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Research Report

Early stage ovarian immature teratoma, surveillance or chemotherapy after surgery? A propensity score matched analysis

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ABSTRACT

Objective: To compare the survival outcomes between surveillance and adjuvant chemotherapy in patients with stage I ovarian immature teratomas (ITs) who underwent fertility sparing surgery.
Methods: In this retrospective cohort analysis, patients with stage IA Grade 2–3, stage IB and IC ovarian ITs who underwent surveillance after surgery between 2016 and 2021 from Peking Union Medical College Hospital were identified. A 1:1 propensity score matching was performed in patients who had adjuvant chemotherapy by age, stage, and grade.
Results: A total of 16 patients without adjuvant chemotherapy were identified. There were 3 stage IA and 13 stage IC patients. The median age at diagnosis was 14.5 years old (range 3–30). There were 6 patients who had grade 1 tumor, 5 grade 2, 5 grade 3. After a mean follow-up period of 27.4 months, a patient with stage IA grade 2 IT who underwent ovarian cystectomy had recurrence in the same ovary. 16 patients who received adjuvant chemotherapy were screened as controls. The tumor stage and grade were similar in two groups. The median age was older in the chemotherapy group. Of the 16 matched patients there was one recurrence. There was no statistical difference in 3-year disease-free survival (DFS) between surveillance group and chemotherapy group ($p = 0.808$).
Conclusion: We did not observe survival differences or recurrence rates between patients who underwent adjuvant chemotherapy or those who did not with stage I ovarian ITs. Our study suggests surveillance may be safe and preferable in early-stage IT patients who underwent complete tumor resection.

1. Introduction

Immature teratomas of the ovary are rare representing about 1% of all ovarian cancers (Ray-Coquard et al., 2018). They are mainly diagnosed in pediatric and adolescent patients with the majority in stage I disease (Mangili et al., 2011; Veneris et al., 2020). The pathologic grade, based on the quantity of immature neuroepithelial component, is considered a significant prognostic factor (Norris et al., 1976). Other prognostic indicators are stage and completeness of surgical resection (Mangili et al., 2010). Previous case series reports have shown that a lower recurrence can be achieved in patients receiving adjuvant platinum based chemotherapy (Gershenson et al., 1986). Thus, the standard of care has been cytoreductive surgery followed by chemotherapy for all patients with ovarian IT except stage I, grade 1tumors. Following this treatment schema, the 5-year overall survival rate of ovarian ITs is more than 95% (Armstrong et al., 2021; Mann et al., 2008). However, the chemosensitivity of ITs is under debate as in the growing teratoma syndrome which has been attributed to chemoresistance. A pediatric intergroup research (INT 0106) from the Children's Oncology Group (COG) has proven that complete resection of tumor is curative for pediatric and adolescent patients with ovarian ITs, regardless of grade (Cushing et al., 1999). Since then, the approach of pediatric and adolescent patients has differed from adults. However, recent retrospective studies in adult ITs also suggested similar recurrence rate between surveillance and postoperative chemotherapy in patients with stage I ovarian ITs of any grade (Mangili et al., 2010). In addition, salvage surgery and chemotherapy in patients with recurrence can achieve complete remission with long term disease-free survival (Mangili et al., 2010). Since adjuvant chemotherapy does not decrease the risk of recurrence, an alternative approach of surveillance alone has been proposed in stage I disease. The primary aim of this study is to assess the survival and recurrence rate in patients with stage IA G2-3 and

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IB-IC ITs who underwent surveillance versus adjuvant chemotherapy after fertility preserving surgery.

2. Methods

The Peking Union Medical College Hospital (PUMCH) Institution Review Board approved this retrospective cohort study. Before the year 2016, all patients with ovarian ITs underwent adjuvant chemotherapy after complete resection of tumor except stage I grade 1 disease. Since the concept of chemotherapy in stage I ovarian ITs was changing, some institutions started to adopt active surveillance after cytoreductive surgery especially in pediatric patients. In our institution, the practice was slightly changed after 2016. For patients with stage I ovarian ITs, a consultation of risk and benefit regarding adjuvant chemotherapy was conducted by gynecologic oncologists and pediatricians. A shared decision about surveillance or chemotherapy was made by physician and patients or their guardians. Patients who finally decided to undergo surveillance were included in surveillance group. The medical records of patients with stage IA G2-3 or IB-IC ITs who were treated at PUMCH between January 2016 to November 2021 were reviewed. The following information was collected for analysis: the age of diagnosis, clinical presentation, tumor markers, tumor size, surgical details, stage, pathological grade, follow-up, relapse details and outcome. Patients were staged according to the FIGO classification of ovarian tumors. The histological grade of the tumor was based on degree of immaturity, presence and amount of the neuroepithelial component. Tumor tissue was evaluated by central pathology review to confirm diagnosis and tumor grading. Mixed germ cell tumor containing immature teratoma elements were excluded from this study.

2.1. Surgery

The patients who received fertility sparing surgery were included. The uterus and at least one ovary were preserved. Either unilateral salpingo-oophorectomy (USO) or cystectomy was performed, aiming to achieve no residual tumor macroscopically. Surgical route was documented as open or minimal invasive surgery (MIS).

2.2. Chemotherapy

In patients who underwent adjuvant chemotherapy, cisplatin, bleomycin and etoposide (PEB)/ vinblastine (PVB) were given within 14 days after initial surgery. The PEB regimens were cisplatin (100 mg/m^2, divided in d1-3), etoposide (100 mg/m^2, d1-3) every 3 weeks and bleomycin (20 IU/ m^2, maximum 30 IU, d2) every week for 3 or 4 courses. The PVB regimens were cisplatin (100 mg/m^2, divided in d1-3), VCR (1–1.5 mg/m^2, d1-2) every 3 weeks and bleomycin (20 IU/ m^2, maximum 30 IU, d2) every week for 3 or 4 courses.

2.3. Follow-Up

After treatment completion, patients were followed every 3–6 months for the first 2 years, 6–12 months for 3–5 years, then annually thereafter. Patients were actively followed by the physician with 100% follow-up. Site of recurrence was documented as locoregional (intra pelvis), distant and multiple. Distant recurrences were identified as metastases beyond the pelvis, intraperitoneal tumor dissemination, or metastases to abdominal viscera. Disease-free survival (DFS) was defined as the time (months) from diagnosis to disease recurrence. Overall survival (OS) was defined as the time (months) from initial diagnosis to death from all causes. Data on patients with no evidence of disease recurrence or death were censored at the date of last follow-up.

2.4. Statistics

A propensity score matching (PSM) method was utilized to select patients in the chemotherapy group from 2001 to 2021. A propensity score was developed through a multivariable logistic regression model. Three covariates, age (<19,≥ 19), FIGO stage (IA, IC) and pathological grade (G1, G2-3) were included in the model. Patients from the chemotherapy group were matched 1:1 to patients from the surveillance group using a caliper width ≤ 0.02 standard deviations of the logit odds of the estimated propensity score. Statistical analysis was carried out using SPSS Statistical Package version 25 for MAC (IBM Company, Armonk, NY, USA). Disease-free survival curves were calculated using the Kaplan–Meier method and compared using the log-rank test. Statistical difference was considered significant when p value was < 0.05.

3. Results

From 2016 to 2021, 16 patients with stage IA G2-3 and IC of any grade ITs treated with fertility-sparing surgery alone were identified from the PUMCH Rare Cancer Registry. Another 16 patients who underwent adjuvant chemotherapy after surgery were matched to the surveillance group by stage, grade and age. Supplementary 1 summarizes patient demographics and tumor characteristics.

In the surveillance group, the median age at diagnosis was 14.5 years old (range 3–30). The major clinical manifestation was abdominopelvic mass (87.50%). Serum alpha-fetoprotein (AFP) level was elevated in 9 patients (56.25%), CA125 in 5, CA199 in 3 and NSE in 2 patients before surgery. All the patients underwent fertility sparing surgery of either cystectomy (n = 10) or unilateral salpingo-oophorectomy (n = 6): 9 received open surgery and 7 received laparoscopic surgery. There were 3 patients with FIGO stages IA (18.75%) tumor and 13 IC (81.25%); 6 grade 1 tumor (37.50%), 5 grade 2 (31.25%) and 5 grade 3 (31.25%). The median diameter of the tumor was 10 cm (range 5–17 cm). Menstruation was not affected after treatment in all 8 patients of reproductive age. After surgery, three patients accomplished pregnancy and successful delivery without any adverse events. There were no evidence of malformations or other disabilities in the fetus or newborns.

In the chemotherapy group, the tumor stage and tumor grade were similar to the surveillance group. The median age was older in the chemotherapy group, as compared to the surveillance group (21.5 vs 14.5). The demographic features of chemotherapy group are shown in Supplementary 2. There was no statistical difference in tumor characteristic between the two groups. (Table 1).

The median follow-up time was 24 months (range: 10–69) in the surveillance group and 57.5 months (range: 6–72) in the chemotherapy group. Each group had one recurrence during follow-up. In the surveillance group, a 25-year-old patient who underwent laparoscopic cystectomy suffered recurrence in the residual ovary 4 months after

Table 1
Characteristic of surveillance vs chemotherapy group.

	Surveillance group (n = 16)	Chemotherapy group (n = 16)	Effect size
Age			1.00
≤19	8	8	
> 19	8	8	
Stage			1.00
IA	3	3	
IC	13	13	
Grade			1.00
1	6	6	
2–3	10	10	
Surgery			0.127
Open	9	13	
MIS	7	3	
AFP			0.723
normal or unknown	7	9	
abnormal	9	7	

AFP, Alpha Fetoprotein.

initial surgery. She received unilateral salpingo-oophorectomy and adjuvant chemotherapy after relapse. In the chemotherapy group, one patient with previous USO experienced recurrence on the contralateral ovary 25 months after treatment. She underwent unilateral salpingo-oophorectomy with adjuvant PVB chemotherapy. There were 3 patients in the chemotherapy group who had developed ovarian cysts and received cystectomy with pathological confirmation of mature teratoma. The recurrence rate of grade 2 or 3 ITs in the surveillance group was the same as in the chemotherapy group. By the time of last follow-up, all patients had no evidence of disease (NED). Details of recurrences and management are shown in Table 2.

There was no statistical difference in 3-year disease-free survival (DFS) between surveillance group and chemotherapy group (follow-up time censored at 72 months, Log Rank $p = 0.808$) (Fig. 1).

4. Discussion

In this matched cohort study, we did not observe differences in recurrences between patients with or without adjuvant chemotherapy after complete resection of stage I grade 2 and 3 ovarian ITs.

Fertility-sparing surgery followed by surveillance is considered the standard approach for stage IA G1 ITs. The indications for adjuvant chemotherapy in patients with stage IA G2-3 and IB-IC is controversial. The National Comprehensive Cancer Network (NCCN) guidelines recommend adjuvant chemotherapy for adults with stage IA G2-3 and IB-IC disease, while observation or chemotherapy may be considered for children or adolescents with select stage IA or IB tumors (Armstrong et al., 2021). The 2018 FIGO cancer report suggests that only patients with stage IA G1–2 ITs can be observed after primary conservative surgery (Berek et al., 2018). The European Society for Medical Oncology (ESMO) and the European Society of Gynecologic Oncology (ESGO) guidelines (Ray-Coquard et al., 2018; Sessa et al., 2020) recommend active surveillance for properly staged patients with stage IA G2-3, especially when postoperative tumor markers were negative. For stage IC patients, ESGO guidelines suggest a different strategy in stage IC1 and IC2/IC3 patients. Chemotherapy is recommended in patients with stage IC2 and IC3 ITs (maximum 3 cycles) and is optional in stage IC1 patients (Sessa et al., 2020).

More recently, several studies have evaluated active surveillance alone as a strategy instead of adjuvant chemotherapy for pediatric and adolescent patients with stage I ITs. Studies from the Pediatric Oncology Group and the Children's Cancer Group (Cushing et al., 1999; Marina et al., 1999) indicated that surgery alone is curative for most girls and adolescents with ITs, even when associated with increased level of serum AFP or microscopic yolk sac tumor (YST). A study of 7 pediatric trials and 2 adult trials with 179 patients (98 pediatric patients and 81 adult patients) who had underwent complete tumor resection without adjuvant chemotherapy were analyzed (Pashankar et al., 2016). This study reported that the 5-year event-free survival (EFS) and the overall survival (OS) were 91% and 99% respectively, similar to what is reported in the literature for those receiving post-operative chemotherapy (Pashankar et al., 2016). In pooled analysis, adjuvant chemotherapy did not appear to show additional survival benefit in stage I pediatric patients, thus there are interests in evaluating surveillance as a strategy in adolescent and adult patients. Since ITs often occur in young female of reproductive age, avoidance of cytotoxic chemotherapy can help preserve fertility. Two studies (Dark et al., 1997; Patterson et al., 2008) focusing on adult patients suggested that stage IA malignant ovarian germ cell tumors (MOGCTs) are adequately managed by surgery followed by surveillance. Another study (Palenzuela et al., 2008) showed that patients with stage IC and IX MOGCTs may benefit from adjuvant chemotherapy. There is a lack of evidence in adult patients with stage I ITs. Stage I IT is a type of special MOGCT type with relatively slow growth rate, low recurrence rate and the potential of transformation into mature teratoma (Pectasides et al., 2008). In addition, there are reports that chemotherapy may induce the ITs epithelial transformation and rapidly growing, which is defined as growing teratoma syndrome (GTS) (Van Nguyen et al., 2016). Because of this, we made the assumption that complete tumor resection without chemotherapy may be safe in patients with stage I ITs of any age group.

In our institution, we adopted the strategy of active surveillance in stage I ovarian ITs in 2016. From 2016 to 2021, only one patient suffered tumor relapse in the same ovary 2 months after initial resection, which we hypothesize may be due to microscopic residual tumor. None of the 13 patients with stage IC disease experienced recurrence within the follow-up period.

Tumor grade is another important prognostic factor. Chemotherapy is typically recommended in patients with higher grade tumors. However, recent studies focusing on high grade stage I ITs concluded that there was no statistic difference in OS and malignant relapse between patients who did and did not receive adjuvant chemotherapy (Bergamini et al., 2020; Nasioudis et al., 2021). We did not observe any survival benefit from chemotherapy in patients with grade 2 or 3 ITs in this study. We concluded that active surveillance may be acceptable in patients with higher grade if tumor is confined in the ovary and can be completely resected.

Since most patients of ITs are young women of reproductive age, one needs to consider the possibility of the toxic effect of chemotherapy agents to fertility. Gershenson et al. (2007) reported that for patients with MOGCTs, fertility-sparing surgery plus chemotherapy had effects on sexual function. Compared with controls, survivors had significantly greater reproductive concerns ($p < 0.0001$), less sexual pleasure ($p = 0.017$), and lower scores on the total Sexual Activity Scale Score ($p = 0.007$). We consider it safe to complete pregnancy after surgical treatment of early stage ITs without chemotherapy in patient of reproductive age.

We consider the complete resection of tumor in the initial surgery as the key for successful close surveillance. Oophorectomy is safe, allows for complete resection and reduces the likelihood of tumor spillage (Oltmann et al., 2010). The role of cystectomy as a conservative surgical procedure instead of oophorectomy is still debated. Beiner et al (Beiner et al., 2004) reported cystectomy followed by adjuvant chemotherapy to be satisfactory for early-stage ITs. However, there is a lack of evidence about the oncological safety in cystectomy alone in patients with stage I ITs. The ESGO guidelines do not recommend cystectomy as the only treatment in patients with ITs. If an initial cystectomy or tumorectomy has been done with no indication for adjuvant treatment, additional surgery to remove the residual ovary is required to reduce the risk of recurrence (Sessa et al., 2020), since cystectomy may be associated with local recurrence (Renaud et al., 2019). Our study suggests cystectomy seems to be a risk factor for recurrence which may be due to possible microscopic residual tumor in the ovary. Oophorectomy with close surveillance may be superior to cystectomy followed by chemotherapy in this patient setting. Cystectomy may be preferable in patients with stage IB disease, which is rare.

Table 2
Relapsed patient details.

	Surveillance group	Chemotherapy group
Follow-up time (month) (mean, SD)	27.4	47.9
Recurrence (n)	1	1
Stage, Grade	IA, G2	IC, G3
Surgery	CYT	USO
Site of recurrence	Same side, local	Different side, local
Time to recurrence (month)	2	25
Treatment	Surgery followed by PEB	Surgery followed by PVB
Outcomes	CR	CR

SD, standard deviation; CYT, cystectomy; USO, unilateral salpingo-oophorectomy; PEB, cisplatin, bleomycin and etoposide; PVB, cisplatin, bleomycin and vinblastine; CR, complete remission.

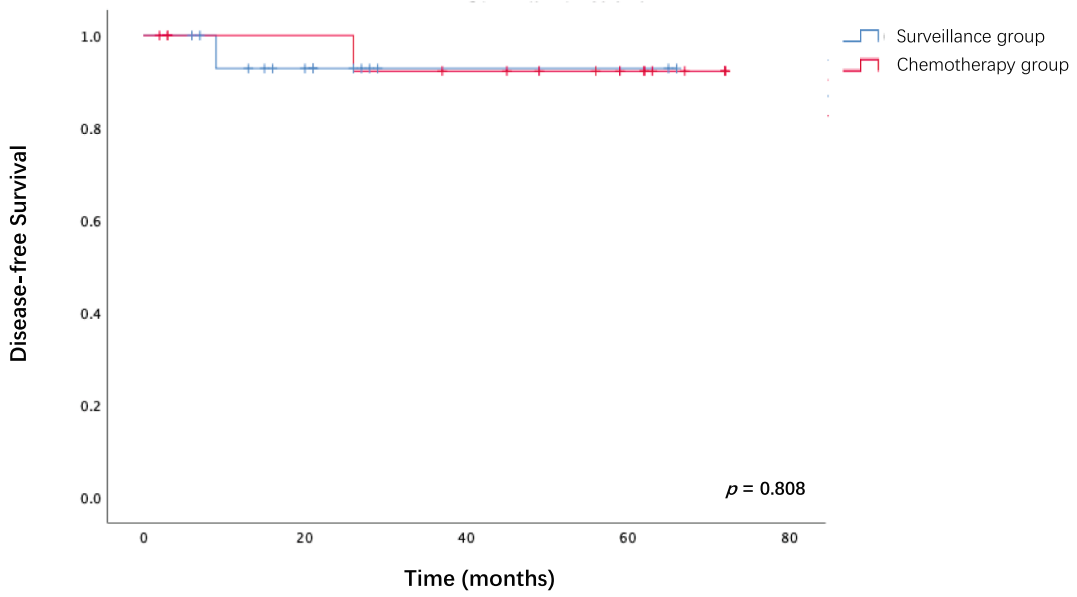

Fig. 1. DFS of patients of surveillance vs chemotherapy group.

The strength of this study is that a single institution was able to collect the number of cases reported of a rare disease, which allowed for analysis of detailed information and long-term follow-up. We used the matched method to balance the baseline characteristics, in order to minimize the bias between two groups.

However, there are several limitations to our study. It is a retrospective study with unavoidable, inherent biases. The sample size was small because of the low incidence of this disease.

Given the rarity of this disease and different opinions of post-operative approach, a randomized prospective trial in this population may be difficult and need collaborative efforts. AGCT1531, which is a phase 3 clinical trials including active surveillance for low risk pediatric and adult patients with germ cell tumors, has been sponsored. We anticipate that data from this study will provide more important insight into the role of chemotherapy in ITs and may lead to a dramatic shift in the management of all age IT patients.

In conclusion, our study showed that active surveillance after conservative surgery may be a safe and acceptable alternative approach for patients with stage IA G2-3 and IC of any grade immature ovarian teratoma. The survival outcomes of these patients after recurrence were not compromised after secondary cytoreductive surgery and chemotherapy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2022.100976.

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