillary-mucinous adenoma (IPMA) to IPMN with moderate dysplasia (or borderline IPMN) and then to intraductal papillary-mucinous carcinoma (IPMC) without invasion and eventually to invasive adenocarcinoma [18]. As the disease progresses, IPMN can vary from benign to malignant. The CSS based on sixth AJCC stage and SEER historic stage indicated the significant difference of survival in stages, based on the better CSS of stage I and regional stage compared with higher stages (Figure 3). All of our results highlighted the prominence of earlier diagnosing.

Studies had shown that 20% of patients with BD-IPMN developed pancreatic cancer after a 10-year follow-up in 2010 [19]. Another study reported a 5-year risk of malignancy ranging from 10.9% to 41.6% in patients with BD-IPMN [20]. Therefore, surgical treatment should be considered in IPMN, particularly if limited resections are possible. In our research, we found that surgery in IPMN patients could contribute to a higher survival rate, which applied to both IAPN and OBIPMN cases (Table 3). So, our study also demonstrated the importance of surgery in IAPN if impossible.

In our univariate analysis of CSS for IAPN, the results revealed the correlation between CSS and age of diagnosis or grade. Meanwhile, after adjusted potential confounders assessed with multivariate analysis, age of diagnosis also showed a significant correlation with CSS. Recently, Marchegiani et al. reported the role of age in pancreatic IPMN, which proved that patients ≥50 years old had a significantly higher cumulative risk of developing high-risk stigmata (HRS) over time, and a significantly lower OS compared with those <50 years old [21]. Consistently, our study also demonstrated the better CSS for IAPN patients ≤70 years old referred to >70 years old. But what should be taken into account is that IAPN in younger individuals would have more time to progress toward malignancy.

Niedergethmann et al. reported that invasive IPMN with nodal involvement shows the lowest median survival of 26 months and a 5-year rate of 30%, whereas the 5-year survival for non-invasive IPMN was excellent at 95% [22]. Similarly, our study also indicated the correlation between prognosis of IAPN and nodal involvement. Therefore, we suggest nodal involvement as the strongest independent prognostic factor for IAPN.

Conclusions

Our study demonstrated that IAPN was a relatively uncommon precancerous lesion with several key differences as compared with OBIPMN. Analysis of the SEER database for IAPN clearly demonstrated that IAPN was more common in the younger females compared with OBIPMN, which was more common in elder males. And depending on the special macroscopic location and histological types, patients of IAPN tended to have non-specific clinical symptoms earlier on compared with OBIPMN patients, which promoted earlier diagnosis and a better prognosis. Additionally, the survival analysis indicated better prognosis for patients diagnosed earlier, not only at an earlier age but also at an earlier N stage. Last but not least, we suggest surgery as treatment if impossible.

Availability of data and material

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest.

None.

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