Incidence, prediction, and the long-term outcome of solid pseudopapillary tumor of the pancreas with malignant behaviors: a pooled-analysis

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Research

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Abstract

Background: Microscopic malignancy or gross metastasis of solid pseudopapillary tumor of the pancreas were considered to be malignant behaviors. The clinical status of solid pseudopapillary tumors of the pancreas with malignant behaviors (SPTM) are unclear. This study was to perform a review and pooled-analysis to determine the incidence and predictors of SPTM, and explore the survival and prognostic factors.

Methods: A registered meta-analysis (PROSPERO: CRD42020163788) was performed. Studies reporting on SPTM and follow-up information were identified between 1960 and 2020 by searching PubMed, Scopus, and Embase. The search process followed the PRISMA guidelines.

Results: A total of 98 articles were included in this study, including 22 articles reporting the incidence of SPTM, and 159 SPTM cases containing survival information in 77 articles. Pooled estimates showed that the incidence of SPTM in solid pseudopapillary tumors of the pancreas was 22% [95% CI: 19~24%], and tumor size ≥ 5 cm (OR: 2.03 [95%CI: 1.28~3.22]) was the only risk factor for predicting the occurrence of SPTM. The 5-, and 10-year survival rates of SPTM patients after complete surgical resection were 92% and 77%, respectively. Larger tumors (diameter ≥ 5 cm) ($p=0.046$), lymphovascular invasion ($p=0.005$), lymph node metastasis ($p=0.02$), cellular atypia (0.018), Ki67 index $\geq 5\%$ ($p=0.001$), tumor recurrence ($p=0.004$), recurrent time <5 years ($p=0.005$) and positive margin ($p=0.003$) were prognosis unfavorable factors for survival. Additionally, lymphovascular invasion (OR:8.25, 95% CI:2.26-30.1), lymph node metastasis (OR:25.28, 95% CI:3.01-211.74), extrapancreatic invasion (OR:9.07, 95% CI:2.36-34.84), cellular atypia (OR:16, 95% CI:3-85.3), and Ki67 $\geq 5\%$ (OR: 7.88, 95%CI: 1.53~40.51) increased the risk of recurrences of resected SPTM.

Conclusion: Tumor size is an important factor in predicting the occurrence of SPTM before operation, and complete surgical resection can provide SPTM patients a expected long-term survival. Proved clinicopathological factors by current research will help to determine prognosis and recurrence, and close follow-up of five years or more after operation is essential.

Introduction

In 1959 Frantz first described a rare pathological entity of the pancreas, which was officially named as solid pseudopapillary tumor of the pancreas by the World Health Organization (WHO) in 1996^[1]. Since 2000, the number of reported related cases of solid pseudopapillary tumor of the pancreas has apparently increased, hence this entity has been more recognized^[2]. This tumor usually presents benign behavior, however potential malignancy such as lymphatic vascular invasion, neurological invasion, invasion of peripancreatic tissue, metastasis and recurrence and all that, happened occasionally with unpredictable prognosis^[3]. In patients with malignancy, some died in a short time due to the rapid progression of the disease, while certain peoples survived for long-term despite repeated postoperative relapses^[4, 5]. Unfortunately, the biological behavior and clinical course of solid pseudopapillary tumor of the pancreas

with malignant behaviors (SPTM) have not been well studied due to the low incidence. Although some studies have pay attention to the prediction and prognosis of SPTM, no consistent and reliable conclusions have been reached, and these investigations are almostly small samples and single center^[6, 7]. This research aimed to conduct a large sample analysis of the incidence and predictors with focusing on the survival and prognostic factors of SPTM through available articles in database.

Methods

Literature search

We registered meta-analysis (PROSPERO: CRD42020163788) berfore search. Databases of PubMed, Scopus, and Embase were searching from January 1960 to January 2020 using the following search terms: (solid pseudopapillary tumor) AND (pancreas). Only articles published in English were included. Because the various names of the tumor were using previously such as ‘solid cystic tumor’, ‘papillary cystic tumor’, ‘solid and papillary epithelial neoplasia’ , ‘Frantz’s tumor’ [and the like](#), these terms were included in the backward search from the bibliographies of relevant articles. The study was carried out on the basis of the PRISMA statement^[8].

Selection criteria

solid pseudopapillary tumors of the pancreas with capsule invision, lymphovascular invasion, perineural invasion, lymph node metastasis, parenchyma invasion, extrapancreatic invasion, cellular atypia, mitosis, elevated Ki67, synchronous metastasis and postoperative recurrence were difined as SPTM. Inclusion criteria (1). investigated the incidence of SPTM; (2). discussed the association between risk factors and prediction of SPTM; (3). these case reports providing survival information of SPTM patients; (4). full text available would be included. Excluded criteria (1). review articles/letters, abstracts, comments; (2). duplicate publications; (3). patients with other primary tumor; In case of overlapping cohorts, the publication with the most relevant and comprehensive data was considered.

Data extraction

Data extraction was independently performed by two investigators (Li YF and Wang SJ). Extracted data included the incidence and predictors along with revelant event number and total number, and available individual clinicopathological information such as age, sex, tumor size, symptoms, tumor location, treatment, capsule, malignant behaviors, resection margin status, recurret time, survival time and status.

Statistical analysis

R software was performed to complete the meta-analysis of incidence and predictors of SPTM. The command ‘metaprop’ was utilized for calculation of pooled incidence rates. Odds ratios (OR) with 95% confidence intervals (CI) of predictive factor were computed using ‘meta’ command. A random-effects model was used for more reliable results. Heterogeneity was evaluated by I^2 , with $I^2 < 50\%$ or $P < 0.1$ was

considered to be low heterogeneity. Publication bias was explored using funnel plots and Egger's tests if more than ten articles are analyzed^[9]. For available individual data, categorical and continuous variables were reported as number with percentages and median with ranges, respectively. Survival was calculated using the Kaplan-Meier method, and were compared by log-rank test. Univariable and multivariate analysis was performed to identify prognostic factors with Cox's proportional hazard model. Chi-squared test or Fisher's exact test were used to evaluate risk factors associated with recurrence. A two-sided $P < 0.05$ was considered statistically significant. Statistical analyses were completed using SPSS software.

Results

The detailed search strategy is depicted in Fig 1. A total of 98 studies were identified^[4-7, 10-103]. All studies were retrospective in nature.

Incidence and predictive factors of SPTM

The incidence of SPTM was reported in 22 articles^[6, 7, 10-29]. Meta-analysis results suggested that the incidence of SPTM in solid pseudopapillary tumors of the pancreas was 22% [95%CI: 19-24%] (Fig 2). As shown in Fig 3-Fig 9, the OR value of clinicopathological data was calculated, and only tumor size $\geq 5\text{cm}$ (OR:2.03, 95% CI:1.28-3.22, $P > 0.05$) was potential predictor of SPTM. Sex (OR:1.25, 95% CI:0.86-1.82), calcification (OR:1.07, 95% CI:0.72-1.60), symptoms (OR:1.25, 95% CI:0.89-1.74), tumor location (OR:0.95, 95% CI:0.69-1.31), composition (OR:1.46, 95% CI:0.89-2.38), necrosis (OR:0.67, 95% CI:0.31-1.43), were not significant associated with the prediction of SPTM. No significant heterogeneity and publication bias (All Egger's test, $P > 0.05$) was found in above analysis (Supplementary material) .

Clinicopathologic feature of available cases

Data on the survival of SPTM was available for 159 patients in 77 articles^[4-6, 30-103]. Among these patients, 131 (86%) were female, predominantly in adult (73%) with a median age of 31 years (rang, 9-78 years). These tumors are relatively large (median size, 8.0 cm), occurring frequently in the pancreatic body and tail (65%). 86 (90%) cases present symptoms. Of the 159 patients, complete resection surgery of removing all lesions (primary lesion, and metastasis if present) was performed in 136 cases, palliative operation in six cases, surgery plus radiotherapy or/and chemotherapy in eleven cases, and only chemoradiotherapy in 6 cases. Among patients who reported the resection margin status, 90% underwent R0 resection. The rates of vascular encasement, capsule invasion, lymphovascular invasion, perineural invasion, lymph node metastasis, parenchyma invasion, extrapancreatic invasion, cellular atypia, and mitosis were 34%, 79%, 35%, 39%, 11%, 46%, 36%, 46%, and 43%, respectively. Ki-67 index was recorded in 33 cases, of which 11 (33%) were more than 5 percent. Synchronous metastasis occurred in 40 (31%) cases, with 35 case in the liver and 61 (38%) cases suffered from postoperative recurrence, with 53 cases in liver. 70% of relapses occurred within five years with the median recurrent time of 36 months (2-192 months). The median survival time was 50 months (rang, 2-284 months), 26 patients died of disease (Table 2). The 3-, 5-, and 10-year disease-specific survival were 88%, 84%, and 76% (Fig 10). The 5-, and

10-year survival rates of 136 SPTM patients after complete surgical resection were 92% and 77%, respectively (Fig 11).

Factors affecting the survival and recurrence of SPTM

By univariate analyses, larger tumors (diameter $\geq 5\text{cm}$) ($p=0.046$), lymphovascular invasion ($p=0.005$), lymph node metastasis ($p=0.02$), cellular atypia (0.018), Ki67 index $\geq 5\%$ ($p=0.001$), recurrence ($p=0.004$), recurrent time <5 years ($p=0.005$) and positive margin ($p=0.003$) were unfavorable factors for survival, but not age, gender, symptoms, tumor location, vascular encasement, capsule, capsule invasion, perineural invasion, parenchymal invasion, extrapancreatic invasion, mitosis, and synchronous metastasis (Table 2). In addition, lymphovascular invasion (OR:8.25, 95% CI:2.26-30.1), lymph node metastasis (OR:25.28, 95% CI:3.01-211.74), extrapancreatic invasion (OR:9.07, 95% CI:2.36-34.84), cellular atypia (OR:16, 95% CI:3-85.3), and Ki67 $\geq 5\%$ (OR:7.88, 95% CI:1.53-40.51) were associated with the relapses of resected SPTM (Table 3).

Discussion

Solid pseudopapillary tumor of pancreas is an uncommon neoplasms with a low malignant potential, and it is estimated that the overall mortality rate of the disease is about 2%^[2]. However, The natural history and biological behavior of SPTM are difficult to determine given its relatively rare appearance. Astonishing, the mortality rate of SPTM patients is as high as 16% in our analysis. Therefore, It is very meaningful to explore the clinical process of SPTM in order to improve survival of these patients.

The present study conclude that the incidence of SPTM is 22%, which ranged from 8–44% in previous small sample study^[6, 25]. The pooled incidence indicated that clinicians should manage the disease with caution not treating lightly, although it is usually benign. Tumor size $\geq 5\text{ cm}$ was the only risk factor for the prediction of SPTM. Relatively large tumors will increase the chance of surrounding tissue invasion, even tumor metastasis, which may be the reason that it predicts malignancy successfully. In our cohort, most tumors harbor indeed larger size than 5 cm. Whether the continuous growth of tumors will lead to changes in tumor biological behavior has not been reported, which's still an enigma. Preoperative evaluation of tumor size is helpful to identify patients with SPTM, and provide a planning for surgical resection of surrounding potentially invasive tissue.

Surgery is considered to be the most effective treatment for SPTM. These tumors are usually large, possibly with local extrapancreatic invasion into adjacent organs and vessels, but surgical resection is usually feasible and curable. In our series, 136 cases undertaked complete resection surgery, of which 4 cases received resection and reconstruction of portal vein, and the 5- and 10-year survival rates of were 92%, and 77%, respectively. Even in 25 patients with liver simultaneous metastasis, the 5- and 10-year survival rate reached 90% and 64% after complete aggressive resection, respectively. Therefore, the surgeon should always aim for complete, en bloc resection including metastases because the survival of SPTM patients with complete resection is satisfactory, even if the liver metastases. In recurrent series, 20

patients died ,but the majority were alive (41/61). Among these 41 patients, reoperation was performed in 25 cases, surgery plus chemotherapy in 8 cases, and only chemotherapy in two cases, and the remaining 6 cases were unknown. Obviously, Aggressive comprehensive management can benefit patients with postoperative recurrence. For unresectable tumor (including major blood vessels invasion or multiple liver metastasis), the effect of non-operative treatment is conflicting^[30, 32, 46, 60]. Due to the limited number of cases and the diversity of treatment strategies, it is not possible to come to a consistent conclusion for the role of these modalities in SPTM treatment. Noteworthy, Nicholas reported that one SPTM patient with unresectable liver metastasis receiving a short course of tamoxifen, survived for 12 years with stable disease^[42]. A previous article described a similar patient who was treated with tamoxifen and the disease was stable^[104]. Moreover, recent foundational research provided the direct evidence that oestrogenic molecules can affect proliferation of solid pseudopapillary tumors expressing oestrogen and progesterone receptors^[105]. Therefore, a possible therapeutic role of tamoxifen is worth studying for unresectable SPTM with the presence of estrogen receptors. Liver transplantation has been used in some cases and there was no liver recurrence during the follow-up period of 2 to 5 years^[63, 66, 76, 102]. However, the experience of this procedure is quite restrictive, and its use is limited by surgical techniques and liver donor resources.

The results of our univariate analysis indicated that many factors like larger tumors (diameter ≥ 5 cm), lymphovascular invasion, lymph node metastasis, cellular atypia, Ki67 index $\geq 5\%$, postoperative recurrence, recurrent time < 5 years and positive margin were associated with the poor prognosis. Furthermore, patients with lymphovascular invasion, lymph node metastasis, extrapancreatic invasion, cellular atypia, Ki67 $\geq 5\%$, and positive margin were associated with a significantly (all $p < 0.05$) increased risk of recurrence. Previous many retrospective studies have not obtained such plump result. The reason why we can get these findings in our study is that we have significantly fewer II class errors Statistically due to all 159 patients harboring malignant characteristics in our study compared only a few or dozens of SPTM patients in other studies. A recent meta analysis assessing the risk factors associated with the postoperative recurrences of solid pseudopapillary tumor identified larger tumors (diameter > 5 cm), lymphovascular invasion, lymph node metastasis, synchronous metastasis and positive margin were prone to suffer from the recurrences of SPTs^[106]. The results of this meta analysis are comparable to ours. Our findings of this study will provide a more reliable basis for clinicians to comprehensively understand and manage the lesions.

Metastasis or recurrence of liver is the main factor affecting the survival of patients with SPTM. In our study cohort, 26 patients died of uncontrollable liver metastasis, including 6 simultaneous metastasis and 20 postoperative relapses. At present, there is no reliable treatment strategy for unresectable metastatic lesions. Therefore, the early detection of liver metastasis for surgical resection is particularly important; Additionally, majority of relapses occurred within five years, which leads to poor prognosis, hence early regular follow-up is considered necessary; In our results, factors affecting recurrence such as lymphovascular invasion, lymph node metastasis, extrapancreatic invasion, and cellular atypia, Ki67 $\geq 5\%$ also decrease the survival of SPTM patients. Therefore, it is strongly recommended that patients with

such high-risk features should be closely followed up for at least five years in order to detect early liver metastasis.

Our research has the following some limitations. 1. In most of the included cases, the lack of complete data made it impossible to carry out multivariate analysis, so as to provide more accurate evidence. 2. Case reports are inherently flawed with significant selection and publication bias, causing possibly result bias. 3. It is possible that some literatures are not included despite searching multiple databases and performing extensive backward search, moreover articles published in non-English language are not included. 4. We did not analyze the immunohistochemical results due to the limitations of available literature. 5. We did not discuss the scope of the operation, because most operations are decided by the operator according to the patient's condition and the doctor's surgical technique. 6. Although our research results are of reference value, more rigorous studies are needed to confirm them in the future. Despite the limitations, this is the first pooled-analysis on the clinical situation of solid pseudopapillary tumor of the pancreas with malignant behaviors.

Conclusion

Tumor size is an important factor in predicting SPTM before operation, which is beneficial to optimize the surgical planning. Whenever feasible, complete resection surgery should be performed. Long-term follow-up, especially close follow-up in the first 5 years after operation, is essential for patients with SPTM.

Abbreviations

SPTM

solid pseudopapillary tumors of the pancreas with malignant behaviors

Declarations

Ethics approval and consent to participate

The current pooled-analysis was performed on the base of previous studies. Thus, it is not necessary for a formal ethical approval because the data are not individualized.

Consent for publication

Not applicable.

Availability of data and materials

Input data for the analyses are available from the corresponding author on request.

Competing interest

The authors declare that they have no competing interests.

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Tables

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Figures

Fig 1 Study selection.

Figure 1

Flow chart of literature screening.

Figure 2

The forest plot of pooled SPTM incidence.

Figure 3

the relationship between the prediction of SPTM and tumor size.

Figure 4

the relationship between the prediction of SPTM and sex.

Figure 5

the relationship between the predicton of SPTM and tumor calcification.

Figure 6

the relationship between the predicton of SPTM and symptoms.

Figure 7

the relationship between the predicton of SPTM and tumor location.

Figure 8

the relationship between the predicton of SPTM and tumor composition.

Figure 9

the relationship between the predicton of SPTM and tumor necrosis.

Figure 10

Kaplan-Meier survival curve of 159 SPTM patients.

Figure 11

Kaplan-Meier survival curve of 136 SPTM patients after complete surgical resection.

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