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Pelvic masses after surgery for immature ovarian teratoma

A 10-year experience of Western China

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Abstract

There are debates on the management of immature ovarian teratoma and its recurrence. This study aimed to report the incidence of pelvic masses after surgery for immature ovarian teratoma and to identify prognostic factors of disease-free survival after surgery, discussing aspects of primary treatment and postoperative management.

Data on the diagnosis and treatment of patients with immature teratomas were collected. Follow-up data were acquired from clinic visits and telephone interviews. Disease-free survival was defined as the time interval between the initial surgery for immature ovarian teratoma and the diagnosis of a new pelvic mass. Survival curves were drawn using the Kaplan-Meire method, and multivariate analysis was performed using the Cox proportional hazard regression model using PASW statistics software.

The estimated 5-year disease-free survival and overall survival were 74.3% (95%CI 63.9%–84.7%) and 96.5% (95%CI 91.6%–100.0%), respectively. The incidence of growing teratoma syndrome and immature teratoma relapse at a median follow-up of 46 months were 20.0% and 7.7%, respectively. Two patients died of repeated relapses or repeated growing teratoma syndrome. Rupture of initial lesions (RR 4.010, 95%CI 1.035–5.531), lymph node dissection (RR 0.212, 95%CI 0.051–0.887) and adjuvant chemotherapy (RR 0.143, 95%CI 0.024–0.845) were independent prognostic factors for disease-free survival.

The development of growing teratoma syndrome is more prevalent than relapse after treatment of immature ovarian teratomas. Lymph node dissection and chemotherapy are recommended to reduce recurrence. Close surveillance and active surgical intervention are important for the diagnosis and appropriate management of new pelvic masses.

Abbreviations: AFP = alpha-fetoprotein, BEP = bleomycin, etoposide, and cisplatin, BVP = bleomycin, vincristine, and cisplatin, CI = confidence interval, FIGO = International Federation of Gynecology and Obstetrics, GCTs = germ cell tumors, GP = gliomatosis peritonei, GTS = growing teratoma syndrome, IOT = Immature ovarian teratoma, LND = lymph node dissection, NCCN = National Comprehensive Cancer Network, NSGCTs = nonseminomatous germ cell tumors, OR = Odds Ratio, RR = relative risk, VAC = vincristine, actinomycin-D, cyclophosphamide.

Keywords: disease-free survival, growing teratoma syndrome, immature ovarian teratoma, prognostic factor, recurrence.

1. Introduction

Immature ovarian teratomas (IOTs) is the most prevalent histology of malignant ovarian germ cell tumors (GCTs),[1] with a recurrence rate of 3.9% to 40% for different stages and grades.[2–7] Thus far, debate exists regarding the management of IOTs.[2]

There are at least 2 types of IOTs recurrence, 1 is of malignant-like histology, hereinafter referred to as "relapse", and another is of benign-like histology, which is called "growing teratoma syndrome" (GTS). The term GTS was originally introduced by Logothetis et al in their study on testicular nonseminomatous germ cell tumors (NSGCTs). GTS is defined as enlarging masses of pure mature teratomatous tissue developing after chemotherapy for GCTs, with normal levels of previously elevated tumor markers, which usually refers to alpha-fetoprotein (AFP).[8]

Unlike the relapse of immature teratoma, GTS has relatively benign biological behavior and is insensitive to chemotherapy or

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radiotherapy.[9] The majority of published studies have indicated surgical resection for GTS instead of escalating chemotherapy.[3,5,10] However, patients with GTS are often suboptimally managed because of a diagnosis failure. Here, we analyzed our 10-year data based on IOTs patients to reveal the incidence of relapse and GTS and provide some insights into the treatment of new pelvic masses after treatment for IOTs.

2. Methods

2.1. Data Collection

The study was approved by the review board of West China Second University Hospital, and written consent was obtained from all patients. IOT patients admitted between January 2009 and June 2019 were identified from the pathology database of West China Second University Hospital, one of the largest referral centers for women in southwest China. The study was conducted in March 2020, and the authors only had access to patients' individual information during the period of data collection. All patients with pathological confirmation of IOTs were included, except those for whom: (1) details of baseline characteristics or primary treatment were unavailable; and (2) no follow-up data. Tissue sections of primary disease and subsequent events from all patients were centrally reviewed and confirmed by 2 experienced pathologists, unless there was inoperable disease for which tissue sample was hard to acquire. Pathologic reports of every surgical specimen were included. Medical records were reviewed for information about baseline characteristics and treatment details, such as surgical findings and chemotherapy regimens. Any test results of serum AFP, CEA, CA125, and CA19-9 levels were also recorded. Details of imaging findings in surveillance of disease recurrences were analyzed. Follow-up data were obtained from outpatient appointments and telephone interviews.

2.2. Statistical analysis

Disease-free survival was defined as the time interval, calculated as months, between primary surgery (not necessarily staging surgery) and identification of a new pelvic/abdominal mass revealed by imaging techniques or a second-look surgery. Survival curves were made with Kaplan-Meire method. Patients who lost to follow-up were censored at their last follow-up. To screen for prognostic factors, we compared disease-free survival between groups using log-rank test. Log-rank test was also used to make comparison between the incidences of relapse and developing GTS, respectively. The rates of lymphadenectomy between patients with recurrences and event-free patients were compared using chi-square test. Clinicopathologic factors that may independently influence the risk of recurrence were identified using the Cox proportional hazard regression model. If there were any cases with missing data, they were excluded from the corresponding analysis. The effects of chemotherapy and lymphadenectomy were assessed in grade II and grade III patients, respectively. Data analysis was conducted using PASW 18.0.0. Statistical significance was set at $P<0.05$.

3. Results

A total of 77 IOTs patients who received medical care in this hospital during the last decade were retrieved from the pathological database. Three of them were excluded because no follow-up records were available. The median follow-up time was 46 months (range, 8–134 months). Four patients were lost to follow-up, 24/33/35, and 60 months after surgery, respectively, among which 3 had no evidence of disease at the last visit.

3.1. Characteristics at presentation of IOTs

The median age of onset was 22 years, ranging from 5 to 45 years. The majority of patients presented with huge pelvic masses and related abdominal pain, and the median of the largest diameter of the tumors was 16 cm, with an interquartile range from 11.8 cm to 20 cm. The preoperative serum AFP level was elevated in 43 of 60 patients, with a median AFP level of 40.6 ng/mL and the highest being 45633 ng/mL. CA125 and CA19-9 levels were also frequently elevated from 50 to 200 U/mL, but seldom exceeded 300 U/mL.

Spontaneous rupture of the tumor was found in 16 patients, while intraoperative rupture occurred in 6 patients. Twenty-six patients had macroscopic ascites, while peritoneal lavage was performed in 38 patients with only 1 positive cytologic finding. During primary surgery, 17 patients presented with gliomatosis peritonei (GP), 8 had positive lymph nodes among 39 who had undergone lymphadenectomy, and all lymphadenopathy were of mature glial tissue. About 44.6% and 39.2% patients had grade II and III disease according to the WHO classification system, only 16.2% patients had grade I disease. However, 70.2% were of International Federation of Gynecology and Obstetrics (FIGO) stage I, while only 6.8% and 23.0% were stage II and III, respectively. None was of stage IV.

3.2. Initial management

All patients were surgically managed as the primary treatment. The pathology of intraoperative frozen sections showed 32 IOTs and 18 mature teratomas. These 18 patients were ultimately diagnosed with immature teratoma on postoperative pathology examination, and a total of 25 patients underwent a second complementary surgery. The median interval between the first and the second surgeries was 39 days. In total, 59 patients (79.7%) underwent unilateral or bilateral salpingo-oophorectomy, while the remaining 15 patients underwent cystectomy, and 6 patients underwent hysterectomy. Fertility was reserved for 67 patients. Staging procedures such as lymph node dissection (LND, 39 patients, 52.7%), omentectomy (48 patients, 66.7%), and appendectomy (16 patients, 21.6%) were performed in 52 patients. A total of 38/52 stage I patients underwent adjuvant chemotherapy, while 4 of the 5 stage II and all stage III patients did so. Fifteen patients did not receive chemotherapy, and most of them had stage I-grade I/II disease (12/15). Bleomycin, etoposide, and cisplatin (BEP) were the most prevalent regimens (54/59), which might be modified as vincristine, actinomycin-D, cyclophosphamide (VAC), bleomycin, vincristine, and cisplatin (BVP) for prevention of lung dysfunction after long-term use of BEP. In addition, paclitaxel, carboplatin, or 5-FU was occasionally added to the regimen in some cases.

3.3. Outcome and statistic analysis

Eighteen patients had recurrences, among which 4 relapsed while 13 developed GTS, and 1 patient developed GTS after treatment for an episode of relapse. The cumulated risk of developing episodes of relapse or GTS was presented as survival curves (Fig. 1). All recurrences were treated surgically, except for 1 patient who had inoperable metastatic disease to the upper liver. Two cycles of chemotherapy with BEP regimen were administered to this patient with no obvious decrease in the volume of hepatic disease as shown by CT imaging. She was assumed to have developed GTS and then managed by Chinese traditional medicine and remained asymptomatic with stable disease for more than 4 years until the end of observation. Three patients had been administered 2–3 cycles of BEP or VAC regimens before undergoing surgery, and pathology revealed pure mature teratomatous tissue. Four patients with relapse and 4 patients with GTS received chemotherapy postoperatively, and both groups had 1 death because of inoperable repeated disease

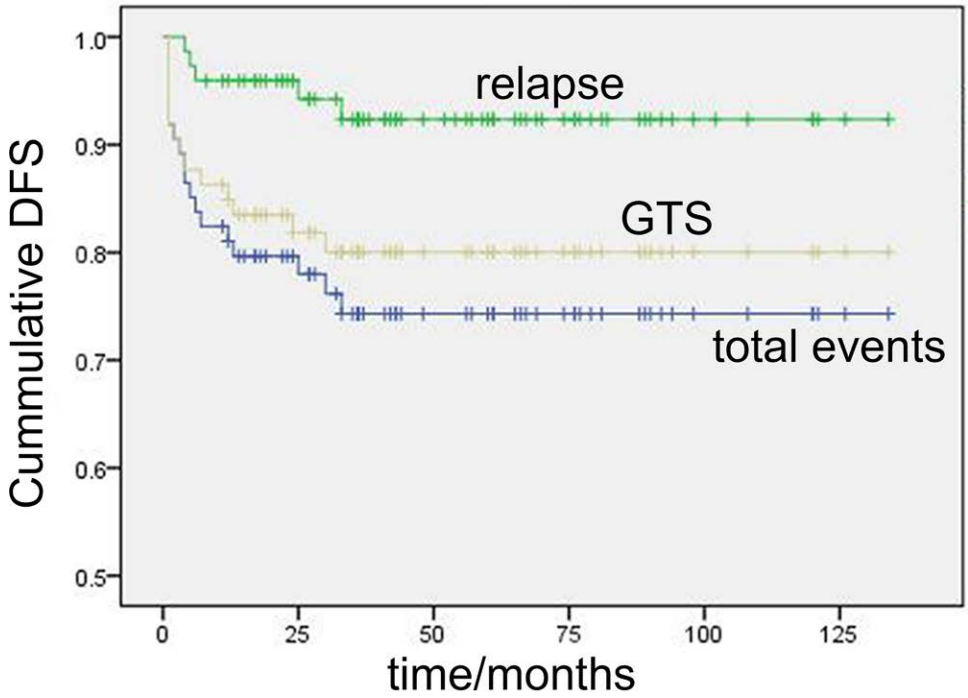

Figure 1. Survival curves calculated by relapse and GTS and a merged curve for total events. DFS = disease-free survival, GTS = growing teratoma syndrome.

insensitive to chemotherapy. Five patients had repeated episodes of recurrence at the end of this study.

The estimated 5-year overall survival and disease-free survival rates for the whole cohort were 96.5% and 74.3%, respectively (95%CI: 91.6%–100.0% and 63.9%–84.7%, respectively). Comparisons of disease-free survival between patients grouped by risk factors are summarized in Table 1 and Figure 2. Multivariate analysis identified both LND, adjuvant chemotherapy, and rupture of IOTs as independent prognostic factors for recurrence (Table 2. LND: RR 0.212, 95% CI 0.051–0.887, P = 0.034; chemotherapy: RR 0.143, 95%CI 0.024–0.845, P = 0.032; rupture: RR 4.010, 95%CI 1.035–15.531, P = 0.044). Other clinicopathological parameters had no significant impact on disease-free survival.

Table 1

Univariate analysis of clinical and pathologic parameters upon initial treatment.

Parameters	Groups	N*	2-year DFS	*P* value
WHO Grade	Grade I	12	91.70%	0.236
	Grade II	33	81.80%	
	Grade III	29	67.90%	
FIGO stage	Stage I	52	80.80%	0.783
	Stage II/III	22	76.80%	
Ascites	<500 mL	57	71.60%	0.265
	≥500 mL	11	80.70%	
Largest diameter	<16 cm	31	74.20%	0.356
	≥16 cm	34	85.20%	
Rupture of ovarian cysts	Yes	22	68.20%	0.317
	Intact orN.A.	52	82.20%	
Lymph node involvement	Positive	8	87.50%	0.806
	Negative	31	90.30%	
Gliomatosis peritonei	Yes	17	88.20%	0.343
	No†	44	77.30%	
Residual disease	Yes	12	51.90%	0.115
	No	62	82.30%	
Lymph node dissection	Yes	38	89.70%	0.003
	No	36	56.70%	
Chemotherapy	Yes	60	82.90%	0.273
	No	14	66.70%	

N.A. = not available.

*Patients with unavailable data were not included.

†Including patients with immature dissemination to the peritoneum and those with no peritoneal deposits.

4. Discussion

The reported rate of developing GTS is low (1.9–7.6%) among male NSGCTs patients.[8,11,12] However, a higher incidence of GTS has been reported in female patients (12%–40%) with GCTs.[5,7,13] The management of GTS and relapse of IOTs is different, despite similar clinical findings. However, the appearance of new masses often confuses clinicians when making clinical decisions. We report our experience of treatment and postoperative management of IOTs patients to clarify the incidence as well as demonstrate factors predictive of recurrence, and to discuss management strategies when new masses appear after treatment for IOTs.

It seems that GTS has become the most prevalent condition when a pelvic mass regrows after treatment for IOTs, given that the estimated incidence of developing GTS and relapse was 20.0% vs 7.7% (P = 0.034) in our cohort. We believe this is a reasonable estimate for Chinese IOTs patients, as supported by the latest work of Wang and Colleagues.[3] Since chemotherapy was introduced in the management of GCTs, the rate of relapse has decreased dramatically[14,15] and the advances in surgery have made the number even smaller. Nevertheless, our study on recurrence after IOTs suggests that there is a growing trend of GTS compared with relapse, and gynecologists should be better aware of this trend when making treatment decisions for these patients.

Although the criteria originally defined by Logothetis to differentiate GTS from relapse have been widely adopted by urologists and gynecologists, it was subtly modified in many later studies on both male and female GTS. For example, in some studies, the newly discovered mass could be a stable mass refractory to chemotherapy, not necessarily growing in

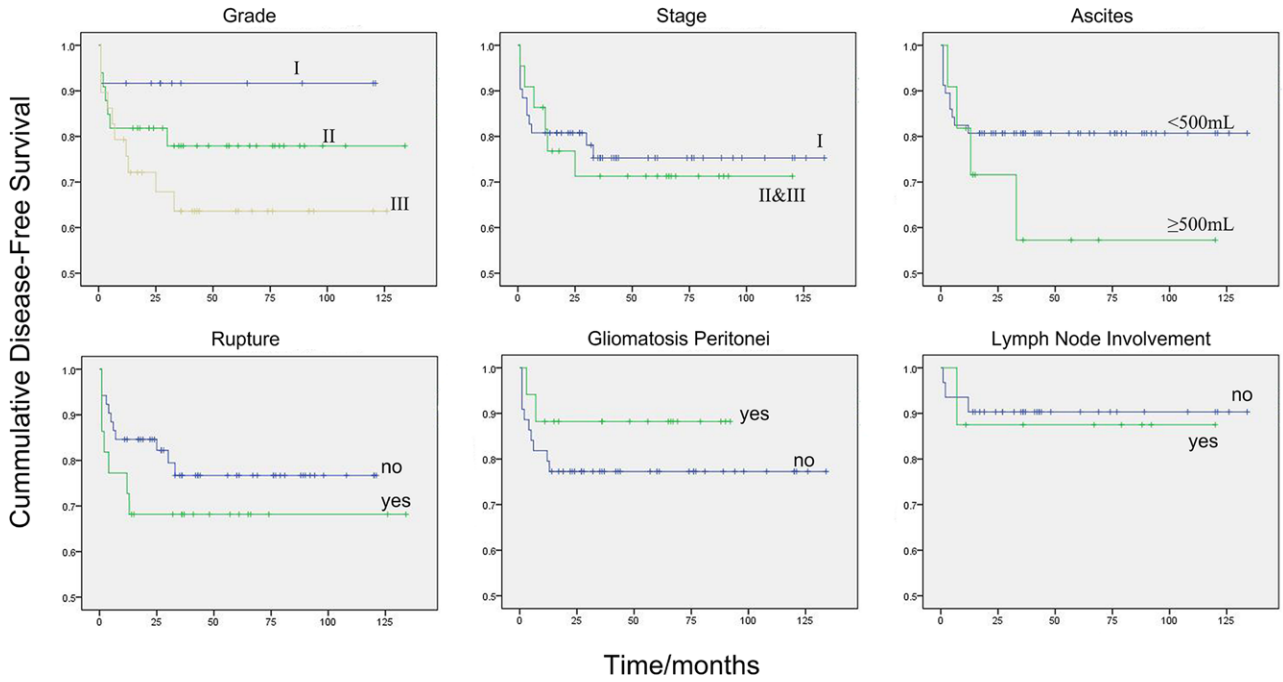

Figure 2. Survival curves grouped by different parameters.

Table 2

Multivariate analysis based on Cox proportional-hazard regression model.

Parameters	Relative risk	95.0% CI for relative risk	*P* value
WHO grade	2.333	0.841–6.474	0.104
Ascites	0.883	0.171–4.550	0.881
Rupture of ovarian cysts	4.010	1.035–15.531	0.044
Peritoneal dissemination*	2.857	0.471–17.341	0.254
Residual disease	2.569	0.461–14.304	0.282
Lymph node dissection	0.212	0.051–0.887	0.034
Adjuvant chemotherapy	0.143	0.024–0.845	0.032

*Including mature and immature metastatic lesions.

size; serum level of AFP could be above the normal range, as long as a decreasing tendency was observed after surgery and/or chemotherapy; patients could also be chemotherapy-naive.[16–19] Four of the 14 GTS patients were chemotherapy-naïve in this study, and the lesion could be identified as early as the time of restaging surgery. Despite the normalization of serum AFP, CA125, serum CA19-9 level could be mildly elevated persistently, in some patients, it even reached a level beyond 200 U/mL. Moreover, we observed normal level of serum AFP during her 2 episodes of relapse in a patient with initially increased serum AFP level; this patient died of repeated relapse 66 months after primary surgery. The above contradictions may reflect more flexible diagnostic criteria for GTS, which means pure mature teratomatous histology is of the most importance.

As relapse and GTS are 2 different patterns of IOTs recurrence that both require early medical intervention, we analyzed our data to identify prognostic factors for recurrence. Surprisingly, survival curves look much alike for early and advanced stages in this cohort, as well as for patients with or without lymph node involvement. In addition, there was a tendency toward better disease-free survival if GP was found during surgery for the initial IOTs (2-year disease-free survival: 88.2% vs 77.3%, P = .343). This is supported by Bentivegna study that IOT patients with GP have excellent survival even if the GP lesions cannot be completely eliminated, because they can remain quiescent for a long time.[20] In multivariate analysis, we incorporated completion of LND instead of stage, as these 2 parameters might be related with each other considering that early stage patients were also less likely to have undergone comprehensive staging surgery. Rupture of IOT lesions, which we believe may have potentiated the formation of immature peritoneal deposits and limited the completeness of primary surgery, was identified as an independent prognostic factor in addition to the performance of LND and administration of chemotherapy.

The value of management for the initial IOT was highlighted by multivariate analysis. LND and adjuvant chemotherapy may have both played protective roles to prevent recurrence. We found that among all the 18 patients who developed a subsequent event, only 3 had undergone LND, and, the only 2 deaths occurred in patients who had no LND in their primary surgery for IOT. In contrast, the LND rate was 62.5% (35/56) in event-free patients (OR 5.833, χ^2 = 8.865, P = 0.003). The value of LND was especially underlined in grade III patients (Fig. 3, upper panel). Despite the recommendation to perform comprehensive staging for GCT patients who chose to preserve fertility,[21] the therapeutic effect of LND has been debated. Incomplete staging has been identified as an independent prognostic factor for worse disease-free survival in patients with GCTs who underwent fertility-sparing surgeries.[4] However, some studies have challenged the role of LND as a fundamental process of staging. In a study of pure IOTs patients, none of the 25% patients without staging surgery developed recurrence at a median follow-up of 46 months.[22] According to Nasioudis et al's investigation of over 2000 young ovarian GCTs patients from the SEER database, only 45.3% of stage I patients acquired LND, but whether LND was performed had no significant impact on cancer-specific survival.[23] Nevertheless, Nasioudis observed a significant decreasing trend over time for hysterectomy and omentectomy but not for LND in young GCTs patients, reflecting the consensus that LND is still an indispensable part of the management. The completion of LND could have implied a more comprehensive staging process.

As adjuvant chemotherapy significantly reduced recurrence in surgically treated IOTs patients, it has become standard for IOTs, except for those with stage 1, grade 1 disease.[15] However,

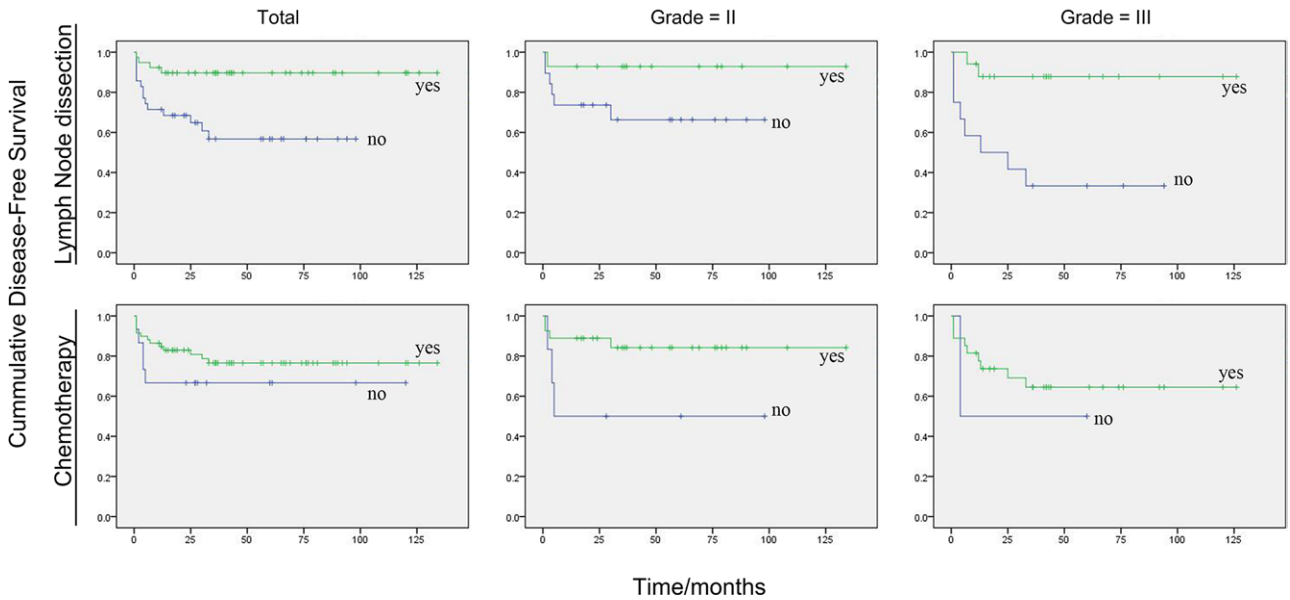

Figure 3. Survival curves of LND and chemotherapy (stratified by grade). Notes: Survival curve for grade I is not available because all cases are censored in one of the arms.

debate also exists regarding the indications to apply chemotherapy. In a pooled analysis of pediatric and adult patients with IOTs from 4 different clinical trials, all adult patients received chemotherapy.[6] In a prospective trial designed for fertility-spared IOTs patients, only those with stage III or grade III disease were treated with platinum-based regimens, while all stage I/II-grade I/II patients underwent surgery alone. In this study, only 2 of the 22 chemotherapy-naive patients developed recurrence at a median follow-up of 47 months and were salvaged successfully, and the authors recommended that chemotherapy was not necessary for stage I/II-grade I/II IOTs.[24] The sample volume in this study was relatively small. However, chemotherapy was identified as an independent prognostic factor for better disease-free survival in our Cox regression model. The incidence of recurrence was extremely high if chemotherapy was obsolete, even in patients with stage I disease (5/15). A potential protective role has also been revealed after grade stratification (Fig. 3, lower panel, 2-year disease-free survival for grade II: 84.2% vs 50.0%, P = 0.054). Chemotherapy could have helped eliminate residual disease. Residual disease has been reported to be strongly correlated with the risk of developing GTS after treatment for IOTs (OR 11.68, 95%CI 4.08–33.42),[3] but it is not an independent prognostic factor of disease-free survival in the present cohort. All of our patients with gross residual disease received more than 4 cycles of platinum-based chemotherapy, except for 1 patient who received only 3 cycles of BEP regimen. Therefore, it is reasonable that the high chemosensitivity of IOTs may counteract the risk of residual disease.

As the management of relapse and GTS are very different, to differentiate these 2 conditions is of vital importance to avoid unnecessary chemotherapy, as well as to prevent inoperable disease. Research on recurrences of GCTs has witnessed a shift to GTS in the past few years. High-dose chemotherapy or TIP regimen (paclitaxel, ifosfamide, cisplatin) is recommended for relapsed testicular GCTs, which has been adopted by the NCCN guidelines for women,[25] while surgery is reserved for GTS as mature taratomatous tissue is constantly refractory to chemotherapy.

The prognosis of resectable GTS is excellent, so close surveillance to detect the lesions when they are operable is of great importance. Spiess et al reported that the growth rate of GTS lesions fluctuated drastically with a 95%CI of tumor volume growth between 0 and 854.5 cc per month.[10] Therefore, there is a high possibility that a long interval between follow-ups may lead to inoperable disease. The only 2 deaths in the present cohort were both caused by inoperable diseases, and both patients had delayed for more than 6 months to assess the possibility of surgery from the time when new pelvic masses were detected. We recommend intensive postoperative surveillance every 3 months or with higher frequency to detect new localized pelvic lesions earlier.

PET/CT and measurement of tumor markers are 2 useful means of diagnosing malignancies, but they have limited value in differentiating relapses and GTSs.[26] As so far, no imaging technique reliably differentiates GTS from viable disease in male patients,[27] but the role of imaging in differential diagnosis of GTS and relapse in female patients has not been fully determined. Three patients underwent PET/CT scanning when recurrences occurred. PET/CT revealed moderate or high uptake of F^{18}-FDG in 2 patients with GTS. The third patient who had PET/CT examination experienced 2 episodes of relapse, typical malignant F^{18}-FDG uptake has been shown during her first episode but not during the second episode. Interestingly, the serum AFP level of the third patient was elevated to 1200 ng/mL before initial treatment for primary IOT, but remained within the normal range during the subsequent episodes of relapse, but with significant elevation of serum CA125 level.

CT scanning is the most widely used imaging modality for post chemotherapy surveillance in male NSGCTs patients.[27] However, transvaginal ultrasonography was the most prevailed method for women patients as it is safe, convenient and cost-effective. It is well understood that mature ovarian teratomas and IOTs both demonstrates lipid materials and calcification changes, but mature ovarian teratomas are usually cystic and IOTs are usually solid, and IOTs has less or smaller foci of fat.[28] The primary lesions of IOTs in our cohort were mostly pure solid or mixed solid-cystic lesion with signal of blood flow, while lesions of subsequent recurrences were mostly mixed solid-cystic lesion or pure cystic lesion. Signal of fat and calcification were identified in both the primary disease and subsequent disease. It was quite different from the condition in male patients, which are often presented with intraperitoneal solid masses.

Table 3

Clinical characteristics of 18 patients with recurrences.

	Original IOTs					Episodes of recurrences						
Patient no.	Age	Stage	Grade	Imaging	AFP	Event	Imaging	AFP	Event	Imaging	AFP	Outcome*
01	28	III	II	◐	/	GTS	◐	normal	GTS	◐	normal	†22
02	27	I	III	/	elevated	GTS	○	normal	GTS	●	normal	41
03	15	I	II	/	/	GTS	○	/				36
04	17	III	III	◐	elevated	GTS	○	normal				38
05	26	II	III	●	elevated	GTS	◐	normal				54
06	14	III	III	/	elevated	Relapse	◐	normal	Relapse	●	normal	†66
07	17	I	II	◐	/	Relapse	◐	elevated	GTS	○	normal	106
08	18	III	III	◐	elevated	GTS	◐	normal				82
09	26	I	III	○	/	GTS	◐	normal				22
10	22	I	III	◐	elevated	Relapse	◐	normal				33
11	26	I	II	/	normal	GTS	○	normal				8
12	22	I	III	◐	elevated	GTS	/	normal				21
13	16	I	I	◐	/	GTS	○	normal				70
14	15	I	III	/	elevated	Relapse	/	elevated				33
15	21	I	II	/	/	GTS	◐	normal				52
16	45	I	III	/	normal	Relapse	◐	elevated				60
17	15	I	II	/	/	GTS	/	/	GTS	◐	normal	102
18	27	II	II	/	/	GTS	◐	normal	GTS	◐	normal	59

IOTs = immature ovarian teratomas; GTS = growing teratoma syndrome; ○ = cystic, ◐= solid-cystic, ●= solid, / = data not available or tests not performed.

*Outcome was calculated for survival months.

†Deaths.

The characteristics of fat and calcification in IOTs lesions are often scattered small foci. Green et al suggested in their review that larger amounts of fat and calcification could be present in the GTS lesion than in the primary tumor.[27] Intralesional fat, calcification or cystic changes on CT scan, combined with normal tumor markers (AFP), can help in differential diagnosis of GTS and IOTs relapse.[29] In the present cohort, among the 39 patients who had both detailed profile of imaging and baseline tumor markers of their primary IOTs disease, 29/39 (74.4%) had solid or solid-cystic lesions with high serum-level of AFP, which are typical of IOTs, while the other ten patients (25.6%) had cystic primary lesions or with normal serum level of AFP. For episodes of recurrences, IOTs relapse could be pure solid or solid-cystic changes on imaging, with elevated or normal serum level of AFP; GTS were solid-cystic or pure cystic changes on imaging, with normal serum level of AFP among them all (Table 3).

Given that GTS is more prevalent than relapse after treatment for IOTs, gynecologists and chemotherapists should raise their concern about differential diagnosis to give correct treatment. From our experience, we propose early surgical intervention when a metastatic mass is detected to prevent the development of inoperable disease and to obtain pathologic evidence for complementary therapy, especially when the previously-elevated serum AFP level decreased to a normal range and with cystic lesions.

5. Conclusions

The prognosis of surgically treated IOTs patients is good, with an estimated 5-year overall survival rate of 96.5%. LND may play a vital role in reducing the incidence of recurrence, and adjuvant chemotherapy is strongly recommended in the initial treatment, even for stage I patients, if prevention of recurrences is the principal purpose. Although there is a recurrence rate of 20%, it can usually be salvaged by early detection and intervention. We propose intensive surveillance for IOTs to reduce the possibility of developing inoperable diseases. GTS seems to be more prevalent than IOTs relapse; therefore, we recommend active surgery to eliminate gross lesions and avoid unnecessary chemotherapy. This study was limited by its retrospective design. Additionally, this study is based on the experience of a single institute, and the findings may not be suitable for patients in other regions.

Author contributions

Sixia Xie: conceptualization, methodology, analysis and interpretation of data, original draft, revision and editing.
Xibiao Jia: study design, formal analysis, analysis and interpretation of data, critical review of the manuscript.
Tingting Li: data curation, analysis and interpretation of data, original draft, revision
Yuanyuan Xu: methodology, aata collection, critical review of the manuscript.
Weiwei Wu: case retrieval, pathology review, critical review of the manuscript.
Yichao Qiu: data acquisition, critical review of the manuscript.
Shuang Yuan: data acquisition, critical review of the manuscript.
Xue Peng: data curation, critical review of the manuscript.
Hongjing Wang: conceptualization, resources, supervision, funding acquisition, critical review, and final approval of the manuscript.

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