Objective: The aim of this study was to evaluate clinicopathologic characteristics, treatment outcome, and reproductive function in women diagnosed with ovarian immature teratoma (IT). Our standard chemotherapy regime is currently etoposide/cisplatin (EP), creating a unique opportunity to evaluate this protocol in ovarian ITs.

Materials and Methods: This study is a retrospective analysis. Twenty-seven women older than 18 years with ovarian IT stages IА to IIC were identified and included in this study. Patients were treated at 1 institution, Health Sciences Center, Women's Hospital, Winnipeg, Manitoba, Canada, between 1983 and 2013.

Results: The median age at diagnosis was 27.0 years (range, 18–36 years). Twenty-two (82%) presented with an International Federation of Gynecology and Obstetrics stage I disease, 3 (11%) had stage II, and 2 patients (7%) had stage III disease. The histologic grade distribution was grade I in 9 patients (33%), grade II in 3 patients (11%), and grade III in 15 patients (56%). Initial management was surgical for all patients: 3 (11%) hysterectomy and bilateral salpingo-oophorectomy, 1 (4%) cystectomy only, and 23 (85%) unilateral salpingo-oophorectomy. Twenty-one patients (78%) received adjuvant therapy. The median follow-up was 60 months (range, 36–72 months). One patient recurred (histological grade III) 6 months after surgery and had a complete clinical response to 4 cycles of EP chemotherapy. Twelve patients reported an attempt to conceive resulting in 10 pregnancies (8 after chemotherapy).

Conclusions: Ovarian IT is a curable disease. Fertility-sparing surgery should be offered. Adjuvant treatment with cisplatinum-based chemotherapy, typically with bleomycin, etoposide, and cisplatin, is still considered the standard in stages greater than stage IА grade I. Etoposide/cisplatin as a primary chemotherapy regime for early- or advanced-stage disease is an effective treatment with minimal adverse effects and high tolerability. This is the first published study examining EP as a primary treatment modality for IT. Further studies are needed to strengthen these findings.

Key Words: Pure immature teratoma of the ovary, Vincristine/actinomycin D/cyclophosphamide, Etoposide/cisplatin
Immature teratoma (IT) is a rare tumor representing 1% of all teratomas, 1% of all ovarian cancers, and 35.6% of malignant ovarian germ cell tumors. It is found either in pure form or as a component of a mixed germ cell tumor, occurring primarily during the first 2 decades of life. These neoplasms are typically composed of tissue from 2 or 3 germ cell layers: ectoderm, mesoderm, and endoderm. Histologically, there are varying amounts of immature tissue, most frequently with neural differentiation.

Immature teratoma is the only ovarian germ cell neoplasm that is histologically graded. Grade is based upon the proportion of tissue containing immature neural elements. Histological grade in these tumors is considered an important prognostic factor that predicts extra ovarian spread and overall survival. Because of the rarity of this tumor, data on efficacy of treatments are limited to single-arm clinical trials and small retrospective reviews that combine all germ cell tumors patients together often with small patient numbers (9–276 patients). Only few series in the literature reported IT separately and discussed its management. The largest is by Norris et al in 1976, which described 58 patients

Adjuvant chemotherapy has improved overall survival after surgery when compared with historical controls. These gains in outcome date back to one of the original studies by Smith et al in 1975, which reports that combination chemotherapy with vincristine, actinomycin D, and cyclophosphamide (VAC) resulted in the survival of 75% of women with nondysgerminomas (n = 20). Cisplatin-based chemotherapy is now considered the standard of care for patients in whom adjuvant treatment is indicated. At least 90% of women with early-stage ovarian germ cell tumors (stage I and II) and up to 75% of those with advanced disease (stage III and IV) are long-term survivors. Currently, the most widely used combination is bleomycin, etoposide, and cisplatin (BEP). Alternatively, etoposide/cisplatin (EP) can be used to decrease toxicity and increase compliance. Although no randomized trials have been performed on these combinations, they appear to have equivalent activity in testicular germ cell cancers. There are no prospective trials to inform clinicians of the optimal number of treatment cycles, 3 cycles of BEP are usually administered for patients at a low risk of recurrence, and 4 or more cycles are administered to high-risk cohorts.

In our study, we present our experience with pure IT over the past 30 years with regards to presentation, diagnosis, management strategies, reproductive outcomes, and survival. Our standard chemotherapy regime is currently EP creating a unique opportunity to evaluate this protocol in ovarian IT.

**MATERIALS AND METHODS**

This study is a retrospective analysis of patients with IT who were referred to the Division of Gynecologic Oncology at CancerCare, Winnipeg, Manitoba, Canada. It is the only tertiary care center in Manitoba. All female patients with an unequivocal diagnosis of IT and older than 18 years, over a 30-year period (1983 to 2013), were included. Patients with mixed germ cell tumors or any other histologic diagnosis were excluded.

After institutional ethics board approval (REB #H2013:426; December 15, 2013), patients were identified within the cancer registry database by the Department of Epidemiology at the University of Manitoba. Clinical data were abstracted from our electronic patient files, which contained all clinical visits, diagnostic imaging results, laboratory results, surgical reports, and all relevant consults. Follow-up information was obtained until August 2014.

Data recorded for each patient included demographics, pathology of tumor, type and details of surgery, residual disease, stage, serum tumor markers levels (eg, α-fetoprotein [α-FP], β-subunit of human chorionic gonadotrophin [β-hCG], lactate dehydrogenase, alkaline phosphatase, and CA-125), type of chemotherapy regimen, adverse effects of chemotherapy, details of any further therapy, and clinical status at follow-up. Surgical stage was assigned retroactively as outlined by the International Federation of Gynecology and Obstetrics (2014). Histologic grading of IT was according to the criteria proposed by Norris et al in 1976.

Before 1994, our standard chemotherapy regime was 12 cycles of VAC every 21 days. Subsequently, primary treatment was 4 cycles of EP every 21 days (Table 1).

Time to progression was calculated from the date of initial surgery to the time of progression or recurrence. Overall survival was defined as time from the date of initial surgery to the time of death or last follow-up.

**RESULTS**

Between 1983 and 2013, 1332 patients with ovarian malignancy were treated at our institute. Germ cell ovarian malignancy was identified in 133 patients (10%). Twenty-seven women (20%) were treated for IT. Four patients had mixed histology (yolk sac, dysgerminoma, and IT). The median age at diagnosis was 27 years (18–36 years). The most frequent symptom that led to diagnosis was increased abdominal girth over 4 to 6 weeks (81%). Three patients presented with acute abdominal pain and had confirmed torsion during surgery (11%). One patient found to have a pelvic mass while being investigated for abnormal menstrual cycles, and 1 patient had an incidental diagnosis at the time of surgery for suspected ectopic pregnancy. Of the patients identified, 22 (82%) presented with an International Federation of Gynecology and Obstetrics stage I disease, 3 (11%) had stage II disease.

**TABLE 1. Chemotherapy regimes**

| Regimen | Duration and Dosage |
|---------|---------------------|
| VAC*    | Cisplatin 20 mg/m² daily 1 to 5 |
| Actinomycin D 350 mg/m² daily 1 to 5 |
| Cyclophosphamide 150 mg/m² daily 1 to 5 |
| EP†     | Cisplatin 20 mg/m² daily 1 to 5 |
|         | Etoposide 100 mg/m² daily 1 to 5 |

*Twelve cycles repeated every 21 days.
†Four cycles repeated every 21 days.
(pelvic metastases), and 2 patients (7%) had stage III disease (with upper abdominal metastases). The histologic grade distribution was grade I in 9 (33%), grade II in 3 (11%), and grade III in 15 (56%; Table 2). Five patients (19%) had a concurrent mature cystic teratoma involving the opposite ovary.

The mean tumor diameter was 18 cm (5–30 cm). The masses were encapsulated and had smooth outer surfaces. All were visibly cystic, although the cysts were often only a few millimeters in size and distributed throughout the solid portions. Bone, hair, and cartilage were present in 50%. The histologic pattern varied greatly. In grade I tumors, there was usually an abundance of mature tissue, but these were intermixed with primitive mesenchymal tissue, with occasional mitotic figures. Immature cartilage was often present.

Grade 2 neoplasms contained fewer mature tissues. All of the primitive features of grade I tumors were accentuated. In addition, there were multiple foci of immature neuroepithelium in the form of rosettes and irregular gland-like spaces. In grade III, mature elements were less frequent, if present at all. Neuroepithelial clusters were common, occupying 4 or more low magnification fields. Immature cartilage was frequently identified.

Tumor markers were available for 20 patients. CA-125 level was elevated in 2 patients with a complete normalization after the second cycle of chemotherapy. Two patients had elevated α-FP level that also normalized after 4 cycles of EP, without any evidence of endodermal sinus tumor after review by gynecologic pathologist. One patient had an elevated β-hCG level that also normalized after surgery for suspected ectopic pregnancy (Table 2).

Initial management was surgical for all the patients. For 3 women who presented with early-stage disease (IA, IB, and IC), surgical management included total abdominal hysterectomy, bilateral salpingo-oophorectomy (BSO), and staging procedures (omentectomy, peritoneal biopsies, pelvic lymphadenectomy, and pelvic washings). Due to the young age of this patient population, a more conservative surgical approach of unilateral salpingo-oophorectomy (USO), with or without surgical staging, was adapted even in the presence of advanced-stage disease. Fifteen of 27 patients were referred after initial surgery by a general gynecologist. These represent the group that had no staging procedure performed. All operative reports indicated that there was no visible pathology within the pelvis or upper abdomen. One patient had a unilateral cystectomy, and 1 patient had a USO with ovarian cystectomy of the other ovary. Optimal surgical cytoreduction was accomplished in 25 of 27 patients (Table 2).

Six stage I patients were treated with postoperative conservative management alone. These patients were followed clinically, with abdominopelvic examination at regular intervals.

Postoperative systemic chemotherapy was administered to 21 patients (78%). Primary chemotherapy with VAC was used between 1983 and 1994 in 11 patients (5 stage IA [3 grade I and 2 grade III], 1 stage IB, 4 stage IC, and 1 stage II). Etoposide/cisplatin was used between 1994 and 2013 in a total of 10 patients (4 stage IA grade III, 3 stage IC, 1 stage II, and 2 stage IIIC; Table 3). Transient alopecia, nausea, and vomiting were universal, but only 1 patient had dehydration severe enough to warrant hospital admission due to VAC treatment. Two patients in the VAC group had severe constipation that required admission to the hospital for management, and 6 patients had grade III neuropathy that led to discontinuation of vincristine. Two patients in the EP group required blood transfusion, and 1 required a treatment delay due to severe neutropenia. Etoposide/cisplatin was otherwise tolerated well, and all the patients completed a full course of 4 cycles. Bleomycin was not given to any patients during the study period, and there were no treatment-related deaths.

One (3.7%) malignant recurrence occurred. Stage II grade III patient who initially refused postoperative adjuvant chemotherapy presented with right lower quadrant pain 6 months postoperatively. Computed tomography scan was performed and documented a tumor recurrence in the pelvis.

### TABLE 2. Patient's characteristics

| Age, mean (range), y | 27 (18–36) |
|----------------------|------------|
| Grade                |            |
| I                    | 9 (33%)    |
| II                   | 3 (11%)    |
| III                  | 15 (56%)   |
| Stage                |            |
| IA                   | 12 (44%)   |
| Grade I              | 4 (15%)    |
| Grade II             | 1 (4%)     |
| Grade III            | 7 (26%)    |
| IB                   | 1 (4%)     |
| IC                   | 9 (33%)    |
| II                   | 3 (11%)    |
| III                  | 2 (7%)     |
| Tumor markers        |            |
| Elevated CA-125 level| 2 patients |
| Elevated α-FP level  | 2 patients |
| Elevated β-hCG level | 1 patient  |
| Type of surgery      |            |
| Cystectomy           | 1 (4%)     |
| USO                  | 22 (81%)   |
| BSO                  | 1 (4%)     |
| Hysterectomy and BSO | 3 (11%)    |
| Chemotherapy         |            |
| VAC                  | 11 patients|
| EP                   | 10 patients|
| Fertility outcome    |            |
| Spontaneous vaginal  |            |
| delivery             | 7 patients (9 deliveries) |
| Cesarean delivery    | 3 patients (5 cesarean deliveries) |
| Follow-up, median    | 60 (36–72) |
| (range), mo          |            |

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The median follow-up after treatment in the gynecology oncology clinic for all the patients was 60 months (36–72 months); no patients were lost to follow-up. At the time of this study, according to the electronic database and patient files, all patients were still alive and following up with their family physicians with no evidence of disease and no documented secondary malignancies; the median database follow-up is 276 months (36–360 months).

**DISCUSSION**

Pure IT is a rare disease with limited data to guide our treatment choices. In this single-center review, we confirmed that IT was the second most common germ cell malignancy with a rate of 20% of all malignant germ cell tumors.

The mean age at presentation was 26 years. Abdominal distension and mass was the most common presenting symptom (81%). Immature teratoma of the ovary is almost always unilateral. A contralateral mature cystic teratoma was seen in 19% of cases (5/27). These observations are within the range reported by other studies.\(^2,15,16\) No patient in our study presented with a para-neoplastic syndrome, such as limbic encephalitis.\(^17\)

Preoperative tumor marker levels were available in 20 of 27 cases. CA-125 level was elevated in 2 patients, α-FP level was raised in 2 patients, and β-hCG level was elevated in 1 patient. There was no evidence of other germ cell or epithelial tumor. Although α-FP is widely used as a tumor marker for IT,\(^18\) it has been reported that α-FP level in IT is not correlated to either stage or grade.\(^19-22\) All other tumor markers were negative.

The prognosis associated with IT depends on the stage and grade of the tumor.\(^2,15,23\) Fertility-sparing surgery in the form of USO should be the primary treatment modality in young patients.\(^24-26\) Although optimal debulking is the standard recommendation in advanced disease, conservative surgery may not compromise the chances of cure given the high rate of chemotherapy sensitivity seen in these tumors.\(^27\) In our series, fertility-sparing surgery was undertaken in 24 of 27 patients, including 2 stage III patients, with complete recovery and no evidence of recurrence.

Stage IA grade I IT is treated adequately with surgery alone. The rate of recurrence in this group of patients is low (15%–25%); if it occurs, the patient can be effectively salvaged with chemotherapy.\(^23,28-30\) In our study, 3 such patients were treated conservatively with USO and regular clinic visits only. There were no recurrence, and they are still alive and well.

Combination chemotherapy using BEP is the current standard of care for the remaining stages and grades. Treatment results in an overall disease-free survival of more than 95% and 75% in early- and advanced-stage disease, respectively. The

### TABLE 3. Chemotherapy by stage and grade

| Tumor Stage and Grade | Postoperative Chemotherapy, n (%) | Chemotherapy Treatment Regime |
|-----------------------|----------------------------------|------------------------------|
| Stage IA (n = 12)     | 8 (67)                           | VAC                          |
| Grade I (n = 5)       | 2 (40)                           | VAC                          |
| Grade II (n = 1)      | 0                                | VAC                          |
| Grade III (n = 7)     | 6 (85)                           | EP, 2 VAC                    |
| IB (n = 1)            | 1 (100)                          | VAC                          |
| Grade I               | 0                                | VAC                          |
| Grade II              | 1 (100)                          | VAC                          |
| Grade III             | 0                                | VAC                          |
| IC (n = 9)            | 7 (78)                           | VAC                          |
| Grade I (n = 3)       | 2 (67)                           | VAC                          |
| Grade II (n = 1)      | 0                                | VAC                          |
| Grade III (n = 5)     | 5 (100)                          | EP, 2 VAC                    |
| II (n = 3)            | 3 (100)                          | EP, 2 VAC                    |
| III (n = 2)           | 2 (100)                          | EP                           |
| Total 27              | 21 (%)                           |                              |

Bold values indicate total number of the patients in that stage who received chemotherapy.

She began treatment with EP chemotherapy and had a complete clinical response (Table 4).

After completion of first-line systemic chemotherapy, all patients had a complete clinical remission. Ten second-look laparotomies were done over the study time frame, with no evidence of disease. Second-look laparotomies had been abandoned by the time the EP protocol was considered the current regime.

All the women who were treated with fertility-sparing surgery had regular menstrual cycles within 3 months of completing treatment. Twelve patients attempted to conceive after treatment. Fourteen successful pregnancies and deliveries were reported in 10 patients (6 patients each had 1 pregnancy, and 4 patients had 2 pregnancies each). Seven patients had 9 spontaneous vaginal delivery, and 3 patients had a total of 5 cesarean deliveries. Seven of these 10 patients received adjuvant chemotherapy (all received EP) after fertility-preserving surgery with a median period from chemotherapy treatment of 60 months (Table 2). There were 2 reported spontaneous miscarriages, 1 preterm delivery at 36 weeks gestational age, no reported cases of ectopic pregnancy, and no other major pregnancy complications.

### TABLE 4. Recurrence

| Patient | Age, y | Stage | Grade | Surgery | Postoperative Treatment | Time to Relapse, mo | Site of Relapse | Treatment of Relapse | Outcome               |
|---------|--------|-------|-------|---------|-------------------------|--------------------|-----------------|---------------------|----------------------|
| 1       | 33     | II    | III   | USO     | None                   | 6 mo postoperative | Right pelvic side wall | EP > 4 cycles       | 60 mo follow-up (still live and well) |
optimal number of cycles of chemotherapy is not clear. Many experts advise 4 to 6 cycles of chemotherapy depending on the decline of serum tumor markers or responses on diagnostic imaging.\textsuperscript{12,13} Alternative regimens have included a modified 3 days BEP EP, and POMB-ACE (cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide, and etoposide).\textsuperscript{5,32} Some reports have shown that EP may be an effective chemotherapy regime for recurrent germ cell ovarian tumors after BEP.\textsuperscript{5,12} However, most of the germ cell tumors in these studies were endodermal sinus tumors and mixed germ cell tumors. Only 1 retrospective trial reported EP as a first-line chemotherapy regime for germ cell tumors, and it was in tumors of the testes.\textsuperscript{11} This is, therefore, the first oncology trial to show high efficacy and response of IT of the ovary to EP chemotherapy alone as a primary first-line treatment.

In our center, VAC was used up till 1994, and then EP was implemented as a primary treatment in all the IT patients with early high grade or advanced stage. Ten patients in our study including 2 stage IIIC patients with gross residual disease postoperatively and 1 stage II patient with documented recurrence received EP as primary first-line treatment. All patients had complete remission, and no recurrences have been documented after completion of treatment. All participants tolerated the combination chemotherapy well and completed the entire course, without the added complication of fatal pulmonary toxicity due to the bleomycin, which has been reported in 2.8% of patients treated with bleomycin.\textsuperscript{23,31} Eleven patients had VAC as a primary treatment. They received a mean of 6 cycles (range, 3–12 cycles) with complete remission and no evidence of recurrence. Neuropathy and constipation were major adverse effects of the VAC regime, and vincristine had to be removed from the regime often due to adverse effects.

Previous studies have suggested no adverse effects on fertility or teratogenicity after fertility-preserving surgery and chemotherapy for malignant ovarian germ cell tumors.\textsuperscript{23,32–34} In our population, 12 patients reported an attempt to conceive after treatment, 7 of them after chemotherapy. Fourteen successful pregnancies and deliveries were reported in 10 patients. Available techniques for fertility preservation are present and should be discussed with all the patients. Embryo cryopreservation is the most common. It is well established and successful\textsuperscript{35}; however, it takes a significant time lag, and 2 to 3 weeks are still needed.\textsuperscript{35} Possible contamination with malignant cells is also a theoretical concern. Gonadotropin-releasing hormone agonists, although controversial, may decrease the risk of premature ovarian failure due to gonadotoxic chemotherapy.\textsuperscript{36} Another available option is ovarian tissue cryopreservation.\textsuperscript{37} This procedure is highly invasive, needing general anesthesia and surgical removal of ovarian tissue.\textsuperscript{37} Its use is still regarded as experimental in most countries.

Excellent results have been reported after surgery without chemotherapy in patients who have early-stage IT that is more than IA grade I and II.\textsuperscript{30,38,39} Three patients in our study group (1 stage IC grade I, 1 stage IC grade II, and 1 stage IA grade III) were treated conservatively with surgery and refused chemotherapy. None had disease recurrence, and all were alive at the conclusion of this study. Although we are not recommending this as a standard treatment without more clinical data, the high rates of cure with surgical resection alone are reassuring.

There are several limitations to this study. First, this is a retrospective study, and the results may be subject to bias, incomplete information, or misdiagnosis. To minimize these risks, the charts of all patients were fully reviewed by 2 independent reviewers, and all the pathology was reviewed by a gynecologic pathologist to confirm diagnosis. Second, the total numbers of patients within this study was relatively small. Unfortunately, the rarity of this tumor precludes performing big case series, prospective trials, or randomized control trials.

The English-language literature was reviewed. Six studies that looked at IT patients separately and described their treatment and outcome were identified (Table 5). Norris et al\textsuperscript{2} reported 58 patients with IT with a 5-year overall survival of 65%. Chemotherapy was not offered to any patient. Koulos et al\textsuperscript{40} treated 25 patients with VAC chemotherapy and reported no deaths from IT. Kawai et al\textsuperscript{18} treated 20 patients with VAC chemotherapy or cisplatin, vinblastine, and bleomycin (PVB), with a median follow-up of 62 months and 1 reported death. Williams et al\textsuperscript{4} in their series treated 26 relapsing or advanced-stage IT patients with PVB-based chemotherapy; the reported

| Study               | No. Patients | Median Age, y | Stages of Disease | Chemotherapy Regimes                  | Median Follow-up, mo | Survival       |
|---------------------|--------------|---------------|-------------------|---------------------------------------|----------------------|----------------|
| Norris et al\textsuperscript{2} | 58           | 19            | Stage I to III    | No chemotherapy                       | N/A                  | 65% 5 y        |
| Koulos et al\textsuperscript{40} | 25           | 21            | Stage I to III    | VAC (in 16 patients)                  | N/A                  | 100% 5 y       |
| Kawai et al\textsuperscript{18} | 20           | 22            | Stage I to III    | VAC (in 10 patients)/PVB (in 2)       | 62                   | 95% 4 y        |
| Williams et al\textsuperscript{4} | 26           | 27            | Stage III/IV or recurrent | PVB                                   | 52                   | 54% 2 y        |
| Bonazzi et al\textsuperscript{30} | 32           | 23            | Stage I to III    | BEP (in 8 patients)                   | 47                   | 100% 3 y       |
| Vicus et al\textsuperscript{41}   | 34           | 25            | Stage I to III    | BEP (in 7 patients)                   | 58                   | 87% 2 y progression-free survival |

N/A, not available.
overall survival was 54%. Bonazzi et al. treated 32 patients with BEP chemotherapy; all patients were alive and disease free after a median follow-up of 52 months. Vicus et al. reported 34 patients treated with cisplatin-based chemotherapy. The median follow-up was 38 months with a 2-year progression-free survival of 78 months. Three died from their disease.

To our knowledge, this is the fourth largest series in the literature that consider IT separate from other ovarian germ cell tumors and discuss its management. Our study confirms the high curability of this disease in both early and late stages. All study patients were alive at the conclusion of this trial, with no evidence of disease recurrence. This is also the first clinical trial to show that EP with no bleomycin as a primary chemotherapy regimen has superior long-term outcomes compared to standard BEP chemotherapy, with no evidence of disease recurrence. This is also the first clinical trial to show that EP with no bleomycin as a primary chemotherapy regimen has superior long-term outcomes compared to standard BEP chemotherapy, with no evidence of disease recurrence.

Further research needed to strengthen these findings.

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