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Clinicopathological features, prognosis, and fertility outcomes in Chinese Han women treated for ovarian yolk sac tumor

A retrospective case series study from two tertiary-care academic medical centers

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Abstract

Objective: Ovarian yolk sac tumor (YST) is a very rare malignant tumor in young women. This study aimed to explore the clinicopathological prognostic characteristics and reproductive outcomes of Chinese Han patients.

Methods: To describe a case series study, we reviewed the clinicopathological data of 50 YST patients treated from 2 tertiary medical academic medical centers from January 2009 to December 2019. The Akaike information criterion was used to select variables. The influence of relevant characteristics on prognosis factors was analyzed by the Cox proportional hazard model.

Results: The median follow-up time was 64.5 months (range from 3 to 124 months). The median age was 22.7 years (3 to 34 years). Abdominal pain (54.0%) or mass (42.0%) were the most common clinical symptoms in the early stage of diagnosis. The tumors were located bilaterally in 4 cases. 27 patients, 7 patients, 13 patients, and 3 patients were in stage I, II, III, and IV, respectively. Twenty-one stage I patients and 12 stage II to IV patients underwent fertility-preserving surgery. Of the 50 patients who received postoperative chemotherapy, 49 received the BEP regimen. At the last follow-up, 92% of the patients were still alive. The overall survival rate and disease-free survival rate were 91.6% and 90.6%, respectively. Recurrence occurred in 7 (14%) patients with a median survival time of 16.7 months (range from 3 to 50 months). Six patients had recurrence in the abdominal space. The percentage of Ki67 (P = .01) and tumor size (P = .03) were 2 important prognostic factors in multivariate analysis. In terms of survival outcomes, fertility-preserving surgery can be equivalent to radical surgery. Sixteen patients tried to conceive, and 6 patients with advanced-stage succeeded in 10 pregnancies. Of these, 6 patients successfully gave birth to 6 healthy babies.

Conclusions: The diagnosis of YST of childbearing age is very rare. Because the failure of primary treatment is related to the residual disease after salvage surgery, the fertility and survival results of patients undergoing fertility-preserving surgery are promising.

Abbreviations: AIC = Akaike information criterion, BEP = bleomycin/etoposide/cisplatin, DFS = disease-free survival, FIGO = International Federation of Gynecology and Obstetrics, GOG = Gynecologic Oncology Group, MOGCTs = malignant ovarian germ cell tumors, OS = overall survival, SD = standard deviation, YST = ovarian yolk sac tumor.

Keywords: fertility, independent risk factor, ovarian yolk sac tumor, prognosis

1. Introduction

Malignant ovarian germ cell tumor (MOGCT) accounts for 5% to 10% of ovarian tumors and usually affects young women.[1] The peak incidence focuses on patients aged between 15 and 19 years old.[2,3] Ovarian yolk sac tumor (YST), also defined as endodermal sinus tumor, belongs to the MOGCT group, accounting for about 1% of ovarian malignant tumors.[4] Since most patients diagnosed with YST are young women (infertile or have fertility expectations), maintaining fertility is the primary consideration.[5] Several retrospective studies have demonstrated that fertility-sparing surgery, compared with radical surgery, is effective and practicable.[1,2,6] So far, tubal oophorectomy combined with postoperative chemotherapy will not hurt the

In this study, because anonymous clinical case data were used for data analysis, these data were obtained after each patient's written consent to treatment, so patients do not need to give informed consent to the study.

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fertility of patients and can improve the prognosis of patients. Therefore, the operation is used as a conventional treatment for patients of childbearing age diagnosed with YST.[1,5]

In addition, because MOGCT is highly sensitive to chemotherapy, it is feasible to perform cytoreductive surgery on young patients with advanced MOGCT, followed by chemotherapy and physiotherapy.[2] However, the values of other clinical findings and treatment strategies remain controversial. Additionally, studies focused on the division of race with prognosis and reproductive outcomes are rare. Han nationality accounts for 19% of the world population. The relative rarity of YST hinders the determination of the best treatment scheme, which urges us to analyze its clinicopathological features and prognostic factors. In this study, we included 50 Han female patients diagnosed with YST in 2 large medical centers, and systematically analyzed the clinical characteristics and prognosis of these patients to improve the understanding of this rare disease.

2. Methods

2.1. Patients enrollment

This was a case series retrospective study. From January 2009 to December 2019, we conducted a retrospective study, in which 57 patients diagnosed with YST were retrieved through a search of the medical institution. See Figure S1, Supplemental Digital Content, http://links.lww.com/MD/G858, which illustrates the flow diagram of patient participation. The clinicopathological features, demographics, treatment, follow-up information, and reproductive outcomes of patients are mainly collected from medical records, including clinical charts, laboratory examination results, nursing records, imaging information, and treatment. Clinical staging follows the classification system standard of Federation International of Gynecology and Obstetrics (FIGO, 2018). Fertility-preserving surgery is defined as the patient retaining the uterus and at least one side of the adnexa.[2] The study was approved by the ethics committee(NO. TJ-IRB 20210631). All patient information was strictly confidential.

2.2. Outcomes

The clinicopathological parameters(such as age, FIGO stage, tumor size, specific symptoms, immunohistochemical results, and treatment) were included. Overall survival (OS) was defined as the time from the beginning of treatment to the end of death or follow-up. Disease-free survival (DFS) was defined as the time from the beginning of treatment to the end of recurrence or follow-up.[2] According to the follow-up criteria established by the NCCN oncology clinical practice guidelines, all patients were followed up every 3 months (the first 2 years), every 6 months (3 to 5 years), and then at least once a year.[7] The pregnancy rate is calculated according to the number of healthy babies born or the number of patients who intend to become pregnant. All endpoints were updated in July 2020.

2.3. Statistical analysis

The counting data and measurement data are expressed in standard deviation and percentage, respectively. Survival analysis was visualized by KM curve, and the Cox model was used for prognosis analysis. Considering the number of samples and statistical deviation, the model with the lowest Akaike information criterion (AIC) gives the selectable optimal parameter combination. $P < .05$ was considered to have significant statistical efficacy. The R software (v.3.6.2) was used for all analyses (https://www.r-project.org).

3. Results

3.1. Patients' clinicopathological features and treatment

In this study, 16 patients (stage I) and 15 patients (stage II to IV) underwent pelvic and abdominal aortic dissection, respectively. Among them, 7 patients were diagnosed with lymph node metastasis after operation. Twenty-four patients (stage I) who underwent pelvic and abdominal aortic dissection were diagnosed without lymph node metastasis. Computed tomography scan showed that the nature of an adnexal mass was complex, mainly including cystic and solid components (Fig. 1A). Pathology showed that the lesion had the characteristics of clear cell carcinoma, originated from the ovary, and contained YST components (Fig. 1B). Twenty-one patients (stage I) and 12 patients (stage II to IV) underwent fertility-preserving surgery, respectively. Among them, one patient did not receive surgery, only received chemotherapy, and the other 1 died after 24 months of follow-up. Only one patient did not receive a bleomycin/etoposide/cisplatin (BEP) chemotherapy regimen. Patient characteristics were summarized in Table 1.

3.2. OS and DFS outcomes

To predicate the OS and DFS outcomes, estimated OS rates were 93.9% (1 year), 91.6% (3 years), and 91.6% (5 years), respectively. The DFS rates were 93.9% (1 year), 93.9% (3 years), and 90.6% (5 years), respectively (Fig. 2). Three patients (stage I) and 4 patients (stage II to IV) were diagnosed with progressive disease or relapse. All the patients received cisplatin-based chemotherapy regimens. All recurrence disease occurred with a median of 16.7 (range, 3 to 50) months. Eventually, 4 patients

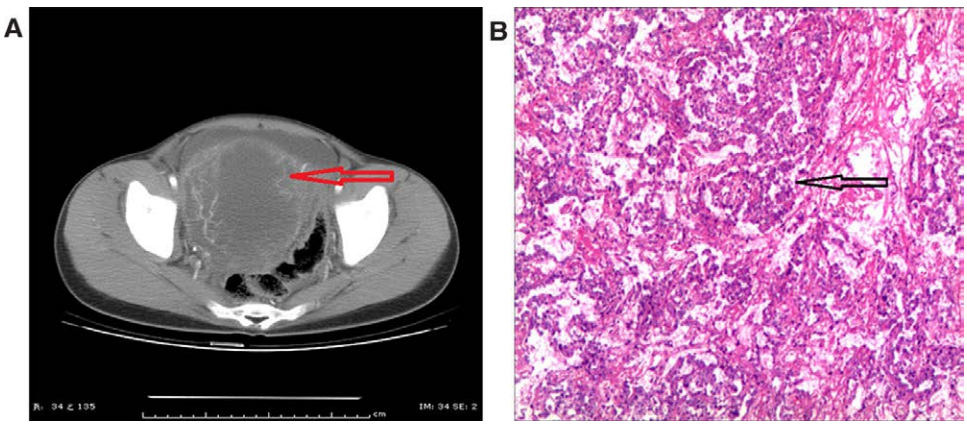

Figure 1. Computed tomography imaging and pathological findings of patients diagnosed with YST. (A) Computed tomography scan on admission. (B) Pathological features of YST. The red arrow indicates the tumor. The black arrow indicates typical pathological signs. YST = ovarian yolk sac tumor.

Table 1

Demographic and baseline clinicopathological features of patients diagnosed with YST.

Variables	Total (n = 50)
Age (y)	
Mean (±SD)	22.7 (±7.13)
<23	23 (46.0%)
≥23	27 (54.0%)
Component	
Mixed	11 (22.0%)
Pure	39 (78.0%)
Marital status	
Married	29 (58.0%)
Unmarried	21 (42.0%)
Pregnant	
Yes	19 (38.0%)
No	31 (62.0%)
Symptom	
Fever	1 (2.0%)
Mass	21 (42.0%)
Menstrual disorders	1 (2.0%)
Abdominal pain	27 (54.0%)
Ki67 (%)	
Mean (±SD)	50.2 (±13.9)
>50	17 (34.0%)
≤50	33 (66.0%)
AFP (IU/mL)	
<1000	8 (16.0%)
≥1000	42 (84.0%)
CA125 (U/mL)	
<35	7 (14.0%)
≥35	43 (86.0%)
CEA (ng/mL)	
<5	46 (92.0%)
≥5	4 (8.0%)
CA199 (U/mL)	
<34	43 (86.0%)
≥34	7 (14.0%)
Surgery	
Both*	1 (2.0%)
Laparoscope	11 (22.0%)
Open	37 (74.0%)
Not performed†	1 (2.0%)
Fertility	
Preserve fertility	41 (82.0%)
No performed	9 (18.0%)
Ascites	
Yes	17 (34.0%)
No	33 (66.0%)
Laterality	
Right	26 (52.0%)
Left	20 (40.0%)
Both	4 (8.0%)
Diameter (cm)‡	
<10	5 (10.0%)
≥10	45 (90.0%)
Chemotherapy	
BEP	49 (98.0%)
EP	1 (2.0%)
FIGO	
I	24 (48.0%)
II–IV	26 (52.0%)

Reference value: CA125 < 35U/mL (normal); CA199 < 34 U/mL (normal); CEA < 5 ng/mL (normal); AFP < 7I U/mL (normal).

BEP = bleomycin, etoposide, cisplatin, FIGO = Federation International of Gynecology and Obstetrics, EP = etoposide, cisplatin, SD = standard deviation.

*Open and laparoscope.

†No surgery was performed.

‡Maximum diameter of tumor.

achieved complete remission after treatment, the rest of the 3 patients died due to progressive diseases, acute neutropenia, and pulmonary infection. Two patients diagnosed with stage II to IV died within 6 months.

3.3. Fertility outcome

In this study, the patients of childbearing age who received conservative surgery and then received BEP chemotherapy successfully gave birth to normal children. In addition, within the follow-up period, a total of 20 patients had normal menstruation, 4 patients had menstrual disorder, and no premenopausal symptoms were found. Sixteen patients tried to get pregnant, and 6 of them successfully got pregnant 10 times. In addition, 6 patients successfully gave birth to 6 healthy infants. The pregnancy rate was 20% and the live birth rate was 12%. The detailed results of fertility results are shown in Table 2.

3.4. Prognosis factors identified by subgroup and variables analyses

In this study, various prognostic factors associated with OS and DFS were analyzed by KM analysis. See Figures S2–S4, Supplemental Digital Content, http://links.lww.com/MD/G858, which illustrates the detailed results of survival outcomes. After stratified by age, Ki67, CA125, CA199, tumor size, FIGO, alpha fetoprotein (AFP), and ascites, there was no significant difference in the remaining variable related OS rates except CA125 (normal vs abnormal, $P = .03$). The age (<23 vs ≥23 years, $P = .2$), Ki67(>50% vs ≤50%, $P = .16$), CA199 (normal vs abnormal, $P = .41$), tumor size (<10 vs ≥10 cm, $P = .24$), FIGO (I vs II–IV, $P = .23$), AFP (normal vs abnormal, $P = .36$), ascites (yes vs no, $P = .55$) showed no significant difference, respectively. Also, there were no significant differences in the DFS rate among these variables, the age (<23 vs ≥23 years, $P = .45$), Ki67 (>50% vs ≤50%, $P = .23$), CA125 (normal vs abnormal, $P = .95$), CA199 (normal vs abnormal, $P = .23$), tumor size (<10 vs ≥10 cm, $P = .76$), FIGO (I vs II–IV, $P = .70$), AFP (normal vs abnormal, $P = .28$), ascites (yes vs no, $P = .30$), respectively. See Figures S5 and S6, Supplemental Digital Content, http://links.lww.com/MD/G858, which illustrates the detailed results of 5-year OS and DFS. In the univariate analysis, the Ki67 [HR: 0.85, 95% confidence interval (CI): 0.73–0.99, $P = .03$] was associated with OS. In the multivariate analysis, the Ki67 (HR: 0.88, 95% CI: 0.79–0.97, $P = .01$) and tumor size (HR: 0.04, 95% CI: 0.002–0.69, $P = .03$) were independent risk factors for DFS. The detailed results of prognosis were shown in Table 3.

4. Discussion

The number of YST cases in many studies is small.[8–10] Consistent with the results reported in previous studies, the incidence rate of YST in Chinese Han women is also very rare. As far as we know, this is the largest single medical center case analysis of Han Chinese patients treated for YST, we hope this study could contribute to our knowledge about this rare entity. YST is the third most common MOGCT, which mainly occurs in young women (≤35 years). Therefore, maintaining fertility is considered to be a crucial choice.[11] As a rare clinical disease, it is very difficult to study its prognosis, which is mainly due to the lack of case data and long-term effective follow-up.

Clinically, the clinical characteristics of YST are similar to other MOGCT, mainly manifested as abdominal pain or abdominal distension. Some patients may have pelvic mass or no symptoms, so they are easy to be misdiagnosed or ignored. In this study, the tumors detected ranged from 4 to 26 centimeters for the largest diameter (average, 10 cm). Compared with other MOGCT, giant tumors mainly show bleeding areas and invasive edges, resulting in adhesion between tumors and other pelvic organs. Compared with other common epithelial

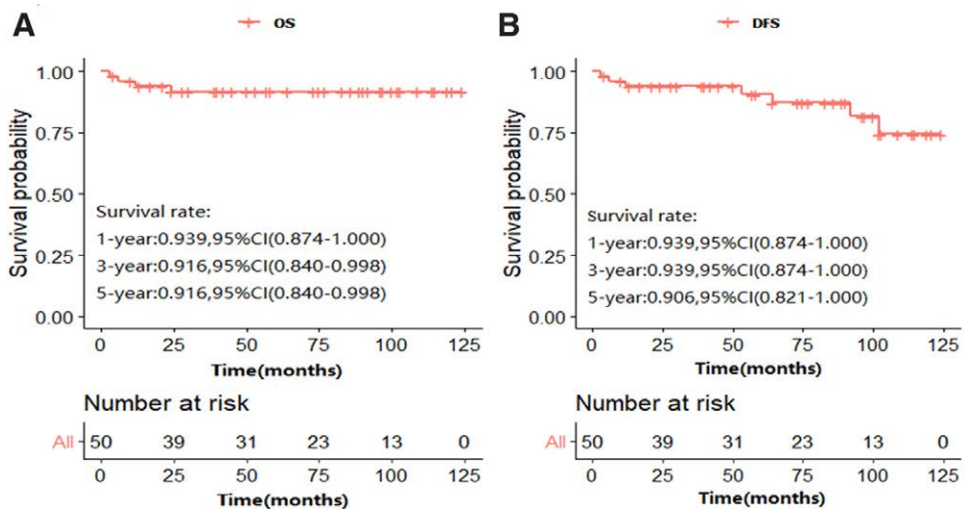

Figure 2. Kaplan–Meier estimates for patients with YST after diagnoses and treatment. (A) Kaplan–Meier survival curve based on overall survival. (B) Kaplan–Meier survival curve based on disease-free survival. YST = ovarian yolk sac tumor.

ovarian cancer subtypes, the age of YST patients tends to be younger. Histopathological diagnosis mainly tended to morphological criteria and immunohistochemical staining. Consistency with previous studies, this study showed that patients with a positive expression such as vimentin, SALL4, Glypican-3, PCK, PLAP, and EMA were found in most patients. A small number of patients showed negative expression of EMA, CD117, CD30, CK7, etc. In this study, the majority of patients with YST were younger, having a median age of 22.7 years. The 5-year OS rate has been reported for >90%.[12,13] However, the incidence of OS in patients with stage III to IV ranged from 10% to 45%, while the reported 5-year survival of stage I to II YST ranged from 66% to 95%.[1,14–17] We showed in our series that the 5-year OS and 5-year DFS of patients with YST were 91.6%, and 90.6%, respectively. BEP combination therapy has been proved to be highly active on MOGCT and has been used clinically as a standard treatment for >30 years.[18] Consistent with the conclusions of previous studies, this study found that the prognosis of the patients was good, which may be related to the patients receiving BEP or EP regimen.[5]

Considering the prognosis of this rare disease, early detection is of equal importance. Several studies have demonstrated P53 protein accumulation in MOGCTs.[19–21] Previous studies have shown that AFP is considered to be a potential biomarker to determine the tumor properties (benign and malignant) in patients with YST. In addition, it should be noted that the increase or decrease of serum AFP can be used as an independent prognostic risk factor in patients with nonspermatogonial germ cell testicular cancer.[22–24] At the same time, previous studies have shown that high serum tumor markers (AFP or hCG) are closely related to the poor prognosis of MOGCT.[25,26] In this study, the serum AFP >1000 ng/mL was presented in the majority of enrolled patients. Age, AFP, tumor diameter, and histology were used to mirror the prognosis but were not found as prognostic factors in the previous studies.[1,15,16] According to previous studies, ascites over 100 mL were identified as an independent prognostic risk factor.[1,16] Meanwhile, the presence of large residual tumors is considered to be an adverse prognostic factor.[13] On the contrary, it has also been reported that the presence of total residual lesions has no significant correlation with poor tumor prognosis, which may be due to the effect of adjuvant chemotherapy regimens on the prognosis of patients.[27] In this study, we found that the lower proliferation rate was negatively correlated with the poor prognosis of patients. Conversely, the high rate of Ki67 positive cells leads to a worse prognosis, which may contribute to the malignant features associated with YST. Our data also demonstrated that the Ki67 index and tumor size were 2 independent predictors of DFS, which might provide practical and clinical guidelines of prognosis for clinicians to prior counsel patients with YST during the period of individual therapy. Besides, CA125 showed a potential predictive role in OS. Additionally, CA 125 in prior to treatment was elevated in more than four-fifths of the patients. This is not surprising because some tumors or inflammatory diseases detected are associated with the increase of CA125, while other tumors or inflammatory diseases are significantly associated with the decrease of CA125. Apart from CA125, increased levels of CA199 and CEA were also found but presented little significant prognostic values. Therefore, CA125 still lacks sensitivity and specificity in evaluating the prognosis of YST, we do not recommend CA125 as an independent prognostic indicator.

For patients diagnosed with invasive tumors (such as YST), how to optimize the treatment strategy to improve the survival rate of patients is still under continuous exploration. Compared with other MOGCTs, YST has very good survival results even in advanced diseases due to its high chemosensitivity.[2,28,29] A clinical study by the gynecological oncology group (GOG) showed that most patients with ovarian germ cell tumors with accurate staging and radical cure can remain disease-free after treatment

Table 2

Reproductive outcome after complete remission.

Classification	No (%)
Primary infertility at diagnosis*	2/50 (4%)
Attempting conception	16/50 (32%)
Not attempting conception	15/50 (30%)
Pregnant before diagnosis	19/50 (38%)
Patients achieving pregnancy	6/50 (12%)
Stage I	5
Stage II–IV	1
Total number of pregnancies	10/50 (20%)
Normal pregnancy	6
Abnormal pregnancy	4
Miscarriage†	2/50 (4%)
Termination	1
Ectopic pregnancy‡	1

*Additional endocrine dysfunction.
†Spontaneous abortion.
‡Tubal ampullary pregnancy.

Table 3

Results of univariate and multivariate analyses of OS and DFS in patients with YST.

	DFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value*	HR (95% CI)	*P* value	HR (95% CI)	*P* value*
Age (y)†	0.96 (0.87–1.06)	.39	-	-	0.96 (0.84–1.09)	.51	-	-
Ki67 (%)†	0.92 (0.84–1.01)	.07	0.88 (0.79–0.97)	0.01	0.85 (0.73–0.99)	.03	-	-
AFP (IU/mL)								
<1000	1				1			
≥1000	0.42 (0.08–2.16)	.30	-	-	-	.99	-	-
CA125 (U/mL)								
Normal	1				1			
Abnormal	0.93 (0.11–7.79)	.95	-	-	0.16 (0.02–1.10)	.06	-	-
CA199 (U/mL)								
Normal	1				1			
Abnormal	-	.99	-	-	-	.99	-	-
Ascites								
No	1				1			
Yes	0.42 (0.08–2.24)	.31	-	-	0.51 (0.05–4.90)	.56	-	-
Diameter (cm)								
<10	1		1		1			
≥10	0.59 (0.07–4.96)	.63	0.04 (0.002–0.69)	0.03	0.28 (0.03–2.71)	.27	-	-
FIGO								
I	1				1			
II–IV	1.35 (0.30–6.10)	.70	-	-	3.69 (0.38–35.45)	.26	-	-

Reference value: CA125 < 35 U/mL (normal); CA199 < 34 U/mL (normal); CEA < 5 ng/mL (normal); AFP < 7 IU/mL (normal).

CI = confidence interval, DFS = disease-free survival, FIGO = Federation International of Gynecology and Obstetrics, HR = hazard ratio, OS = overall survival.

*Based on the Akaike information criterion.

†Continuous variable.

with bleomycin, etoposide, and cisplatin.[1,30] In addition, once effective chemotherapy is detected, the need for lymph node dissection in YST treatment may need to be fully evaluated again.[1] However, more studies in the future are required to explore the role of lymphadenectomy in patients with suspected lymph node metastasis and adjuvant treatment for prognosis.

Our findings are particularly instructive for patients diagnosed with YST in the future. Since adolescents or young women account for a large proportion of patients diagnosed with YST, fertility-preserving surgery should be reconsidered to ensure the safety of tumors.[31] The results of this study showed that all patients who underwent fertility-preserving surgery were as effective as radical surgery, and there were no statistical differences in menstruation and fertility. Consistent with previous literature reports, fertility-preserving surgery is at least as effective as radical surgery,[13] consistent with our studies. Besides, it has been reported the incidence of bilateral YST is between 3% and 8.5% in the literature.[9,32] In the present study, the bilateral involvement rate was 8.0%, consistent with the literature review. Therefore, if the uterus and ovary (nonprimary side) are invaded by cancer foci, careful examination is necessary to ensure that there is no tumor involvement. Fortunately, even patients with disseminated diseases also have methods to retain fertility.[27] Taken together, we recommended the fertility-sparing approach should be reconsidered to make sure that surgery does not result in potential visible disease.

Our results provide valuable insights into the diagnosis, treatment, and prognosis of Chinese Han women with YST. However, this study inevitably has some limitations. First, this is a retrospective case series study, which only includes a small sample size of 2 top-three medical centers. In the future, large-scale population-based studies are still needed to explore the long-term prognosis of YST. Second, this study spans as long as 10 years. Major changes in clinical practice, especially the chemotherapy regimen that may affect our results, may cause potential bias to the results. Third, our research focuses on women of childbearing age. For the clinicopathological characteristics and treatment of postmenopausal patients, further research is still needed in the future.

5. Conclusions

This case series retrospective study provides an epidemiological basis for YST in a single-center cohort of the Chinese Han population. Patients with YST usually present with abdominal pain and masses. Fertility-preserving surgery has a good survival effect for young women with YST, even in the late stage. Patients with poor prognosis factors such as the Ki67 index and tumor size may be considered for aggressive treatment. The reproductive outcome is promising in patients who received fertility-sparing surgery, future studies must be evaluated in a clinical trial as to optimal chemotherapy regimens and prognosis prediction. Taken together, these results provide valuable insight into YST, and contribute to the prolongation of knowledge that is adequately available for this rare tumor.

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Author contributions

Du He initiated the research, Zaiping Wang collected data, Bo Wang conducted the analysis, and Li Qin wrote the manuscript. Du He and Li Qin contributed to the design of the study and provided critical reviews of the manuscript.

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