Gynecologic Oncology Reports 58 (2025) 101715

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Oncologic and fertility outcome in patients with advanced stage ovarian immature teratomas

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ARTICLE INFO

Keywords:
Ovary
Germ cell tumors
Immature teratomas
Fertility sparing surgery

ABSTRACT

Background: Immature teratomas represent rare malignant ovarian germ cell tumours, typically involving young women. The majority of germ cell tumors (60%–70%) are diagnosed at an early stage, showing an optimal prognosis. However, advanced stages represent about one third of these patients. We report the oncologic outcome of this population, investigating also fertility outcomes in patients who underwent fertility preservation.
Methods: Clinicopathological data were retrospectively collected and analysed from a cohort of 17 post-pubertal patients with advanced stage immature teratomas in a single centre between 1980 and 2024.
Results: Among 17 patients included in the study, 76.5 % (13/17) underwent fertility-sparing surgery (FSS) and 23.5 % (4/17) radical surgery. Adjuvant chemotherapy was administered in 82 % (14/17) of patients. After a median follow up of 237 months (range 68.0–289.0), 2 patients had persistent disease after receiving chemotherapy and 3 showed relapse. Of these, two had a second relapse. All patients are alive without evidence of disease at the last follow up. Also 46 % (6/13) of women treated with FSS reached pregnancy.
Conclusions: FSS appears to be safe and effective in the treatment of advanced stage immature teratoma. Despite surgical interventions and the administration of chemotherapy in the majority of patients, fertility outcome is satisfactory.

1. Introduction

Immature teratomas are rare diseases, accounting for less than 1 % of ovarian tumours, with a yearly-adjusted incidence of 1–2 cases/1.000.000 in Europe (Smith et al., 2006; Gatta et al., 2011). They typically involve adolescents and young women. Differently from mature teratomas (dermoid cysts), embryonic tissue indicates the malignant potential of the tumour. In particular, immature neuroectoderm consent to discriminate between mature and immature disease, and the number neuroectodermal foci defines the grade of disease. Stage of disease plays a pivotal prognostic factor. The staging system conventionally adopted is the International Federation of Gynecology and Obstetrics (FIGO) staging system, also used for epithelial ovarian cancer (Prat, 2014). Although most immature teratomas are diagnosed at an early stage (60–70 %), it's not infrequent a systemic spread of disease, with an upgrade of staging and a worsening of the outcome (Solheim et al., 2014). Surgery represents a mainstay of treatment for these patients, followed by adjuvant chemotherapy. According to European Society for Medical Oncology (ESMO) guidelines (Ray-Coquard et al., 2018), National Cancer Committee Network guidelines (Armstrong et al., 2019) and European Society of Gynecological Oncology guidelines (Sessa et al., 2020); fertility-sparing surgery (FSS) with preservation of the uterus and at least one adnexa is considered the standard surgical treatment for young patients with early stage immature teratomas. This conservative management should be considered even in case of advanced disease because of the sensitivity of the tumour to

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https://doi.org/10.1016/j.gore.2025.101715
Received 22 January 2025; Received in revised form 3 March 2025; Accepted 4 March 2025
Available online 11 March 2025

chemotherapy (Ray-Coquard et al., 2018; Armstrong et al., 2019; Sessa et al., 2020). However, these recommendations derive from small cohorts of patients with malignant ovarian germ cell tumours including a small number of patients with immature teratomas. This study reports the oncologic outcome of the largest series in literature of patients with advanced stage ovarian pure immature teratomas treated at our Institution. Moreover, data on pregnancy rate of patients treated with a fertility-sparing approach were collected.

2. Materials

Patients with advanced stage immature teratoma treated at IRCCS San Gerardo dei Tintori Hospital, Monza, between 1980 and 2024 were enrolled. All cases were reviewed by a dedicated pathologist and defined according to the World Health Organization criteria (Kurman, nd). In patients who were referred to our Hospital after performing primary surgery elsewhere, formalin-fixed paraffin embedded tissue was requested and reviewed by our dedicated pathologist. Tumor stage was defined according to the 2014 FIGO classification (Prat, 2014). Tumour grade was defined in a three-grading system according to the number of neuroepithelial foci (Norris et al., 1976). Inclusion criteria were a diagnosis of advanced stage pure immature teratoma (stage II-IV according to FIGO staging) and the post-pubertal age (intended as post-menarche period). Patients' characteristics including age at diagnosis, symptoms of presentation, stage and grade of disease, surgical management and follow-up data on oncologic outcomes and subsequent pregnancies were collected. Follow-up records were updated until July 2024. Tumor markers, such as carbohydrate antigen 125 and alpha-fetoprotein, were generally collected during diagnostic workup, even if they are not available for all patients.

FSS, intended as removal of all visible disease with preservation of uterus and at least one adnexa, was carried out in women with childbearing desire. Radical surgery (RS) was defined as hysterectomy with bilateral salpingo-oophorectomy and every surgical procedure aimed to remove all the visible disease if possible. Adjuvant chemotherapy was proposed in each case and consisted in bleomycin/etoposide/cisplatin (BEP) or bleomycin/vincristine/cisplatin (BVP) regimen. In case of persistent or relapse disease, different included other mono- or multi-drugs schedules were administered. Patients' follow-up included a surveillance schedule with gynaecological examination, transvaginal ultrasound, alpha-fetoprotein measurement every 3 months for the first 2 years, then every 6 months until the fifth year of follow-up, then yearly. In some cases, laparoscopy was performed in order to evaluate chemotherapy response in those who had residual tumor in addition to CT scan, in particular prior to the 2000 s. (Ray-Coquard et al., 2018). With the improvement of radiodiagnostic techniques, the use of diagnostic laparoscopy was almost abandoned in the last decade.

Descriptive statistics were used to characterise the patient population. Clinicopathological features and treatment variables were evaluated for association with relapse. Institutional review board approved the study.

Written informed consent was obtained from the patient for publication. Ethical approval for the study was obtained and the study was approved by the Institutional Review Board (or Ethics Committee) of Comitato Etico Brianza (protocol code 3930).

3. Results

Seventeen post-pubertal patients with advanced stage ITs were treated or referred to our Institution and considered in the analysis. Demographic, clinical and pathological characteristics of patients are shown in Table 1.

Patients included in the study were followed up for at least five years, median follow up was 237.5 months (68–289 months). Median age at diagnosis was 22.4 years (12–45 years). Abdominal pain was the symptom of presentation in 41.1 % of patients (7/17), abdominal swelling in 29.4 % (5/17), ascites in 11.8 % (2/17), while for one patient it was an incidental finding. In 11.8 % (2/17) of patients, symptoms of presentation were not recorded. Stage II, III and IV were reported in 23.5 % (4/17), 70.6 % (12/17) and 5.9 % (1/17) patients, respectively. The rate of patients with grade 1, 2 and 3 was 11.7 % (2/17), 35.3 % (6/17) and 52.9 % (9/17), respectively. Treatments and oncologic outcomes are reported in Table 2.

All patients underwent upfront laparotomic surgery. FSS was carried out in 76.5 % (13/17) of patients, while the remaining 23.5 % (4/17) underwent radical surgery. Two of these patients of 25 and 17 years old underwent demolitive surgery in other Institutions and then were referred to our Centre. The remaining two patients who had a demolitive treatment had completed their childbearing desire. After primary debulking surgery, no evidence of disease was obtained in 70.6 % (12/17) of patients, in particular 3/4 who underwent RS and 9/13 after FSS. Residual disease was <1 cm in three patients and >1 cm in two. Adjuvant chemotherapy was administered in 82.4 % (14/17) of cases, while the remaining 17.6 % (3/17) of patients underwent clinical surveillance. They were diagnosed with stage IIB grade 1, stage IIB grade 2 and stage

Table 1
Demographic,clinical and pathological characteristics of patients included in the analysis (N = 17).

	Median (min–max)
Age at diagnosis	22.4 (12–45)
Symptoms of presentation	
Abdominal pain	7 (41.1 %)
Abdominal swelling	5 (29.4 %)
Ascitis	2 (11.8 %)
Incidental finding	1 (5.9 %)
Not known	2 (11.8 %)
Stage of disease at diagnosis	
II	4 (23.5 %)
III	12 (70.6 %)
IV	1 (5.9 %)
Grade of disease at diagnosis	
G1	2 (11.7 %)
G2	6 (35.3 %)
G3	9 (52.9 %)

Abbreviation. SD = Standard deviation; G1 = grade 1; G2 = grade 2; G3 = grade 3.

Table 2
Treatment and oncologic outcomes (N = 17).

Decade of surgery	
1980–1989	2 (11.8 %)
1990–1999	10 (58.8 %)
2000–2009	4 (23.5 %)
2010–2019	1 (5.9 %)
Type of surgery	
FSS	13 (76.5 %)
RS	4 (23.5 %)
Residual tumour after surgery	
No evidence of disease	13 (76.5 %)
Residual tumour	4 (23.5 %)
Adjuvant chemotherapy	
Yes	14 (82.4 %)
No	3 (17.6 %)
Mean cycles of chemotherapy	4 (3–6)
Relapse	
Fertility-sparing	1 (5.9 %)
Demolitive	2 (11.8 %)
Persistence	
Fertility-sparing	2 (11.8 %)
Demolitive	0 (0 %)
Median time to relapse	7.7 (2–24)
Follow up (months)	**Median (min–max)**
	237.5 (68.0–289.0)

Abbreviation. FSS = Fertility sparing surgery; RS = Radical surgery.

IIIA grade 1 diseases, respectively. BEP regimen was the preferential schedule used as adjuvant schedule, while BVP schedule was used just in one patient. The mean number of cycles of adjuvant treatment administered was 4 (range 3–6).

Relapses and persistent diseases details are shown in Table 3.

In two patients the diagnostic laparoscopy after adjuvant chemotherapy revealed persistent disease, and they underwent a second surgery and subsequent further chemotherapy. They both had a complete response and are alive after 45 and 96 months. Three patients experienced relapse, diagnosed with CT scan, after 24, 36 and 5 months after the end of first-line chemotherapy, and two of them were treated with surgery alone while one with surgery and second line chemotherapy. Two patients had a second relapse, both with stage IIIC grade 3 disease at initial diagnosis. The first patient had the second relapse one year after the first with the presence of nodules on the hepatic surface. The patient underwent surgery and 10 cycles of chemotherapy, with no evidence of disease until the last follow up. The second patient had the second relapse 14 months after the first and underwent another FSS with the removal of a pelvic nodule The patient remained free of disease until the last follow up.

Concerning fertility outcome, we excluded from the analysis patients treated with radical surgery (4/17). Table 4 shows the fertility rate of our population.

Among the 13 patients who underwent FSS, 46.2 % (6/13) got pregnant. A total of 8 babies were born, 6 by spontaneous delivery and 2 by caesarean section; 3 spontaneous abortion and 1 extrauterine pregnancy were recorded. One patient obtained the pregnancy with ART, while in all other cases conception was spontaneous. patients who did not conceive, 15.4 % (2/13) of them were not interested in obtaining pregnancy and the remaining 23.1 % (3/13) were not able to reach pregnancy. Data on fertility for two patients were not available.

Table 4
Fertility outcome in FSS population (N = 13).

Median age	19.5 (12–34)
Number of pregnancies before diagnosis	
0	11 (84.6 %)
≥ 1	2 (15.4 %)
Fertility outcome	
No pregnancies	
- No desire	2 (15.4 %)
- Infertility	3 (23.1 %)
Pregnancies	**6 (46.2 %)**
N/A	2 (15.4 %)

Abbreviation. FSS = Fertility sparing surgery; N/A = Not available.

4. Discussion

Management of advanced stage immature teratoma remains nowadays an area of discussion. Data on this topic is lacking due to the rarity of the disease. Few studies on advanced stage malignant ovarian germ cell tumours are published in literature, and oncological safety of FSS have been poorly investigated in this setting (Chan et al., 2008; Mangili et al., 2011; Zanetta et al., 2001; Thomakos et al., 2018). Initial management of these patients should take in consideration some aspects, including age, desire of pregnancy, resectability of disease and operability of the patient. In case of bulky, non-resectable disease, or poor performance status of the patient, neoadjuvant chemotherapy may be a feasible approach (Brown et al., 2014), and this is also an option in case of young patients, in order to make fertility sparing treatment more easily achievable. In fact, immature teratomas are strongly chemosensitive and platinum-based chemotherapy could be considered as a first line approach, at least for grade > 1 (Bonazzi et al., 1994; Bergamini et al., 2021). Talukdar et al (Talukdar et al., 2014) suggested neoadjuvant chemotherapy as a feasible approach in women with advanced stage malignant germ cell tumor of the ovary, with the aim to reduce tumour load and preserve fertility with subsequent surgery. However, no patient with advanced stage immature teratoma was reported in neoadjuvant chemotherapy group, but only patients with dysgerminoma, endometrial sinus tumour and mixed cell germ tumours. Despite the rationale, this approach is not the current standard of care (Brown et al., 2014). In fact, residual disease seems not to play a role in determining the overall survival of patients with advanced stage malignant ovarian germ cell tumours, as we noticed in our study and also reported by Nasioudis et al (Nasioudis et al., 2019). The rationale of the primary cytoreductive approach is, likewise for epithelial ovarian cancer, the removal of chemoresistant clones. (Bafna et al., 2001). In our case series, all patients underwent primary debulking surgery, with the majority of them (13/17, 76.5 %) having no evidence of disease after surgery. 14/17 patients received adjuvant chemotherapy, and complete response was achieved in 88.2 % (15/17). Persistent disease was observed in 2 patients Adopting this strategy, our recurrence/persistence rate is perfectly in line with previous literature (Mangili et al., 2011). In fact, relapse occurred in 3 patients, who were treated with a combination of surgery and chemotherapy, with no death for disease recorded. Also, secondary relapses, which have occurred in 2 patients, were promptly treated. Interestingly, no relapse limited to the other ovary or the uterus were observed in patients who underwent FSS, justifying the almost abandoned role of radical surgery in this setting of patients. Medical treatment is strongly recommended by international guidelines for patients with advanced stage disease (Ray-Coquard et al., 2018; Armstrong et al., 2019; Sessa et al., 2020). Platinum-based chemotherapy used to induce a maturation of the immature component of the tumours into mature glia, a non-malignant component (Bonazzi et al., 1994), and its introduction in clinical practice for germ cell tumors of the ovary has improved outcomes for this population (Gershenson, 2007). However, this data is

Table 3
Characteristics of patients with recurrence and relapse features.

	Age at diagnosis	Stage	Adjuvant CT	Time to relapse	Site of relapse/persistence	Treatment at relapse	OS (months)	VS
1	24	IIIB G2	BEP schedule x 3	24 months	Meso-colic and diffuse peritoneal surface nodules	Surgery alone	384	NED
2	25	IIIB G1	BVP schedule x 4	Persistence	Omental mass + peritoneal nodules	Surgery + CT (DEC schedule x 3)	279	NED
3	14	IIIB G2	BEP schedule x 6	36 months	2 pulmonary nodules	Surgery alone	266	NED
4*	45	IIIC G3	BEP schedule x 5	5 months	Hepatic lesions + peritoneal nodules	Surgery + CT (TIP x 4).	68	NED
5*	15	IIIC G3	BEP x 6	Persistence	Pelvis + right diaphragm + retrohepatic mass	Surgery + CT (TIP x2).	215	NED

Abbreviations. G1 = Grade 1; G2 = Grade 2; G3 = Grade 3; RS = Radical surgery; FSS = Fertility-sparing surgery; RT = Residual tumor; NED = No evidence of disease; CT = Chemotherapy; BEP = bleomycin/etoposide/cisplatin; BVP = bleomycin/vinblastine/cisplatin; DEC = decitabine; TIP = paclitaxel/ifosfamide/cisplatin; VS = Vital status.
* Patients who exSperienced two relapses.

still controversial for ITs. Data on surveillance only are actually reassuring for any grade stage I disease (Bergamini et al., 2020; Marino et al., 2024). Also, grade 1 disease is considered similar to "normal tissues", less aggressive and on the counterpart less sensitive to chemotherapy, which probably plays a more marginal role in this setting (Bonazzi et al., 1994; Bergamini et al., 2021; Bergamini et al., 2020). Interestingly, Out of three patients followed only with strict surveillance who did not receive chemotherapy administration did not show relapse during the follow up period. They were diagnosed with stage II disease in two cases and stage IIIA in the remaining case, showing grade 1 and one grade 2 disease. However, this should not be considered a recommendation for clinical practice, and indications for adjuvant chemotherapy remain the standard in advanced stage disease (Ray-Coquard et al., 2018; Armstrong et al., 2019). Concerning fertility, surgery and chemotherapy often has been associated with fertility impairment (Thomakos et al., 2018; Somigliana et al., 2006; Lee et al., 2006). However, Cisplatin-based schedules, as BEP or BVP, show less toxicity on fertility, with maintenance of menstrual cycles after treatment in approximately 90 % of cases (Gadducci et al., 2014). Sporadic reports reported high pregnancy rates after treatment for malignant ovarian germ cell tumours (Chan et al., 2008; Mangili et al., 2011; Zanetta et al., 2001; Thomakos et al., 2018; Lee et al., 1989; Yang et al., 2018; Tamauchi et al., 2018; Vasta et al., 2024; Marino et al., 2024), and very few data are relative to advanced stage disease. In any case, good fertility outcomes without affecting overall survival are shown (Zanetta et al., 2001; Tamauchi et al., 2018; Tangir, 2003; Park et al., 2017; Nasioudis et al., 2017). In our series, 46.2 % (6/13) of patients who underwent FSS obtained a pregnancy, similar to other series. Tamauchi et al show an optimal live birth rate in patients with malignant ovarian germ cell tumours who tried to conceive after FSS, but only 20 % of patients with advanced stage disease reached pregnancy (Tamauchi et al., 2018). Similarly, Zanetta et al reported an optimal fertility rate in their population, however no data on advanced stage was reported (Zanetta et al., 2001). Recently, the Multicenter Italian Trials in Ovarian Cancer (MITO) group administered a questionnaire to 114 ovarian germ cell tumors survivors. Of 38 patients who attempted conception, 76.3 % (29/38) conceived, of whom 6 who presented advanced stage disease at diagnosis, showing good results in this underrepresented population.

The main limitations of the present study are its retrospective design and the small sample size of the population analysed, which hampered a statistical analysis. However, this study reported a large single-centre case series on a population of patients with advanced stage pure ovarian immature teratoma, which enlightened the feasibility of a fertility-sparing surgery followed by adjuvant chemotherapy with an optimal control of the disease without a great impairment in fertility.

5. Conclusions

Our results show optimal survival rate in advanced stage immature teratomas of the ovary treated with primary surgery. Patients treated with FSS showed a good fertility outcome in the majority of cases along with optimal survival rates. Due to the rarity of disease, only small numbers of patients are addressed in each case series. For this reason, more multicentric studies, including larger populations, should be considered to better define the ideal approach for these patients. Also, prospective registries are needed.

CRediT authorship contribution statement

Marino Giuseppe: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Negri Serena:** Conceptualization, Investigation, Data curation, Writing – review & editing. **Testa Filippo:** Conceptualization, Investigation, Data curation, Writing – review & editing. **Giuliani Daniela:** Investigation, Data curation, Writing – review & editing. **De Ponti Elena:** Methodology, Formal analysis, Data curation, Writing – review & editing. **Bombelli Martina:** Investigation, Data curation, Writing – review & editing. **Pecis Cavagna Giorgia:** Investigation, Data curation, Writing – review & editing. **Lugotti Daniele:** Investigation, Data curation, Writing – review & editing. **Jaconi Marta:** Conceptualization, Methodology, Investigation, Data curation, Writing – review & editing. **Casiraghi Alessandra:** Conceptualization, Methodology, Investigation, Data curation, Writing – review & editing. **Bianchi Tommaso:** Conceptualization, Investigation, Data curation, Writing – review & editing. **Grassi Tommaso:** Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Bonazzi Maria Cristina:** Conceptualization, Writing – review & editing, Supervision. **Fruscio Robert:** Conceptualization, Methodology, Data curation, Writing – review & editing, Visualization, Supervision.

Funding

None.

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.

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