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Ovarian cystectomy in the treatment of apparent early-stage immature teratoma

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Abstract

Objective: To investigate the role of ovarian cystectomy in patients with early-stage immature teratoma.

Methods: A retrospective review was undertaken on patients diagnosed pathologically with immature teratoma and with malignant lesions confined to the ovary. Patients were included if they had been treated between January 1997 and December 2015 at the Obstetrics and Gynaecology Hospital of Fudan University, Shanghai, China. Relevant demographic and clinical data were retrieved from the medical records.

Results: Forty-three patients were included in the study; 14 underwent ovarian cystectomy (group 1) and 29 underwent unilateral salpingo-oophorectomy (USO; group 2). Three of the patients who underwent USO relapsed and required a second surgical intervention. The 5-year disease-free survival rates were 100% and 88%for groups 1 and 2, respectively. There were no significant differences between the two groups in terms of survival or postoperative fertility outcomes. Univariate and multivariate analysis further revealed that ovarian cystectomy was not a poor prognostic indicator for disease-free survival.

Conclusion: These current data suggest that ovarian cystectomy can be considered for patients with apparent early-stage immature teratoma as it preserves fertility as much as possible without adversely impacting upon survival.

Keywords

Immature teratoma, cystectomy, unilateral salpingo-oophorectomy, survival, comprehensive staging surgery, chemotherapy

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Introduction

Pure immature teratomas are the second most common type of malignant ovarian germ cell tumour (MOGCT) and constitute approximately 30% of all MOGCT cases.[1] This tumour principally manifests in girls and young women, for whom the preservation of fertility is extremely important.[2] Fortunately, immature teratoma is a potentially curable condition as most cases exhibit excellent sensitivity to chemotherapy.[3,4] This provides physicians with a significant chance of preserving fertility, even in patients with advanced stages of disease. Furthermore, most of the patients are diagnosed at an early stage.[5] For example, in a Canadian cohort of 34 patients, 32 patients (94.1%) were diagnosed with International Federation of Gynecology and Obstetrics stage I.[6] The National Comprehensive Cancer Network (NCCN) recommends that for these early-stage patients the standard treatment should be fertility-sparing surgery in the form of unilateral salpingo-oophorectomy (USO) with comprehensive staging procedures.[7]

However, carrying out salpingo-oophorectomy will inevitably compromise fertility as the affected ovary is permanently resected. In order to preserve fertility as much as possible, ovarian cystectomy is undoubtedly better than excising the whole ovary as this practice would minimize loss of normal cortex tissue. Several studies have investigated ovarian function following cystectomy in other conditions, such as ovarian endometrioma.[8–10] One study reported a transient reduction in anti-Müllerian hormone (AMH), an indicator of ovarian reserve; however, after 6 months, the AMH levels had recovered and by 12 months after surgery they had returned to normal.[8] Another study reported a slight but nonsignificant reduction in serum AMH if cystectomy was implemented without using bipolar coagulation.[9]

However, cystectomy may involve a risk of leaving residual tumour within the remaining ovarian tissue. Immature teratomas are characterized by the fact that if recurrent, these tumours may develop into mature teratomas.[4] For example, a previous study reported that from 34 patients, four patients experienced malignant relapse of immature teratoma, while three patients relapsed in the form of a mature teratoma.[6] Furthermore, even if immature teratomas reoccur in a malignant form, most patients can be treated effectively because such tumours exhibit excellent sensitivity to chemotherapy.[6,11]

Based upon these facts, this present study hypothesized that cystectomy could be considered for immature teratomas in patients diagnosed at an early stage. Because of the rarity of this tumour, there has been no specific study of this type as yet, although there have been a few sporadic cases reported previously (Table 1).[3,6,11,12] In the largest set of seven patients receiving cystectomy; only one patient with a stage IA grade 1 tumour relapsed with a mature teratoma 3 months later.[6] In a study of two patients (one of stage IA grade 1, and the other of stage IA grade 2) undergoing cystectomy without chemotherapy, neither patient relapsed.[11] A report of a single patient (stage IC grade 1) who received bilateral cystectomy followed by three cycles of the bleomycin, etoposide and cisplatin (BEP) regimen demonstrated that the patient did not relapse over a 39-month follow-up period.[12] These 10 cases support the hypothesis that cystectomy might be a safe option for patients with early-stage immature teratomas.[6,11,12]

This present study reviewed a cohort of patients with apparent early-stage immature teratoma over a 19-year period in an Obstetrics and Gynaecology Hospital in Shanghai, China. The aim of the study was to investigate whether performing cystectomy instead of USO would compromise the

Table 1. Previous case series of patients with pure immature teratomas undergoing cystectomy.[6,11,12]

Study	*n*	Stage, grade	Chemotherapy	Follow-up, months	Relapse
Vicus et al. 2011[6]	7	NA	NA	NA	1 relapse (stage IA, grade 1) in the form of a mature teratoma
Mangili et al. 2010[11]	2	Stage IA, grade 1 and Stage IA, grade 2	No	NA	No
Reddihalli et al. 2015[12]	1	Stage IC, grade 1	BEP (3 courses)	39	No

NA, not applicable; BEP, bleomycin, etoposide, and cisplatin.

survival rates of patients with early-stage immature teratoma.

Patients and methods

Patient population

This retrospective study enrolled consecutive patients surgically treated in the Department of Gynaecology, Obstetrics and Gynaecology Hospital of Fudan University, Shanghai, China between January 1997 and December 2015. Inclusion criteria were as follows: (i) pathological diagnosis of a pure immature teratoma; (ii) gross confinement of malignant lesions to the ovary (or ovaries) as reported in the surgical report; (iii) patients who received fertility-sparing surgery. The exclusion criteria were as follows: (i) patients with malignant tumours originated from sites other than the ovaries; (ii) patients possessing immature teratoma and other histological types of MOGCT at the same time as revealed by the pathological report; (iii) patients with malignant lesions of immature teratoma outside of the ovaries as reported in the surgical report; (iv) patients whose fertility was not spared during surgery.

This study was approved by the Ethics Committee of the Obstetrics and Gynaecology Hospital of Fudan University (approval number: 2016-21). Written informed consent was obtained from all patients.

Data collection

The following parameters were retrieved from medical records: age, parity, tumour diameter, β-human chorionic gonadotropin (β-HCG) levels, the widely-used tumour markers serum cancer antigen (CA) 125 and alpha-fetoprotein (AFP), histopathology, surgical details and information relating to adjuvant chemotherapy. Patients were followed in the outpatient department to determine clinical outcome such as recurrence, death or survival, along with reproductive outcome, such as resumption of menstruation and pregnancy.

All histological slides were reviewed by two independent pathologists. Immature teratomas were graded according to the criteria developed previously.[13] Fertility-sparing surgery was defined as preservation of the uterus and at least part of an ovary. Comprehensive staging surgery included cytological analysis of the peritoneal cavity fluid, excision of suspicious nodules of the peritoneum, infracolic omentectomy and pelvic lymphadenectomy.

Statistical analyses

All statistical analyses were performed using the SPSS® statistical package, version 16.0 (SPSS Inc., Chicago, IL, USA) for Windows®. Continuous variables are described as mean ± SD. The Student's *t*-test

was used to compare continuous variables while χ^2-test or Fisher's exact test were used to compare categorical variables. Spearman correlation analysis was used to investigate the correlations between covariates. Survival analysis was constructed using the Kaplan–Meier method. Following univariate analysis with *log*-rank test, a Cox regression model was employed to account for the potential effects of confounding factors. A P-value < 0.05 was considered statistically significant.

Results

During the 19-year study period, 51 females with pure immature teratoma were identified. Of these, 47 patients (92.2%) had malignant lesions confined to the ovary. Application of the full inclusion criteria resulted in a final cohort of 43 patients with a mean ± SD age of 22.0 ± 6.0 years (range, 10–39 years). The mean ± SD tumour diameter was 147.6 ± 43.3 mm (range, 46–250 mm). None of the patients tested positive for β-HCG. Serum CA125 and AFP was available for 35 and 33 patients, respectively. In total, six and eight patients were classified as being within the normal range for CA125 (<35 U/ml) or AFP (<10 ng/ml), respectively. The study cohort included 22, 15 and six patients of grade 1, 2 and 3, respectively. Spearman correlation analysis revealed that the AFP level was positively correlated with tumour grade ($r = 0.37$, $P < 0.05$) and the detection of immature teratoma in frozen tissue sections ($r = 0.47$, $P < 0.05$).

All patients exhibited unilateral immature teratomas, although 12 patients also possessed a mature teratoma in the contralateral ovary (Table 2). Comprehensive staging surgery (cytological analysis of the peritoneal cavity fluid, infracolic omentectomy and pelvic lymphadenectomy) was performed in only three patients. Nevertheless, cytological analysis of peritoneal washings, lymph node dissection, and omentectomy were performed in 14, 10, and 10 patients, respectively. None of these samples tested positive for malignancy and no residual lesions were left in any patients. In total, 32 of 43 patients (74.4%) received adjuvant chemotherapy following surgery. The BEP and cisplatin, vincristine, and bleomycin (PVB) regimens were administered to seven and 14 patients, respectively. In addition, the vincristine, actinomycin, and cyclophosphamide (VAC) regimen, an older regimen used to treat MOGCTs in the 1990s,[14–16] was provided to one patient.

From the study cohort, 14 patients received ovarian cystectomy and were categorized as group 1. Ovarian cystectomy was carried out in these patients for the following reasons: (i) frozen sections during surgery presented a primary diagnosis of mature teratoma (one patient) or suspected immature teratoma but without proof of immature neural tissue (12 patients); (ii) the lack of frozen sections for analysis (one patient). The 29 remaining patients received USO and were categorized as group 2. Demographic and clinical data for these two groups are presented in Table 2. AFP levels were significantly higher in group 2 ($P = 0.013$). Furthermore, a significantly higher proportion of patients in group 2 underwent cytological analysis of peritoneal washings ($P = 0.013$), omentectomy ($P = 0.012$) and pelvic lymphadectomy ($P = 0.012$). There was no significant difference in age, tumour size, tumour grade or CA125 level.

Three patients (7.0%) were lost during the median follow-up period of 41 months (range, 4–207 months); one was from group 1 and the other two were from group 2. Three patients, all from group 2, experienced a relapse. Detailed information relating to recurrence in the three patients from group 2 is presented in Table 3. None of the patients in either group died during follow-up. There was no significant between-group difference in the 5-year DFS, which was 100% for group 1 and 88%for group 2 (Figure 1). Univariate

Table 2. Demographic and clinical characteristics of 43 patients diagnosed with apparent early-stage immature teratomas undergoing either cystectomy (group 1) or unilateral salpingo-oophorectomy (group 2).

Characteristics	Group 1 $n = 14$	Group 2 $n = 29$	Statistical significance[a]
Age, years	22.0 ± 3.6	22.0 ± 7.0	NS
Nulliparous	14 (100)	25 (86.2)	NS
Tumour size, mm	151.1 ± 33.6	145.9 ± 47.7	NS
Serum CA125, U/ml	92.8 ± 82.9	171.4 ± 165.8	NS
Serum AFP, ng/ml	40.9 ± 72.6	552.7 ± 884.5	$P = 0.013$
Comprehensive staging surgery	0 (0)	3 (10.3)	NS
Peritoneal cytology	1 (7.1)	13 (44.8)	$P = 0.013$
Omentectomy	0 (0)	10 (34.5)	$P = 0.012$
Pelvic lymph node dissection	0 (0)	10 (34.5)	$P = 0.012$
Laterality			
Left	5 (35.7)	11 (37.9)	NS
Right	9 (64.3)	18 (62.1)	NS
Both	0 (0)	0 (0)	NS
Mature teratoma in contralateral ovary	4 (28.6)	8 (27.6)	NS
Tumour grade			
1	9 (64.3)	13 (44.8)	NS
2	5 (35.7)	10 (34.5)	NS
3	0 (0)	6 (20.7)	NS
Adjuvant chemotherapy	8 (57.1)	24 (82.8)	NS
BEP	4	13	
PVB	4	10	
VAC	0	1	
Median cycles of chemotherapy	4 (4–7)	4 (2–6)	NS
Clinical status			
Relapse	0 (0)	3 (10.3)	NS
Dead	0 (0)	0 (0)	
Fertility outcome			
Normal menstruation	12 (85.7)	25 (86.2)	NS
Amenorrhoea	1 (7.1)	1 (3.4)	NS
Live births	5 (35.7)	6 (20.7)	NS

Data presented as mean ± SD, *n* of patients (%) or median (range).

[a]Student's *t*-test was used to compare continuous variables and χ^2-test or Fisher's exact test were used to compare categorical variables.

BEP, bleomycin, etoposide, and cisplatin; PVB, cisplatin, vincristine and bleomycin; VAC, vincristine, actinomycin, and cyclophosphamide; NS, no significant between-group difference ($P \geq 0.05$).

analyses using *log*-rank tests showed that the following factors were not poor prognostic factors for DFS: age (≥25 years), laterality, tumour grade, comprehensive staging surgery, the practice of cystectomy, CA125 level (≥500 U/ml), AFP level (≥40 ng/ml), or more than three cycles of chemotherapy. There was no significant difference in DFS of patients treated with either the BEP or PVB regimens. However, univariate analyses showed that use of the VAC regimen was significantly associated with DFS ($P < 0.001$) when tested by *log*-rank test. Multivariate analysis using a Cox regression

Table 3. Clinical details of three patients who underwent unilateral salpingo-oophorectomy (USO; group 2) and subsequently experienced a relapse.

Age	Tumour grade	CA125, U/ml	AFP, ng/ml	Surgery performed and chemotherapy (number of courses)	Recurrence time, months	Nature of recurrent lesion	Treatment after recurrence	Status
28	1	580	47	USO + contralateral ovary biopsy, and VAC (4)	12	Benign	Surgery	Survived
16	3	227.3	3000	USO + contralateral ovary biopsy + LND + OT, and BEP (6)	7	Benign	Surgery	Survived
29	2	157.3	NA	USO + contralateral ovary biopsy, and PVB (4)	2	Benign	Surgery	Survived

CA, cancer antigen; AFP, alpha-fetoprotein; VAC, vincristine, actinomycin, and cyclophosphamide; LND, pelvic lymph node dissection; OT, omentectomy; BEP, bleomycin, etoposide, and cisplatin; NA, not available; PVB, cisplatin, vincristine and bleomycin.

model showed that the use of the VAC regimen was not a prognostic factor for DFS.

Prior to surgery, all patients had regular menstruation cycles except one premenarchal patient in group 2. Data regarding menstrual status and pregnancy after surgery was available for 13 and 26 patients in group 1 and 2, respectively (Table 2). Of these, 12 patients (85.7%) in group 1 and 25 patients in group 2 (86.2%) resumed normal menstrual cycles. Five patients (35.7%) in group 1 and six patients (20.7%) in group 2 delivered healthy babies at term, while the other patients were unmarried or taking contraceptive measures. No miscarriages were reported. There were no significant differences between the two groups in terms of the resumption of normal menstrual cycles or pregnancy rate.

Discussion

Pure immature teratomas are rare and represent less than 1% of all ovarian cancers.[17] A study undertaken in 580 patients diagnosed with ovarian teratoma identified only 24 immature cases (4.1%).[18] The majority of patients are diagnosed at an early stage.[6] In this present study, 92.2% (47/51) of patients were diagnosed with apparent early-stage teratoma with lesions confined to the ovary. Survival is closely associated with disease stage. For example, the overall survival rate was 91.6% when all stages were considered, but only 80% for patients with advanced stages of disease.[12] This present study demonstrated a 5-year overall survival rate for our cohort of apparent early-stage patients of 100%. Patients with a higher tumour grade are reported to have a higher rate of recurrence.[19] However, in this present cohort, tumour grade was not found to be a useful prognostic factor for DFS. This may be due to the excellent survival rate of this present cohort of early-stage patients.

The standard surgery for patients with early-stage teratoma, as recommended by

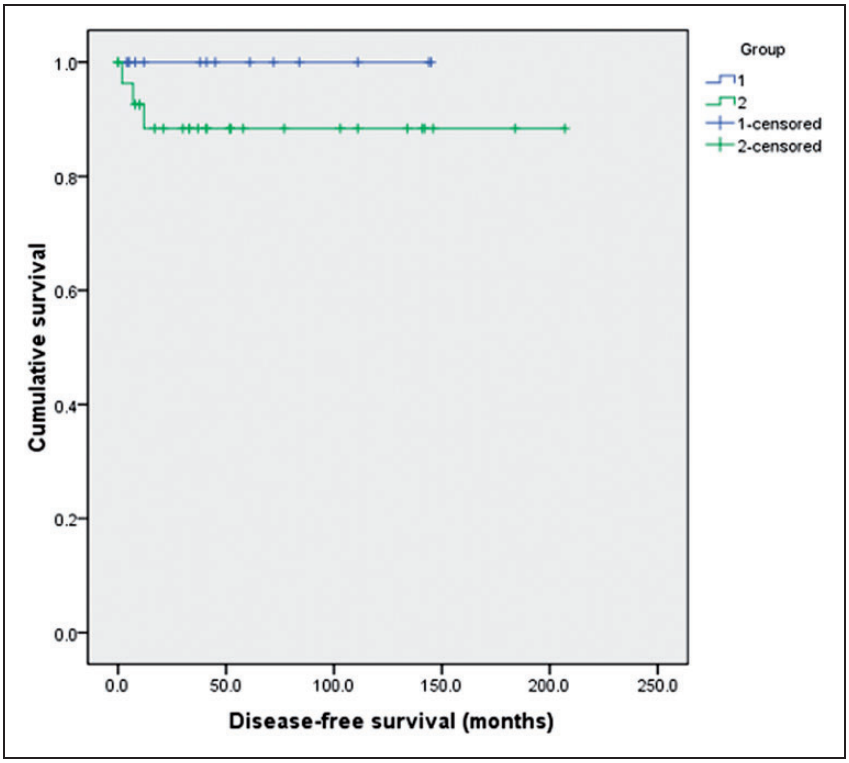

Figure 1. Disease-free survival (DFS) curve of patients undergoing cystectomy (group 1) or unilateral salpingo-oophorectomy (USO; group 2). There was no significant difference in DFS between the two groups. The colour version of this figure is available at: http://imr.sagepub.com.

the NCCN, is USO plus comprehensive staging.[7] Routine biopsy of the unaffected ovary is unnecessary because immature teratoma is almost always unilateral.[3] It has also been suggested that comprehensive staging procedures can be omitted without compromising survival. For example, of 23 patients with pure immature teratomas who did not receive comprehensive staging, only one patient relapsed and recovered after four cycles of etoposide and cisplatin chemotherapy.[3] Another study, based upon the 'Surveillance, Epidemiology, and End Results' programme, showed that lymphadenectomy does not provide any significant benefit to the survival of patients affected by immature teratoma.[20] In this present cohort of 43 patients, only three patients received comprehensive staging surgery but the survival outcomes were satisfactory. The overall analysis in the present study also showed that comprehensive staging surgery was not a useful prognostic factor for DFS. Collectively, this suggests that comprehensive staging procedures can be omitted for patients with apparent early-stage teratoma without compromising survival. In fact, some researchers have considered that the role of surgical staging in this disease was to avoid adjuvant chemotherapy for low grade early-stage tumours.[12]

In the present study, none of the 14 patients who received cystectomy relapsed during follow-up and cystectomy was not shown to be a poor prognostic factor for DFS. Furthermore, none of these 14

patients were comprehensively staged during surgery. These current findings suggest that the application of cystectomy without comprehensive staging surgery is a safe option for patients with apparent early-stage teratoma.

The BEP protocol is the standard chemotherapy regimen recommended by the NCCN and is the most widely used strategy.[7] However, the PVB regimen can also be effective and is widely used in China.[21] In this present study, there was no significant difference in the survival rates of patients treated with either the BEP or PVB regimens. The NCCN supports the omission of adjuvant chemotherapy in patients with stage I, grade 1 immature teratoma based upon the fact that comprehensive staging is adopted.[22] Over recent years, the role of chemotherapy in the treatment of early-stage immature teratoma has become increasingly questioned. For example, the MITO-9 trial strongly suggested that physicians should not adopt chemotherapy in the primary setting but rather apply this strategy only in cases of recurrence for all grades of stage I tumour.[11] Furthermore, a recent report showed that adjuvant chemotherapy did not reduce the chance of relapse in paediatric patients although the situation in adult patients was not clear.[23] This present study also considered whether it was safe to omit both staging procedures and chemotherapy and perform only cystectomy for these early-stage patients. In the 14 patients receiving cystectomy, none were comprehensively staged while eight patients received adjuvant chemotherapy. However, the present study was not able to reach a definitive conclusion because no relapses were observed in this group of patients.

This present study demonstrated that there were no significant differences between cystectomy and USO in terms of the resumption of normal menstruation or pregnancy rate following surgery. However, several young patients were not ready for pregnancy, were unmarried, or were taking contraceptive measures.

In this present cohort, cystectomy was performed mainly (13/14, 92.9%) in patients with frozen sections that failed to confirm the presence of immature neural tissue, although malignancy was suspected in 12 patients according to gross examination. This casts doubt over whether patients in the cystectomy group possessed malignant lesions smaller than those of the USO group, which may further impact upon prognosis of the patients. The quantity of malignant lesions, more specifically the immature neural tissue, is closely related to the grade of the tumour.[24,25] If hardly any immature neural tissue can be detected under high-power microscopy when sampling properly, then the tumour should be designated grade 1.[13] However, the final pathology report proved that eight patients were diagnosed with grade 1 while the other five were verified as grade 2. When preparing samples for frozen sections, only one small piece of tissue was sampled. Both the experience of the pathologist and the limited volume of sampled tissue may have resulted in the failure to collect a sample that included malignant tissue.

Twenty-five patients (25/33, 75.8%) in this present cohort presented with abnormal serum AFP levels. The Pediatric Oncology Group and the Children's Cancer Group have reported that 44.8% patients with immature teratomas were confirmed to have co-existing microscopic foci of endodermal sinus tumour (EST), especially in grade 2 or 3 tumours.[26] Although no microscopic foci of EST were reported in this present study, if the tumours had been examined more closely, then tiny EST foci might have been detected. Spearman correlation analysis showed that the AFP level was positively correlated with tumour grade in the present study. Although significantly higher AFP levels were found in group 2 compared with group 1, no significant

difference in the tumour grades was detected between the two groups. Furthermore, although AFP levels differed between the two groups, elevated AFP (≥40 ng/ml) before surgery was not a prognostic factor for DFS in this present cohort.

This study had several limitations. First, it was retrospective and may have been affected by selection bias. Secondly, the sample size was small. Unfortunately, it was difficult to compile a larger cohort, or to carry out either a prospective or randomized controlled trial, because of the rarity of this tumour. Any disparity between the two groups did not appear to impact upon the results.

In conclusion, to the best of our knowledge, this is the first study to investigate the role of cystectomy in patients with apparent early-stage immature teratoma. These present data suggest that cystectomy could be considered for patients with apparent early-stage immature teratoma without compromising survival.

Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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