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Clinical Characteristics and Prognosis of Osteoclast-like Giant Cell Tumors of the Pancreas Compared with Pancreatic Adenocarcinomas: A Population-Based Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDE 1 Mingfang Xu
ABCD 2 Wei Chen
ABCD 1 Dong Wang
EFG 3 Mao Nie

1 Cancer Center of Daping Hospital, Third Military Medical University, Chongqing, P.R. China
2 Department of Orthopaedic Surgery, People's Hospital of Fengjie County, Chongqing, P.R. China
3 Department of Orthopaedic Surgery, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, P.R. China

Corresponding Author: Mao Nie, e-mail: 302218@cqmu.edu.cn
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Background: The incidence of osteoclast-like giant cell tumor of the pancreas (OGTP) is very low, and relatively little OGTP clinical data is available. The present study, therefore, sought to conduct a more comprehensive analysis of the clinical characteristics and prognosis of OGTP.

Material/Methods: A large population-based cohort analysis was conducted using the Surveillance, Epidemiology and End Results (SEER) registry. We conducted a systematic assessment of the demographic and clinical characteristics of these patients, in addition to assessing available prognostic and therapeutic data corresponding to their disease. We further compared overall survival (OS) in these OGTP and pancreatic adenocarcinoma (PA) patient cohorts, adjusting for sex, grade, stage, and surgical treatment by propensity score matching (PSM).

Results: We included a total of 47 OGTP patients and 73 150 PA patients in the present analysis. The mean ages of PA and OGTP diagnosis were 68.0 and 62.8 years, respectively. Compared with PA patients, OGTP patients were more likely to be female (70.2% versus 48.7%, *P*<0.01), to have early-stage disease, to have lower rates of lymph node metastasis (17.0% versus 28.8%, *P*<0.01) and distant metastasis (17.0% versus 45.1%, *P*<0.01), and to have higher rates of tumor resection (70.2% versus 15.4%, *P*<0.01). OGTP patients also had a significantly longer median OS than did PA patients (13 months versus 6 months; hazard ratio [HR] 0.55, 95% confidence interval [CI] 0.37–0.57, *P*<0.0001). No significant differences in tumor site preferences were detected. Our findings also suggested that being female, having early-stage disease, and undergoing surgical resection may be associated with a more favorable prognosis in patients with OGTP.

Conclusions: OGTP patients had distinctive clinical characteristics and a better prognosis compared with PA patients. Understanding these differences will help clinicians accurately recognize these diseases. Radical resection was beneficial to the survival of OGTP patients.

MeSH Keywords: Pancreatic Neoplasms • Population Characteristics • Prognosis

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Background

Pancreatic cancer can manifest as a wide range of pathological types. It is generally divided into epithelial and non-epithelial tumors according to histological differentiation. Epithelial neoplasms can be exocrine or endocrine, and exocrine neoplasms can be categorized into ductal neoplasms or acinar neoplasms [1]. Ductal adenocarcinoma occupies the first among all types, making up 80% to 90% of pancreatic cancer cases. In contrast, osteoclast-like giant cell tumor of the pancreas (OGTP) is an extremely rare type of pancreatic cancer which was first reported by Juan Rosai in 1968 [2]. These tumors are non-endocrine in origin, with high rates of malignancy and poor differentiation. Similar osteoclast-like giant cell tumors (OGCs) have similarly been detected in many other sites in the body, including in the thyroid, skin, urinary tract, lungs, parotid gland, breast, and in various soft tissues [3–13]. In pancreatic manifestations, such OGCs most often present in the context of ductal adenocarcinoma, with a histological appearance consistent with that of giant cell tumors of the bone. Two primary cell populations, including mononuclear stromal cells and giant multinucleated reactive cells, compose OGTP tumors which appear similar to osteoclasts [14]. The specific origin of these osteoclast-like cells in OGTP remained controversial, with different studies suggesting them to be of epithelial or mesenchymal lineages [15–18].

Given the rarity of this condition, no large-scale clinical studies of OGTP are available at present, with the bulk of relevant publications instead being case reports. This has led to significant speculation regarding this condition. For example, some researchers have proposed that OGTP does not exhibit any sex-bias with respect to its development and that it has a relatively good prognosis as compared to other pancreatic tumors owing to the fact that OGTP typically only exhibits localized spreading, with metastasis to lymph nodes and distant sites being slow to develop and rarely reported [19]. In contrast, however, some researchers have reported OGTP to be more common in females [20] and to have a worse prognosis [21,22]. The site preferences for OGTP tumors similarly remains controversial. As such, there is a clear need for further comprehensive studies of OGTP in order to guide oncologists and to allow them to make correct diagnostic and treatment decisions. To that end, we conducted the present large cohort to compare OGTP and pancreatic adenocarcinoma (PA) using the SEER database.

Material and Methods

Ethics

The Research Ethics Committee of Daping Hospital approved the present study. No patient consent was required for the use of data contained in the SEER database, as in the USA cancer is considered to be a reportable disease.

Population

Both pancreatic adenocarcinoma, NOS (not otherwise specified) and carcinoma with OGTP patient cases contained in the National Cancer Institute SEER database (*http://seer.cancer.gov/*) were identified for inclusion in the present analysis, with cases that were not adenocarcinoma, NOS, or carcinoma with osteoclast-like giant cells being excluded. Any patients with pathologically confirmed PA or OGTP that were included in the SEER database from 2001–2016 were eligible for inclusion in the present analysis. In total, we identified 96 741 PA patients and 90 OGC patients during this time period. Of the OGC patients, tumors were of pancreatic origin in 50 cases. The second most common tissue of origin in these patients was the breast (21 out of 90 cases), with manifestations in other tissues being significantly rarer, including 6 lung/bronchus, 3 liver, 3 thyroid, 1 biliary, 2 urinary/bladder, 1 ureter, 1 salivary gland, 1 gallbladder, and 1 kidney/renal pelvis OGC cases. Patients were excluded if they were diagnosed based upon death certificate or autopsy, had an unknown age of diagnosis, were of unknown sex, were of unknown race, had an undetermined disease site, had an unknown disease stage, had an unknown pathological type, had uncertain overall survival, or had unknown surgical status. After exclusion there were 73 150 PA patients and 47 OGTP patients enrolled in this analysis. Pancreatic cancer histology was grouped based upon ICD-O-3 histology codes as follows: carcinoma with osteoclast-like giant cells (IDC, 8500/3) and adenocarcinoma, NOS (IDC, 8140/3).

Statistical analysis

Chi-squared tests were used for comparing categorical data, which were given as numbers and percentages, while continuous data were given as mean (median) range and were compared via Student's *t*-tests. Patient survival from date of diagnosis until death due to any reason or date of last follow-up was measured, with the Kaplan-Meier approach being used for survival curve preparation and log-rank (Mantel-Cox) tests being used for comparing survival outcomes. Differences between groups in baseline characteristics were balanced via propensity score matching (PSM) analysis. Based upon 1–3 matches, successful matching of all 47 OGTP patients was achieved. Covariates entered into the propensity model included sex, grade, stage, and surgical treatment. After PSM, there were 47 cases in the OGTP group and 141 cases in the PA group, and there were no significant differences in age, race, gender, year of diagnosis, site, grade, stage, survival status, surgical treatment, N staging, or M staging between the 2 groups. All *P* values were 2-sided, and $P<0.05$ was the significance threshold. SPSS v23 (IBM Corp, NY, USA) was employed for statistical testing.

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Table 1. Demographic and clinic characteristics of patients with OGTP and PA between 2001 and 2016 in SEER database demographic.

Diagnosis	Before PSM			After PSM		
	OGTP (%)	PA (%)	*P*-value	OGTP (%)	PA (%)	*P*-value
N	47	73150		47	141	
Age at diagnosis			0.001			0.32
<49	2 (4.2)	4467 (6.1)		2 (4.2)	21 (14.9)	
50–59	17 (36.2)	13186 (18.0)		17 (36.2)	47 (33.3)	
60–69	19 (40.4)	21311 (29.1)		19 (40.4)	49 (34.8)	
70–79	5 (10.6)	21554 (29.5)		5 (10.6)	12 (8.5)	
≥80	4 (8.5)	12632 (17.3)		4 (8.5)	12 (8.5)	
Race			0.638			0.86
White	37 (78.7)	59010 (80.7)		37 (78.7)	116 (82.3)	
Black	5 (10.6)	8895 (12.2)		5 (10.6)	13 (9.2)	
Other	5 (10.6)	5245 (7.2)		5 (10.6)	12 (8.5)	
Sex			0.003			0.63
Female	33 (70.2)	35616 (48.7)		33 (70.2)	106 (75.2)	
Male	14 (29.8)	37524 (51.3)		14 (29.8)	35 (24.8)	
Year of diagnosis			0.022			0.46
2001–2005	5 (10.6)	19054 (26.0)		5 (10.6)	11 (7.8)	
2006–2010	15 (31.9)	24422 (33.4)		15 (31.9)	59 (41.8)	
2011–2016	27 (57.4)	29674 (40.6)		27 (57.4)	71 (50.4)	
Site			0.821			0.74
Head	24 (51.1)	38551 (52.7)		24 (51.1)	78 (55.3)	
Other	23 (48.9)	34593 (47.3)		23 (48.9)	63 (44.7)	
Grade			<0.001			0.70
I–II	0 (0)	13493 (18.4)		0 (0)	2 (1.4)	
III–IV	41 (87.2)	11045 (15.1)		41 (87.2)	123 (87.2)	
Unkown	6 (12.8)	48612 (66.5)		6 (12.8)	16 (11.3)	
Stage			<0.001			0.95
Localize	9 (19.1)	5958 (8.1)		9 (19.1)	30 (21.3)	
Regional	27 (57.4)	25103 (34.3)		27 (57.4)	78 (55.3)	
Distant	11 (23.4)	42089 (57.5)		11 (23.4)	33 (23.4)	
Status			<0.001			
Alive	11 (23.4)	3856 (5.3)		11 (23.4)	28 (19.9)	0.76
Dead	36 (76.6)	69294 (94.7)		36 (76.6)	113 (80.1)	
N staging			<0.001			0.58
N0	30 (63.8)	31732 (43.4)		30 (63.8)	87 (61.7)	
N1	8 (17.0)	21055 (28.8)		8 (17.0)	33 (23.4)	
Unknown	9 (19.1)	20363 (27.8)		9 (19.1)	21 (14.9)	

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Table 1 continued. Demographic and clinic characteristics of patients with OGTP and PA between 2001 and 2016 in SEER database demographic.

Diagnosis	Before PSM			After PSM		
	OGTP (%)	PA (%)	*P*-value	OGTP (%)	PA (%)	*P*-value
M staging			<0.001			0.83
M0	32 (68.1)	27974 (38.2)		32 (68.1)	96 (68.1)	
M1	8 (17.0)	32956 (45.1)		8 (17.0)	28 (19.9)	
Unknown	7 (14.9)	12220 (16.7)		7 (14.9)	17 (12.1))	
Surgery			<0.001			0.72
yes	33 (70.2)	11281 (15.4)		33 (70.2)	93 (66)	
No	14 (29.8)	61869 (84.6)		14 (29.8)	93 (66)	

OGTP – osteoclast-like giant cell tumor of the pancreas; PA – pancreatic adenocarcinoma; PSM – propensity score matching; SEER – Surveillance, Epidemiology and End Results.

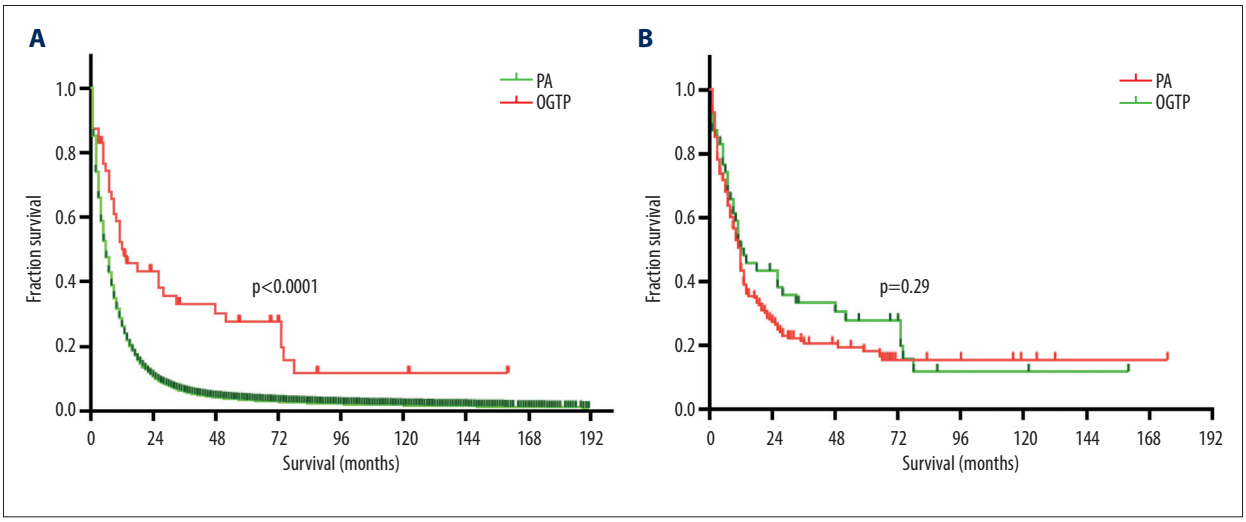

Figure 1. (**A**) Kaplan Meier curves suggested that OGTP patients had significantly longer survival than PA patients before PSM (13 months versus 6 months; HR 0.55, 95% CI 0.37–0.57, *P*<0.0001). (**B**) Kaplan-Meier survival curves demonstrating no significant extension in survival for OGTP patients relative to PA patients after PSM (13 months versus 12 months; HR 0.92, 95% CI 0.63–1.34, *P*>0.05). OGTP – osteoclast-like giant cell tumor of the pancreas; PA – pancreatic adenocarcinoma; PSM – propensity score matching; HR – hazard ratio; CI – confidence interval.

Results

Patients characteristics

Through a search of the SEER database, we identified 73 150 total PA patients and 47 OGTP patients who were diagnosed between 2001 and 2016. OGTP patients had a mean age of 62.8 years at the time of diagnosis, whereas in PA patients this age was 68 years at time of diagnosis. Table 1 shows the demographic and clinical characteristics of these 2 patient cohorts before and after PSM. There were significant differences between these OGTP and PA patient cohorts with respect to age at diagnosis, sex, staging, lymph node involvement, distant metastasis, rates of surgical treatment, and survival outcomes before but not after PSM. In contrast, no significant differences in patient race, year of diagnosis, or tumor site preferences were observed between these groups. Significantly more OGTP patients were alive as of last follow-up relative to PA patients (23.4% versus 5.3%, *P*<0.001).

Survival analysis

We next compared survival curves for patients with PA and OGTP (Figure 1A), revealing that OGTP patients had a median

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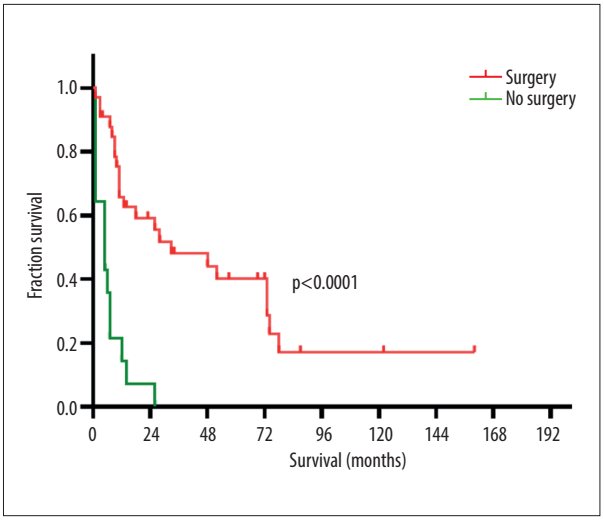

Figure 2. Kaplan-Meier curves indicated that patients with OGTP that underwent surgical resection had significantly longer survival than those who did not undergo resection (33 months versus 5 months; HR 0.07, 95% CI 0.03–0.21, *P*<0.0001) OGTP – osteoclast-like giant cell tumor of the pancreas; HR – hazard ratio; CI – confidence interval.

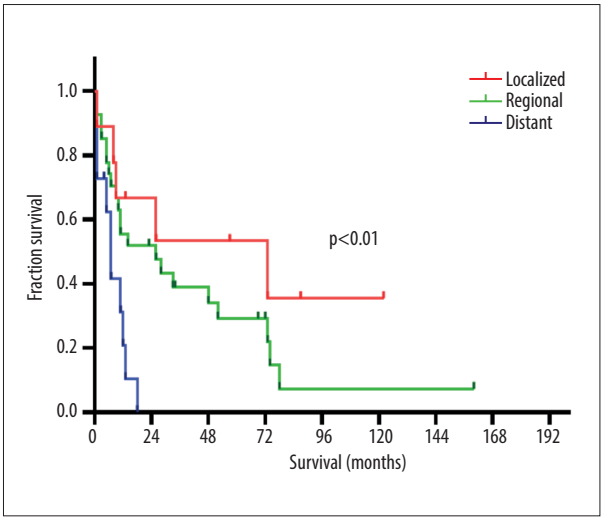

Figure 3. Kaplan-Meier curves indicated that the mOS of OGTP patients with localized, regional, and distant staging were 73, 26, and 7 months, respectively (*P*<0.01). mOS – median overall survival; OGTP – osteoclast-like giant cell tumor of the pancreas.

overall survival (mOS) of 13 months (range: 1–160 months), whereas PA patients had a mOS of 6 months (range: 1–227 months) (HR 0.55, 95% CI 0.37–0.57) before propensity score matching. This indicated a significant difference in mOS between these 2 patient cohorts *P*<0.0001). However, the survival curves were not significantly different after PSM (Figure 1B). We then compared OGTP patient survival outcomes as a

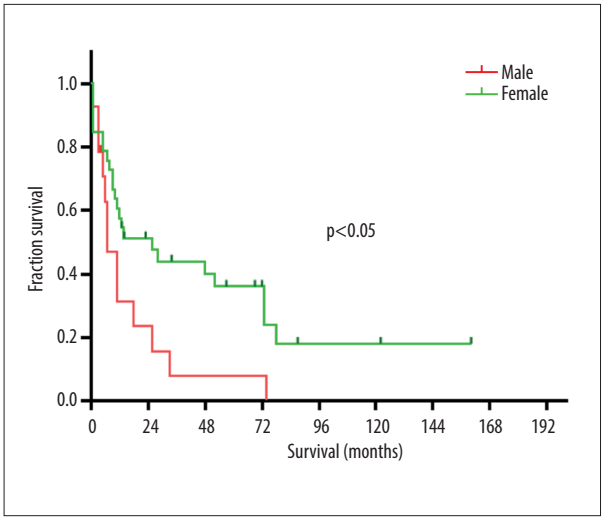

Figure 4. Kaplan-Meier curves indicated that females had a better prognosis than males (36 months versus 7 months, HR 0.38, 95% CI 0.17–0.88, *P*<0.05). Abbreviations: HR, hazard ratio; CI, confidence interval.

function of whether or not patients underwent tumor resection (Figure 2), revealing that those patients treated via surgical resection had significantly better survival outcomes than those patients who did not undergo surgery (33 months versus 5 months, HR 0.07, 95% CI 0.03–0.21) (*P*<0.0001). We further compared OGTP patient outcomes as a function of disease stage (Figure 3), revealing localized, regional, and distantly metastasized OGTP to have mOS values of 73, 26, and 7 months, respectively (*P*<0.01). When OGTP patient survival was compared based upon patient sex (Figure 4), we found females to have a significantly better prognosis than male patients (36 months versus 7 months, HR 0.38, 95% CI 0.17–0.88) (*P*<0.05). Lastly, we compared OGTP patient survival outcomes according to patient age, race, or tumor site preference (Figure 5), indicating no significant differences in survival as a function of these variables (*P*>0.05).

Discussion

OGTP is a very rare form of adenocarcinoma that makes up just 1.4% of all pancreatic cancers, and it has been defined by the World Health Organization as a form of undifferentiated carcinoma exhibiting osteoclast-like giant cells [23]. While OGCs are detectable in a wide range of tissue types, the pancreas seems to be the most commonly affected tissue [24]. In the SEER patient cohort analyzed in the present study, we similarly observed higher rates of OGC incidence in the pancreas relative to other organs. At present, no large-scale clinical studies of OGTP have been conducted, with current understanding of this disease being largely restricted to case reports and review articles. As such, we conducted the present study

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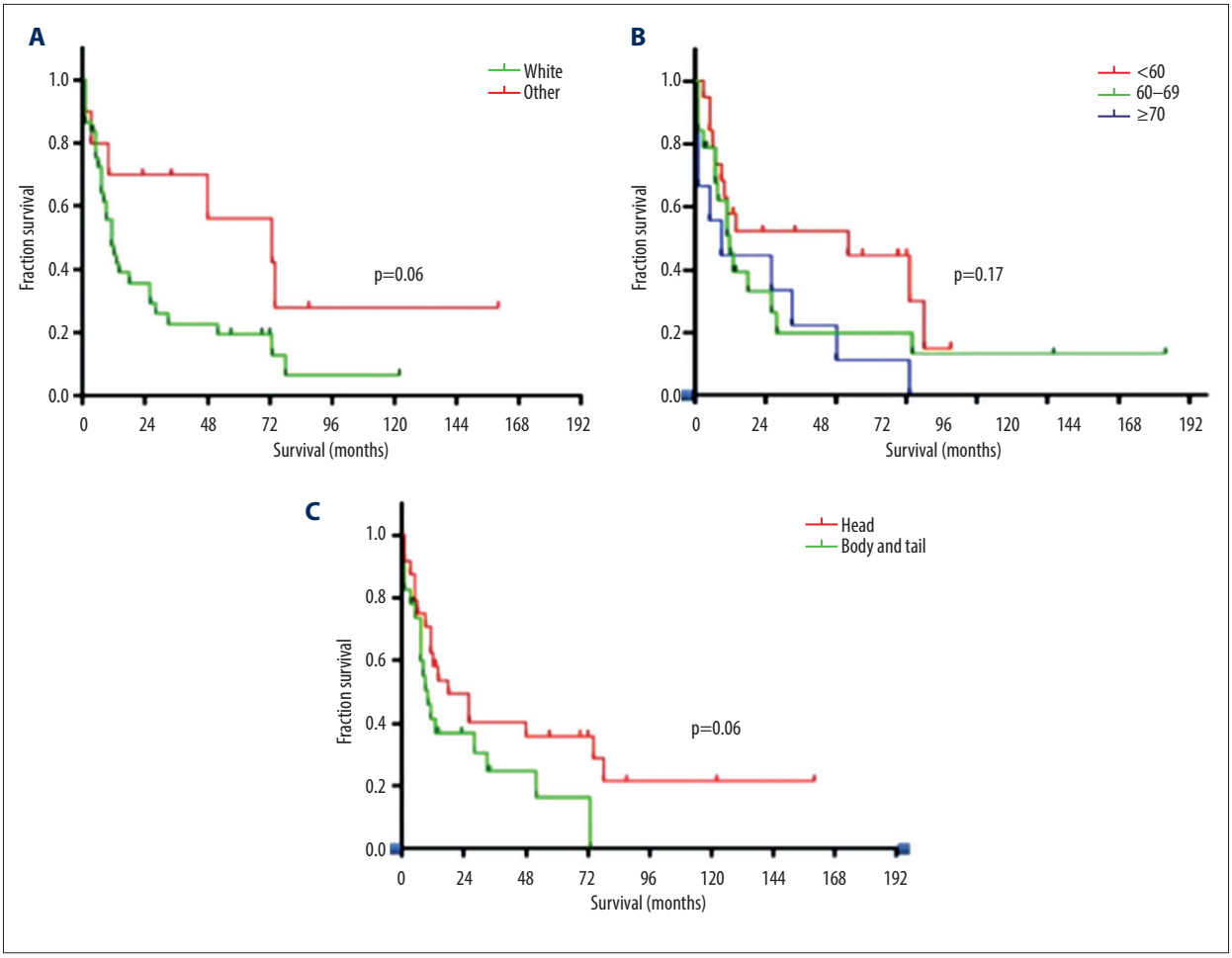

Figure 5. (**A–C**) Kaplan-Meier curves indicated that there was no significant difference in OGTP patient survival as a function of patient age, site, or race (*P*>0.05). OGTP – osteoclast-like giant cell tumor of the pancreas.

using the SEER database in an effort to better elucidate the characteristics of OGTP.

Previous studies have suggested that OGTP most commonly manifests without any specific sex-bias in individuals between 60 and 70 years of age, although in some cases it has been reported in individuals as young as 32 years old or as old as 82 years [16,25]. We observed OGTP to be the most common in individuals between 50 and 70 years old (range: 35–90 years), consistent with previous studies, although unlike this previous report we observed a significantly higher rate of OGTP among females (70.2% versus 48.7%, *P*=0.003).

There also remained uncertainty in the literature with respect to the site preferences of OGTP in the pancreas, with PA typically being found to involve the head of the pancreas whereas OGTP most often involves the pancreatic body and tail [26]. As a result, OGTP patients most often initially present with abdominal distension, upper abdominal pain, weight loss, and a palpable mass, whereas PA patients more often first present with jaundice. In contrast to these reports, however, other studies have suggested that OGTP and PA exhibit comparable site preferences within the pancreas [27]. In line with this latter report, we did not detect any significant difference in tumor site preference when comparing OGTP and PA based upon the frequency of tumors involving the head of the pancreas (51.1% versus 52.7%, *P*>0.05). Our results therefore suggest jaundice to also be a likely symptom of OGTP.

Several studies [18,23,28–30] have reported OGTP to be associated lower rates of lymph node and distant metastasis relative to PA, and with better prognosis as a result. However, other reports have suggested the opposite, identifying poorer outcomes among OGTP patients relative to PA patients [21,22]. Given the limited number of OGTP cases reported to date, the prognosis of this condition thus remains unclear. Consistent with the former findings, in this analysis we found OGTP to typically present as an earlier-stage disease, with lower rates of lymph node and distant metastasis and a significantly longer mOS relative to PA (13 months versus 6 months). Importantly,

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among OGTP patients we found that those patients who had undergone surgical tumor resection had a significantly longer mOS than those patients who had not (33 months versus 5 months). This may be a consequence of the higher rates of early-stage OGTP leading to higher rates of surgical treatment and suggests that radical resection was the optimal approach to curing this form of undifferentiated carcinoma.

We observed no significant differences among OGTP patients as a function of patient age, race, or tumor site. Previous studies have not assessed these issues in depth. Our Kaplan-Meier survival curves suggested that there may be a trend towards a poorer patient prognosis among Caucasians and those with tumors in the pancreatic body and tail regions, however, raising the possibility that we only failed to observe any significant results in these analyses due to the limited sample size of the present study.

Luchini et al. [30] found that genetic alterations observed in OGTP were highly similar to known PA driver mutations, including KRAS, CDKN2A, TP53, and SMAD4 mutations, with no unique phenotypic markers specific to OGTP having been identified in their analysis. Another study detected the expression of PD-L1 on tumor cells in 63% of patient cases and found this expression to be linked with a poorer prognosis [31]. This therefore suggested that OGTP treatment might be benefit from anti-PD-1/PD-L1 monoclonal antibody therapy, although further research will be needed to validate this hypothesis and to identify other effective treatment programs.

On imaging, OGTP usually presents as a large cystic tumor with variable areas of hemorrhage and necrosis [20,25]. Hence, pancreatic cystic lesions such as pancreatic cystic tumors, pancreatic pseudocysts, and solid pancreatic tumors must be considered in the differential diagnosis with this tumor type [25,26]. However, a definitive diagnosis can only be established based upon histopathology or cytology. At the microscopic level, this rare tumor type presents with cytomorphological features including bizarre pleomorphic cells, bland OGCs, and mononuclear cells [26].

Although conducted using population-based data, there were still several limitations to the present study, including potential selection bias due to its retrospective nature. Furthermore, as the SEER database does not include any gene expression data, we were unable to compare patient outcomes based upon such parameters. In addition, this database did not contain sufficient detail regarding patient drug usage, surgical treatment, radiotherapy doses, or comorbidities, and as such, we were unable to explore the relationship between those variables and patient outcomes. Differences in the circumstances surrounding data input into this database also have the potential to introduce significant heterogeneity in these results.

Conclusions

In this population-based study, we investigated the clinical characteristics of OGTP patients, potentially enabling oncologists to better recognize and diagnose this tumor. We found that patients aged 50–70 years had the highest incidence of OGTP, with females being more frequently affected. We also found that rates of lymph node and distant metastasis were lower in OGTP patients relative to PA patients, and that these patients also had longer mOS and earlier stage disease. The definitive diagnosis of OGTP can only be determined by histopathology or cytology, and radical resection is an effective treatment.

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