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Non-seminomatous ovarian germ cell tumours in children

M.C. Baranzelli [a], E. Bouffet [b,c], E. Quintana [d], M. Portas [e], A. Thyss [f], C. Patte [g,*]

[a] *Service d'Oncologie Médicale « A », Centre Oscar Lambret, 3 rue F. Combemale, 59020 Lille Cedex, France*
[b] *Service d'Oncologie Pédiatrique, Centre Léon Bérard, 69373 Lyon, France*
[c] *Children's Department, The Royal Marsden NHS Trust, Sutton, UK*
[d] *Pédiatrie Oncologique, Institut Curie, 26 rue d'Ulm, 75231 Paris Cedex, France*
[e] *Service de Pédiatrie, Hôpital d'enfant La Timone, 264 rue St Pierre, 13385 Marseille Cedex, France*
[f] *Centre Antoine Lacassagne, 36 ave de la voie Romaine, 06054 Nice Cedex, France*
[g] *Service de Pédiatrie, Institut Gustave Roussy, 39 rue Camille Desmoulins, 94805 Villejuif Cedex, France*

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Abstract

In this study, we report the results of two consecutive protocols, TGM 85 and TGM 90, of the Société Française d'Oncologie Pédiatrique (SFOP) for patients with non-seminomatous germ cell tumours of the ovary and analyse the rationale for surgical indications, neoadjuvant or adjuvant chemotherapy. TGM 85 and 90 both utilised six drugs, bleomycin, cyclophosphamide, vinblastine, dactinomycin, etoposide and either cisplatin (TGM 85) or carboplatin (TGM 90). Chemotherapy was given in case of unresectable or incompletely resected tumour. Patients who had a complete resection of a localised tumour underwent expectant management and were only treated if progression occurred. 63 patients aged less than 18 years old were enrolled between January 1985 and December 1994. 49 patients had α-fetoprotein (αFP) ± β-human chorionic gonadotropic hormone (βHCG) secreting tumours and 14 had immature teratomas. Median follow-up for surviving patients is 60 months (range: 19–154). The 5-year overall survival is 85% ± 5%. 13 out of 14 patients (93%) with immature teratoma are alive, including 3 of 4 patients (75%) who received chemotherapy for advanced disease. 41 patients (84%) with secreting tumours are alive, including 2 patients who required salvage treatment. Most failures occurred amongst patients with high initial αFP secretion (> 15 000 ng/ml). 39 of 41 survivors (95%) in the non-teratoma group had conservative surgery, allowing the possibility of future pregnancy. High cure rate can be achieved with a conservative approach in non-seminomatous germ cell tumour of the ovary. Whenever possible, fertility should be preserved during the primary operation in children suffering from these tumours.

Keywords: Children; Ovary; Germ cell tumours; α-Fetoprotein; Immature teratoma; Chemotherapy; Surgery

1. Introduction

Malignant germ cell tumours of the ovary account for less than 5% of all ovarian cancers in Western countries [1]. Teratomas, choriocarcinomas, endodermal sinus tumours, dysgerminomas, and mixed types comprise the majority of these tumours, whilst embryonal carcinomas are exceptional. However, in children and teenagers, germ cell tumours are the most frequent ovarian neoplasms [2] and are commonly divided into two groups, dysgerminomas and non-seminomatous malignant germ cell tumours. Non-seminomatous malignant germinal tumours include immature teratomas and malignant germ cell tumours which comprise the following types: yolk sac tumour, associated with a secretion of alpha fetoprotein (αFP), choriocarcinoma associated with a secretion of human chorionic gonadotrophic hormone (βHCG), non-secreting embryonal carcinoma and immature teratoma. Originating from undifferentiated malignant germinal cells, malignant non-seminomatous germ cell tumours of the ovary are histologically similar to their counterparts in other sites such as the testis, the sacrococcyx, the mediastinum or the brain. Yolk sac tumours and choriocarcinomas share characteristics that produce similar features in their management: they are highly malignant, have a propensity to spread, and are frequently chemosensitive. Some of these tumours may contain one single tumour type, but most of them are composed of several malignant components. In contrast, immature teratomas are associated with a risk of loco-regional malignancy and usually do not respond to either chemotherapy or

* Corresponding author. Tel.: +33-1-42-11-4176; fax: +33-1-42-11-5275.
E-mail address: patte@igr.fr (C. Patte).

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radiotherapy. Teratomas often show a mixture of mature and immature tissue. Moreover, all these tumours may contain small amounts of seminomatous elements. This histological heterogeneity and complexity makes the description of this group of tumours and comparisons between series difficult.

In this report, 63 patients aged less than 18 years with malignant non-seminomatous germ cell tumours were treated between January 1985 and December 1994 in two consecutive protocols TGM 85 and TGM 90. Pure seminomas were excluded as these raise different therapeutic questions. In order to facilitate the understanding of the diagnostic and therapeutic approach, tumours containing at least one of the following components, either yolk sac tumour, or choriocarcinoma or both are called 'secreting tumours' since these are generally associated with αFP and/or βHCG secretion. In this article, non-seminomatous germ cell tumours will therefore be divided into secreting tumours and immature teratomas.

2. Patients and methods

2.1. Patients

Amongst 261 patients registered, 109 patients and 152 patients were included in TGM 85 and TGM 90 protocols, respectively. These protocols were designed for patients with non-intracranial malignant germ cell tumours or sex cord-stromal tumours. 97 patients (37 in TGM 85 protocol and 60 in TGM 90 protocol) presented with an ovarian tumour. Amongst these 97 patients, 63 (65%) had a malignant non-seminomatous germ cell tumour of the ovary and are included in this report, 18 (19%) had pure seminomas or seminomas associated with a gonadoblastoma, 15 (15%) had a sex cord-stromal tumour, and one (1%) had an embryonal carcinoma. Mature teratomas were not registered in the SFOP group.

23 patients were treated according to TGM 85 protocol open in January 1985 and closed in December 1989 and 40 according to TGM 90 protocol open in January 1990 and closed in December 1994. The diagnostic strategy and the staging system were similar in both protocols. When a patient with an ovarian tumour had raised tumour markers at presentation (αFP > 15 ng/ml and/or HCG > 25 mUI/ml) and provided differential diagnosis (pregnancy, hepatoblastoma) have been excluded, initial surgery with diagnostic intent was not compulsory. For children less than 6 months old, the αFP level was interpreted according to physiological values for age [3]. Initial staging included complete clinical examination, operation notes and histology report when surgery was performed at presentation, abdominal and pelvic ultrasound, chest X-ray and if possible pre- and postoperative abdominal and pelvic computed tomography (CT) scan. Pre- and postoperative TNM staging was used with the aim of standardising the management of extracranial non-seminomatous germ cell tumours of all locations (Table 1).

2.2. Treatment

TGM 85 was the first SFOP protocol for extracranial germ cell tumours. All patients with extracranial germ

Table 1

Clinical classification TNM-SFOP	
Stage CS I	Localised tumour < 5 cm
	No lymph node involvement
	No metastasis
Stage CS II	Tumour > 5 cm
	No lymph node involvement
	No metastasis
Stage CS IIIA	Tumour of any size
	Locoregional lymph node involvement
	No metastasis
Stage CS IIIB	Tumour of any size
	Locoregional involvement (peritoneal gliomatosis and/or tumoral ascitis)
	With or without lymph node involvement
	No metastasis
Stage CSIV	Metastatic tumour of any size
Postsurgical classification TNM-SFOP	
Stage pSI	Tumour without locoregional extension, completely removed
Stage pSII	Tumour with locoregional extension, with or without lymph node involvement, completely removed, with no metastasis
Stage pSIII	Tumour with locoregional extension, with no metastasis, incompletely removed
• pSIIIa	Microscopic residue
• pSIIIb	Macroscopic residue or tumoral ascitis
Stage pSIV	Tumour with distant metastasis

cell tumours were eligible, regardless of the tumour site. The protocol was open for patients with malignant germ cell tumours and immature teratomas. Patients with mature teratomas are usually not referred to oncology units in France and are not registered in SFOP studies. For the population of patients with ovarian tumours, the objective of the protocol was to improve the cure rate using a staged strategy including adjuvant or neoadjuvant chemotherapy, and to decrease the risk of infertility with a policy of conservative surgery. The objectives of the TGM 90 protocol were identical. An additional objective of this protocol was to reduce late renal and auditive toxicity by substituting cisplatin with carboplatin.

Management differed according to the tumour type.

2.2.1. Secreting tumours

When the tumour was localised and complete resection was felt to be achievable (clinical stages I and II), conservative surgery with curative intent was recommended. Surgical management also included careful exploration of the abdomen, aiming to perform cytological examination of ascites when present and biopsies of suspicious lymph nodes and of the opposite ovary in case of doubt. Patients with completely resected localised tumours (stages I or II, pSI) were followed-up expectantly after surgery. Follow-up was based on tumour markers and imaging of the pelvis. Should tumour markers remain the same or increase and/or pelvic abnormalities or retroperitoneal lymph nodes appear on imaging, patients then proceeded to chemotherapy.

In all other situations (clinical stages III and IV and clinical stages I or II not completely resected) patients underwent chemotherapy. Neoadjuvant chemotherapy was given prior to surgery for unresectable or disseminated tumours diagnosed on tumour markers only and adjuvant chemotherapy was given postoperatively for incompletely resected lesions. When emergency surgery was performed for patients presenting with ovarian torsion or rupture, recommendations were for conservative management rather than aggressive debulking. Chemotherapy incorporated drugs known to be effective in adult non-seminomatous testicular germ cell tumours: platinum compounds, bleomycin, vinblastine, cyclophosphamide, dactinomycin, etoposide and ifosfamide. Protocols are detailed in Table 2. The main difference between TGM 85 and TGM 90 protocols relates to the platinum compound: in protocol TGM 90, carboplatin (400 mg/m^2/d), considered less toxic, replaced previous cisplatin (100 mg/m^2/d) used in protocol TGM 85. The number of cycles of chemotherapy was also different: three in TGM 85 protocol whereas duration of treatment was adjusted to the date of markers' normalisation in the TGM 90 protocol after which patients received two additional cycles of chemotherapy. In protocol TGM 90, second-line treatment comprising ifosfamide, etoposide ± cisplatin was considered when biological remission was not achieved following two cycles of chemotherapy. Patients with evidence of metastatic disease were also allocated to a more intensive protocol in TGM 90. They received six cycles of carboplatin–vinblastine–bleomycin/ifosfamide–etoposide (TGM 90 metastatic).

Patients who received up-front chemotherapy without biopsy underwent resection of the involved gonad at completion of chemotherapy. When initial surgery was incomplete, second-look surgery was recommended only when residual disease was still present on imaging at the time of markers' normalisation. If the markers achieved a plateau or increased, second-line chemotherapy was advocated, surgery being ideally performed in biological remission.

2.2.2. Immature teratomas

Surgery was the mainstay of therapy for these tumours. If complete resection was achieved, no postoperative treatment was considered. When peritoneal implants were present, indication for chemotherapy was dependent upon the histological grading using the Norris classification [4]: chemotherapy was not advocated for mature or grade I or II immature teratoma, whereas patients with grade III tumours underwent chemotherapy according to the ongoing protocol and second-look surgery.

2.3. Response criteria and statistical analysis

Both protocols were evaluated for the following response criteria: complete remission (CR) after induction chemotherapy, continuous complete remission after chemotherapy including second-line treatment for TGM 90 protocol. In the TGM 85 protocol, treatment failure was defined as death, relapse, or an incomplete response after initial chemotherapy. In the TGM 90 protocol, treatment failure was defined as death, relapse, or an incomplete remission after second-line chemotherapy, since patients who did not achieve complete response after four courses of chemotherapy were allocated to a more intensive regimen. Time to event curves were estimated by the Kaplan–Meier method at 5 years [5]. Analysis of survival and event were done as of November 1998, with a median follow-up of 134 and 71 months for TGM 85 and TGM 90 regimens, respectively.

3. Results

63 patients were treated according to these modalities, 23 in the TGM 85 protocol and 40 in the TGM 90.

14 patients (22%) had immature teratoma either associated or not with mature components. Median age

Table 2
TGM 85 and TGM 90 chemotherapy protocols

TGM 85 (one cycle)										
Days		1	2	3	4	5	22	23	24	
Drugs	Dose									
Actinomycin D	10 μg/kg/d	●	●	●	●	●				
CTX	300 mg/m²/d	↓	↓	↓	↓	↓				
Vinblastine	3 mg/m²/d						□	□		
Bleomycin	15 mg/m²/d						–	–		
CDDP	100 mg/m²/d								◇	
Interval between two cycles: 21 days										
TGM 90 (one cycle)										
Days		1	2	3	4	5	22	23	24	
Drugs	Dose									
Actinomycin D	15 μg/kg/d						●	●	●	
CTX	500 mg/m²/d						↓	↓	↓	
Vinblastine	3 mg/m²/d	□	□							
Bleomycin	15 mg/m²/d	–	–							
Carboplatin	400 mg/m²/d			◆						
Interval between two cycles: 21 days										
TGM 90 2nd-line										
Days		1	2	3	4	5				
Drugs	Dose									
Ifosfamide	1.8 g/m²/d	○	○	○	○	○				
VP	100 mg/m²/d	*	*	*	*	*				
CDDP	20 mg/m²/d	◇	◇	◇	◇	◇				
Interval between two courses: 21 days										
TGM 90 metastatic (one cycle)										
Days		1	2	3	4	5	22	23	24	25	26
Drugs	Dose										
Vinblastine	3 mg/m²/d	□	□								
Bleomycin	15 mg/m²/d	–	–								
Carboplatin	400 mg/m²/d			◆							
Ifosfamide	1.8 g/m²/d						○	○	○	○	○
VP	100 mg/m²/d						*	*	*	*	*
Interval between two cycles: 21 days											

Actinomycin D (●), dactinomycin; CTX (↓), cyclophosphamide; □, vinblastine; –, bleomycin; CDDP (◇), cisplatin; ◆, carboplatin; VP (*), etoposide.

for this group was 11.5 years (range 1–17 years). All patients had surgery at presentation. One (7%) presented with acute abdominal pain due to an ovarian torsion. 8 patients (57%) had stage I pSI tumours. 2 patients (14%) had stage III lesions with mature peritoneal gliomatosis and did not receive postoperative treatment. 4 patients (29%) received adjuvant chemotherapy: 1 because surgical staging was doubtful and 3 for tumours associated with haemorrhagic ascitis and peritoneal gliomatosis (stage III, pS3b). 2 of these 3 patients had second-look surgery which showed mature residue in 1 patient and diffuse peritoneal seeding of immature teratoma in the other patient, who eventually died of progression.

Overall, 13 out of 14 (93%) patients are alive with a median follow-up of 50 months (range: 28–89 months) including 10 patients (71%) treated exclusively with surgery.

49 patients (78%) had a secreting tumour, 19 (39%) registered in TGM 85 protocol, and 30 (61%) in TGM 90. The median age at diagnosis was 12 years (3 months–18 years). All 49 patients had αFP-secreting tumours, including 14 (29%) with both αFP and βHCG secretions. No patient presented with isolated βHCG secretion. Clinical and postsurgical stages are detailed in Tables 3 and 4. In 39 patients (80%), the initial diagnosis was based on histology ± tumour markers. 37 had surgery and 2 underwent fine needle biopsy. Concordance between serum markers and histology was observed in 29 cases only. In 10 cases, histology was not

Table 3
Clinical staging in 49 patients with secreting tumours

	TGM 85	TGM 90	*n* (%)
Clinical stage I		1	1 (2)
Clinical stage II	10	11	21 (43)
Clinical stage IIIa		1	1 (2)
Clinical stage IIIb	8 including one patient with bilateral tumour	15 including 2 patients with bilateral tumour	23 (47)
Clinical stage IV	1	2	3 (6)
Total	19	30	49 (100)

Table 4
Postsurgical classification in 37 patients with initial surgery

	TGM 85	TGM 90	*n* (%)
pSI	4	8	12 (32)
pSII	1		1 (3)
pSIIIa	1	1	2 (5)
pSIIIb	9	12	21 (57)
pSIV		1	1 (3)
Total	15	22	37 (100)

in agreement with tumour markers, and disclosed embryonal carcinoma (4 patients), immature (5 patients) or mature (1 patient) teratoma whilst αFP (10 patients) and/or HCG (1 patient) were positive.

12 patients (32%) had pSI tumour (completely resected tumour confined to the gonad) and did not receive postoperative chemotherapy. Active surveillance was set up after ovariectomy. 6 relapses were detected during follow-up evaluation. In 4 cases, they were diagnosed on raised tumour markers only, whereas in 2 cases, they were associated with clinical signs of recurrent tumour. One patient underwent reoperation before chemotherapy. All 6 patients received chemotherapy according to the protocol, and all but one achieved complete biological remission. 4 patients had second-look surgery, which revealed fibrotic tissue. 11 patients remain in complete remission including 6 after surgery only. One patient did not show any response to chemotherapy and died of progression.

25 patients (68%) received chemotherapy for postsurgical non-pSI stage. Amongst these patients, 7 had emergency surgery for acute abdominal symptoms (4 ruptures, 1 torsion, 1 intratumoral bleeding, 1 acute abdominal pain). One patient died during the perioperative period and is not evaluable. One patient progressed during chemotherapy and died of progression. 23 patients achieved complete remission after surgery and chemotherapy. This was obtained following first-line chemotherapy in 20 patients (9 with carboplatin-containing regimen, and 11 with cisplatin-containing regimen) or second-line therapy using ifosfamide and etoposide with platinum compounds in 3 patients included in the TGM 90 protocol. The median time to achieve biological remission was 64 days (range: 23–203 days). 20 patients are in first complete remission including 4 who underwent second-look surgery for residual abnormalities on imaging. Only one of these 4 patients had a microscopically positive second-look laparotomy. 3 patients had bilateral tumours. One had initial hysterectomy with bilateral adnexectomy; 1 patient had limited surgery and achieved remission with chemotherapy. The third patient is the one who progressed during chemotherapy and died of progression. 3 patients relapsed: one is in second complete remission following salvage chemotherapy and aggressive surgery and 2 patients died of progression. Overall, 21 patients in this group are alive, 20 in first remission including a stage IV patient, and 1 patient is in second complete remission. 19 of these 21 patients had conservative surgery and only 2 had mutilating surgery which precluded future fertility.

12 patients received up-front chemotherapy including the 2 patients who had a limited diagnostic biopsy. Clinical stage was II in 5 patients, III in 5 and IV in 2. One patient experienced progression on treatment and died. 2 patients required urgent surgery during initial chemotherapy due to dramatic tumour growth, despite the normalisation of markers. Surgery disclosed mature and immature teratoma in both cases. All other patients responded to chemotherapy and underwent resection of the ovary initially involved after completion chemotherapy and normalisation of markers. 3 patients had microscopically positive findings when operated upon. All 3 are alive in remission. 3 patients relapsed (1 stage II, 1 stage III and 1 stage IV). One achieved a second complete remission whilst the other 2 patients died, 1 of disease and the other from toxicity following high-dose chemotherapy. 9 of the 12 patients in this subgroup are alive, 8 are in first remission and 1 in second remission after conservative surgery.

3.1. Toxicity of chemotherapy

No definite data are available to document haematological or extrahaematological toxicity in this group of patients. In particular, no data are available on long-term renal and ototoxicity. No case of renal failure or bleomycin-related respiratory failure was reported. No toxic death occurred in the TGM 85 and 90 protocols. However, 1 patient died before chemotherapy was initiated. Postmortem examination revealed disseminated foci of sepsis. One other patient experienced toxic death following high-dose chemotherapy with bone marrow transplant for a relapsed tumour. Finally, 1 patient died of secondary leukaemia 60 months after diagnosis. Information on fertility was unavailable at the time of the analysis. Limited data collection in the two largest centres suggest that pregnancy rates amongst patients were comparable to the general population.

3.2. Survival

Overall, amongst the 49 patients with secreting tumours, 41 (84%) are alive. 8 patients died, 6 of them having high level of αFP secretion ($>15\,000$ ng/ml) at the time of diagnosis. The median follow-up for surviving patients is 60 months (range: 19–154). All 3 stage IV patients achieved complete remission with chemotherapy and 2 had conservative surgery. Amongst the 41 surviving patients, 39 (80%) had conservative surgery. Overall 5-year survival in this group is $83\% \pm 11\%$ and

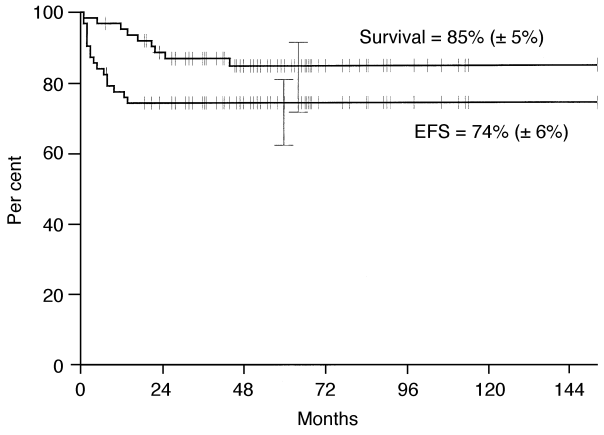

Fig. 1. Overall and EFS (event-free survival) of the 63 patients.

event-free survival 69% ± 11%. Similar outcomes were observed in both protocols, with 3 deaths out of 19 patients (16%) in TGM 85, and 5 deaths out of 30 patients (17%) in TGM 90.

For the 63 patients, the 5-year overall and event-free survival are respectively 85 ± 5% and 74 ± 6% (Fig. 1).

4. Discussion

Eighty per cent of ovarian tumours encountered in children and teenagers (< 18 years of age) are benign. Dermoid cysts and cystadenomas account for the majority of these lesions [6]. Malignant tumours of the ovary in this age group are rare compared with the adult group, since 95% of ovarian neoplasms occur in patients older than 30 years of age. However, these tumours differ from those encountered in older women: adenocarcinoma are exceptional and the most frequent histological types are sex cord-stromal tumours, seminomas or, by and large, non-seminomatous germ cell tumours. Amongst paediatric germ cell tumours, ovarian tumours account for approximately 30% of all cases [6–9]. All authors recognise the peripubertal peak incidence in children aged 10–15 years. In this tumour group, immature teratomas and secreting tumours differ markedly in their natural history and management. For non-secreting immature teratoma, surgery is essential for diagnosis and is the mainstay of treatment, since it is often curative when total resection is achieved. Our results are in agreement with the German experience, where ovarian teratomas showed no relapse after complete resection [10]. Teratomatous tissues are typically chemo- and radioresistant, and indications for adjuvant treatment in this group are still controversial [11]. For the same reasons, surgery is still essential at the time of relapse in teratomas. Immature teratoma is often associated with mature teratoma and the presence of mature peritoneal gliomatosis does not seem to affect the prognosis. Therefore, neither chemotherapy nor radiotherapy is justified in these situations. However, when peritoneal gliomatosis containing grade II or more immature teratoma according to Norris classification [4] is present, the prognosis is dismal and aggressive management is advocated, although its effectiveness is not proven [12]. Other authors consider that the size of peritoneal implant has a prognostic value [10].

For secreting tumours, positivity of serum αFP and/or βHCG is sufficient to ascertain the diagnosis, and the benefit of diagnostic surgery when tumour markers are positive is questionable in advanced stages [13]. These tumours are highly chemosensitive like their counterparts in the testis [14]. Studies reporting on paediatric populations have confirmed the high chemosensitivity of secreting tumours [6,8,9,15–21]. First-line chemotherapy for germ cell tumours always utilises a platinum compound (cisplatin or carboplatin) combined with one or two other cytotoxic agents, such as bleomycin, vinblastine or etoposide [22]. Dactinomycin is progressively abandoned in first-line regimens. Ifosfamide is currently preferred to cyclophosphamide and is reserved for advanced stages or relapses [23]. In the TGM 90 SFOP experience, carboplatin at a dose of 400 mg/m^2/cycle has been shown to be less effective than cisplatin given at a dose of 100 mg/m^2/cycle [24]. Such a difference between cisplatin and carboplatin has also been reported in adults with non-seminomatous germ cell tumours of the testis [25,26]. The United Kingdom Children's Cancer Study Group [18,20] has reported more encouraging results with carboplatin, but the dose used in this study was significantly higher (600 mg/m^2) and the median number of courses per patient was 6, corresponding to a cumulative dose of carboplatin of 3.6 gm/m^2 compared with 1.2 gm/m^2 in our experience. Some groups use different protocols of chemotherapy based on risk factors [8,16,21]. However, prognostic factors in paediatric germ cell tumours are ill-defined. In an analysis of the prognostic factors in TGM 85 and TGM 90 protocols, patients with a high secretion of αFP and advanced stage were more likely to develop treatment failure [27]. An international workshop is ongoing in order to better characterise risk groups. The definition of risk groups based on presenting features such as stage, tumour site and tumour markers might contribute to better define the treatment needs.

For tumours confined to the ovary, cure can be achieved by surgery alone. Expectant management with careful monitoring of tumour markers (every week until normalisation, then every month for 6 months and every 2 months for 1 year) and serial abdominal and pelvic ultrasound allowed chemotherapy avoidance in 50% of the patients in this series. 5 of 6 patients who presented with biological or imaging evidence of progression were salvaged with chemotherapy. The concept of expectant management has been developed in adults' germ cell tumours in the early 1970s [28]. For the

paediatric population, the Société Française d'Oncologie Pédiatrique adopted this strategy in 1985 [29]. Initially proposed for completely resected stage I testicular tumours, the 'watch and wait' concept has been extended to all stage I Ps I tumours of all sites. In children, this expectant management, initially controversial [9,14–16,19] is today widely accepted.

The role of surgery in the treatment of secreting tumours has been made more definitive by advances in chemotherapy. Emergency surgery (8 cases) for advanced tumours was not exceptional in our experience due to the high incidence of rupture or torsion. However, aggressive debulking in this situation exposes the child to gonadal damage, and limited biopsy is the recommended surgical technique when tumour delineation is unclear. In all other cases, systematic evaluation of tumour markers should prevent unnecessary surgery for unresectable tumours. Initial radiological assessment can help to identify patients eligible for exclusive surgery when the tumour is confined to the ovary [30]. The clinical benefit of initial surgery for patients with advanced secreting tumours is unclear. Aggressive initial debulking increases the risk of gonadal damage and subsequent infertility, and has no oncological basis in advanced stage [22,31]. Since survival rate is high even in bulky disease, initial management should preserve as much as possible the potential for a future successful pregnancy. In these advanced forms, our results suggest that up-front chemotherapy or chemotherapy following limited biopsy may be a rational approach. In our experience, the outcome of patients treated with neoadjuvant chemotherapy compares with patients who received postoperative chemotherapy. 21 of 25 patients treated with adjuvant chemotherapy are alive in remission, compared with 9 of 12 patients who received neoadjuvant chemotherapy. Unfortunately, the rarity of ovarian germ cell tumours does not allow this question to be addressed in a randomised clinical trial. Resection of the initially involved gonad has always been performed in our experience even when no residual tumour was present on imaging, and microscopic residue was found in 3 of 9 patients. This argues for systematic surgery at the end of treatment for initially non-operated patients. Salvage surgery during chemotherapy has been considered in 3 patients, due to apparent tumour progression contrasting with a significant decrease in tumour markers. On histology, all 3 patients had large tumours containing a mixture of mature and immature teratoma. This entity described as 'growing teratoma syndrome' is not specifically associated with ovarian tumours and has been described in other sites in adults and children [32–34]. Unlike adult patients with ovarian carcinoma, second-look laparotomy is still controversial in ovarian germ cell tumour [35]. Metastases on the opposite ovary are exceptional and second-look procedures should be reserved for children who have suspicious computed tomography findings. For the exceptional bilateral tumours, surgery should be as conservative as possible, combining ovariectomy or adnexectomy of the bulkiest lesion and tumorectomy on the opposite ovary.

Our $85\% \pm 5$ 5-year survival rate compares with other recent series focusing on germ cell tumours of the ovary. Wollner and colleagues reported a 81% survival rate at 5 years [9]. Survival was 87.8% at 3 years in the series from Bower and associates [36] and 95% at 5 years in the series from Gershenson and associates [37]. These series included adult patients in their analysis. Relapses generally occur early, and all relapses in our experience occurred within 14 months from diagnosis. For patients with secreting tumours, early detection of relapse is possible before any clinical or radiological evidence of progression through routine estimation of serum tumour markers. However, the optimum frequency for follow-up ultrasound or computed tomographic scanning of the pelvis and abdomen remains debatable. Management at the time of relapse is primarily based on chemotherapy for secreting tumours, and on surgery for teratomas. Like their adult counterparts, recurrent secreting tumours in children can be salvaged with intensive chemotherapy. The role of high-dose chemotherapy in paediatric germ cell tumours is however still unsettled.

5. Conclusion

Management of ovarian neoplasm in children differs from adults. Paediatric tumours are histologically distinct from adult adenocarcinomas, and their natural history is therefore different. Most of the teratomas are potentially curable by surgery alone. By contrast, secreting tumours often require a multidisciplinary approach. The respective role of surgery and chemotherapy needs to be assessed at the time of initial diagnosis. Whenever possible, fertility should be preserved by employing conservative procedures at the primary operation in children suffering from these tumours.

Appendix A. Participating institutions:

Institut Gustave Roussy, Service de Pédiatrie, Villejuif, Dr Patte; Centre Antoine Lacassagne, Oncologie-Médicale, Nice, Professor Thyss; Hôpital Jean Bernard, Hémato-Oncologie-Médicale, Poitiers, Dr Millot; CHU Purpan, Médecine Infantile B, Toulouse, Dr Rubie; Hôpital Clocheville, Oncologie Pédiatrique, Tours, Dr Lejars; Hôpital Charles Nicolle, Pédiatrie et Génétique Médicale, Rouen, Professor Vannier; Hôpital Américain, Hémato-Oncologie Pédiatrique, Reims, Dr Behar;

Institut Curie, Pédiatrie Oncologique, Paris, Dr Quintana; Centre Oscar Lambret, Oncologie Médicale A, Lille, Dr Baranzelli; Institut de Puériculture, Service de Pédiatrie I, Strasbourg, Dr Lutz; CHR Hôpital SUD, Clinique Médicale Infantile, Rennes, Professor Le Gall; CHU Hôpital NORD, Service de Pédiatrie, Saint Etienne, Dr Stephan; CHU, Service de Pédiatrie, Angers, Dr Lemoine; Hôpital d'Enfants, Mêdecine Infantile II, Vandoeuvre, Dr Schmitt; Hôpital d'Enfants, Oncologie Pédiatrique, Marseille, Dr Portas; Centre Hospitalier Universitaire, Pédiatrie B, Caen, Dr Boutard; Hôpital TROUSSEAU, Oncologie-Hématologie-Pédiatrique, Paris, Professor Lerverger; Hôpital des Enfants, Service de Pédiatrie, Bordeaux, Dr Perel; Centre Léon Bérard, Oncologie Pédiatrique, Lyon, Dr Frappaz; Hôpital Arnaud de Villeneuve, Hémato-Cancérologie, Montpellier, Dr Marguerite.

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