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Prognostic factors in women treated for ovarian yolk sac tumour: A retrospective analysis of 84 cases

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ABSTRACT

Background: Ovarian yolk sac tumour (OYST) is a very rare malignancy arising in young women. Our study aimed to evaluate long-term outcomes and to identify prognostic parameters likely to help make appropriate risk-based decisions about therapy in this disease.

Methods: This retrospective study is based on prospectively recorded OYST cases at the Institut Gustave-Roussy. A univariate analysis using the logrank test evaluated possible associations between survival and patient or disease covariates. The multivariate analysis was performed using the Cox proportional hazard regression method.

Results: Between 1976 and 2006, 84 patients were registered. Since 1991, most of the patients have undergone fertility-sparing surgery. With a median follow-up of 71 months, the overall 5-year and event-free survival rates are 84% and 79%, respectively. In the multivariate model only the absence of ascites and a favourable serum AFP decline rate were significantly associated with better overall survival.

Conclusions: Patients with a poor prognosis factor such as an unfavourable serum AFP decline may be considered for aggressive treatment whereas those with good prognostic factors could be given less courses of chemotherapy.

1. Introduction

Ovarian yolk sac tumours (OYSTs) are very rare (incidence rate of 0.048/100,000 women-years) occurring mostly in adolescent and young women. They account for 20% of malignant ovarian germ cell tumours (MOGCTs), and are the second most frequent histological subtype of MOGCTs, after ovarian dysgerminoma. Most OYSTs are pure neoplasms although mixed MOGCTs, including a yolk sac component, are not uncommon. Elevated serum alpha-feto-protein (AFP) is one of the hallmarks of OYSTs and positive staining on tissue microarray sections facilitates the diagnosis. OYSTs may

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carry a worse prognosis amongst MOCGTs.[1] Before the era of modern chemotherapy, overall survival (OS) at 3 years was 13%.[2] Cisplatin-based multi-agent chemotherapy has dramatically improved the prognosis of MOGCTs. In the 1990s, the combination of bleomycin, etoposide and cisplatin (BEP) was shown to be highly active against MOGCTs and became the standard treatment for these tumours.[3,4] We recently confirmed these results for the subset of OYSTs: a 5-year OS rate of 94% was observed after surgery followed by BEP chemotherapy.[5]

In mixed OYSTs, the prognosis is thought to result from the YST component.[6] However, very little is known about prognostic factors for OYSTs because the rare published series of OYSTs usually comprises less than 50 patients.[6]

Here, we aimed to study prognostic factors and long-term outcomes in 84 patients treated for an OYST.

2. Methods

2.1. Patient population

This retrospective study is based on prospectively recorded OYST cases at the Institut Gustave-Roussy (IGR, Villejuif, France). Between 1976 and 2006, 84 patients with pure or mixed OYSTs were either treated at IGR or referred there for advice on therapy after surgery.

We chose to include only postpubertal cases because some studies have reported that the physiopathology of OYSTs occurring in children and young women could be different.[7] Information concerning all patients was abstracted from the medical records in accordance with local regulations. Information on the last physician visit reporting the tumour status, menstrual history, hormonotherapy and reproductive history was requested from the corresponding physicians in a questionnaire, for patients who were not followed up at the IGR.

2.2. Staging and tumour classification

Tumours were staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system for ovarian cancers.[8] The histological type was defined according to the WHO classification.[9] All pathologic samples were centrally reviewed at the IGR before 1990. Subsequently, the pathologic samples of 12 patients referred for treatment were not reviewed because the diagnosis was made in academic hospitals. Most of the stage I lesions had not been properly assessed according to FIGO recommendations in patients referred after surgery, especially regarding peritoneal cytology. Stage Ia was therefore defined as a tumour strictly limited to one ovary, with an intact capsule, without ascites and no tumour cells in peritoneal cytology when available. Stage Ic tumours were strictly limited to one ovary but exhibited capsular rupture or ascites >100 mL or ascites with tumour cells, when available.

2.3. Treatment and tumour response

Most of the patients underwent initial surgery at the local hospital and were referred to the IGR thereafter. The majority of them were operated on using a single ovarian procedure without staging surgery. In such cases, completion surgery and restaging were reconsidered only after initial chemotherapy. The presence and the size of residual disease were determined based on the analysis of surgical reports and postoperative imaging studies.

In our institution, surgical paradigms evolved over time. Before the era of highly effective chemotherapy, surgical guidelines recommended radical surgery with bilateral salpingo-oophorectomy, hysterectomy, lymphadenectomy and omentectomy. During the 1990s, given the very good results observed with BEP chemotherapy, a less invasive surgical procedure was advocated in order to spare fertility whenever possible in these young patients. Nowadays, in early-stage disease, our surgical guidelines recommend unilateral salpingo-oophorectomy with peritoneal staging procedures (routine peritoneal cytology, multiple peritoneal biopsies and omentectomy). In advanced disease, unilateral salpingo-oophorectomy, omentectomy and resection of macroscopic lesions on the peritoneum with a fertility-sparing intent should be attempted whenever possible.

Chemotherapy was according to standardised protocols. Most patients received platinum-based combination chemotherapy. Some patients were included in a prospective phase II trial conducted between 1985 and 1990 with high-dose cisplatin consisting of two doses of cisplatin along with vinblastine, bleomycin and etoposide (PVeVB).[10] Since 1996, BEP has become our standard chemotherapy regimen.

Patient follow-up included a clinical examination, blood marker measurements and imaging at least every 3 months during the first year following treatment and at gradually increasing intervals thereafter. A 2-year interval from the end of treatment was strongly advised before allowing pregnancy.

2.4. Serum AFP decline

The half-life of serum AFP was calculated at point 1 after surgery before the first chemotherapy cycle and at point 2 immediately before the second cycle of chemotherapy. AFP values were plotted semi-logarithmically, and the half-life of the AFP decline was calculated between each point using a calculation module MONOTOR-IT – REMISOL (Beckman Coulter Inc.). The method of half-life determination used was derived from the Lange half-life formula ($T_{1/2} = 0.693/M$), where M represents the slope of the line between any two marker values (X and Y), using the following equation $M = \ln X - \ln Y/\text{days}$ between X and Y.

Patients were classified as having an unfavourable AFP decline if the half-life of AFP was >10 days. The marker decline was deemed favourable if the half-life of AFP was $\leqslant$10 days. Patients with AFP normalisation prior to chemotherapy were classified in the favourable group.

2.5. Statistical analysis

Survival curves were calculated using the method of Kaplan–Meier. OS was calculated from the date of the diagnosis to the time of the last follow-up or death. Event-free survival (EFS) was calculated from the date of the diagnosis to the date of

the first event, defined as a relapse, a progressive tumour or death from any cause.

Prognostic factors were evaluated by univariate analysis using the Kaplan–Meier product-limit method to calculate survival probabilities for both EFS and OS at 5 years. Survival differences were compared using the log-rank test. Associations between variables were assessed with the Pearson χ^2 test. To determine the independent prognostic significance of the factors for OS and EFS, a multivariate analysis was conducted using the Cox proportional hazard regression method. Only factors that were significant in the univariate analysis were subsequently incorporated into the multivariate model. A multivariate analysis adjusted on BEP treatment was also conducted.

3. Results

3.1. Patient characteristics and treatment

Patient characteristics are summarised in Table 1. Median follow-up was 68 [3–320] months. Treatment modalities are detailed in Fig. 1 and Table 2. A lumbar aortic lymphadenectomy was performed in 6 patients with stage I and 5 patients with stage IIIc disease. Lymph node metastasis was found only in 2/11 patients, both with stage IIIC disease. None of the 6/11 patients with stage I disease in whom a lymphadenectomy was performed had lymph node metastases.

A single patient with a completely resected stage Ia tumour did not receive chemotherapy. No relapse was observed after 85 months of follow-up.

3.2. Outcome

Estimated 5-year OS and EFS rates were 84% (95% confidence interval (CI): 74–90%) and 79% (95% CI: 69–87%), respectively (Fig. 2). Progressive disease or relapse was diagnosed in 14 patients: 2/4 patients who did not receive cisplatin during initial chemotherapy; 2/3 patients who received an etoposide-cisplatin (EP) regimen; 5/14 patients who received cisplatin-based chemotherapy regimens without etoposide; 1/10 patients who received the PVeVB regimen and 4/52 patients who received the BEP regimen.

All recurrent/progressive disease occurred with a median of 5 months [range 0–10] after the end of treatment. All the 14 patients who experienced disease progression received salvage treatment. Eventually, complete remission (CR) was only achieved in 4/14 (28%) patients. In one patient, a combination of salvage chemotherapy (including high dose chemotherapy plus autologous stem cell transplantation (HD-ASCT)) and surgical resection of the residual mass was used. In a second patient, chemotherapy using cisplatin, vinorelbine, paclitaxel and gemcitabine was followed by a CR. The third patient was treated with PVeVB followed by HD-ASCT. The last patient underwent surgical resection of a limited recurrent peritoneal nodule and did not receive any chemotherapy.

Overall, 15 deaths were observed due to progressive disease ($n = 10$), sepsis ($n = 3$), growing teratoma ($n = 1$) and acute secondary leukaemia ($n = 1$) which occurred 12 years after a CR following the PVeVB regimen.

Table 1 – Patient characteristics ($n = 84$).

Median age (years)	22 [14; 58]
Obstetric history	
Nulligravida	55/84 (65%)
Nulliparous	61/84 (73%)
Stage at presentation (FIGO, 2000)	
Ia	27/84 (32%)
Ic	15/84 (18%)
II	2/84 (2%)
IIIc	33/84 (40%)
IV	7/84 (8%)
Ascites > 100 mL	30/84 (36%)
Median baseline postoperative AFP level (ng/mL) ($n = 73$)	1700 [2; 154,000]
Histological features	
Pure YST	49/84 (58%)
Hepatoid variant	15/49 (30%)
Mixed YST (two components)[a]	29/84 (35%)
YST + mature teratoma	10
YST + immature teratoma	10
YST + dysgerminoma	8
YST + embryonic carcinoma	1
YST + choriocarcinoma	0
Mixed YST (three components)	6/84 (7%)
YST + dysgerminoma + embryonic carcinoma	3
YST + mature teratoma + immature teratoma	1
YST + immature teratoma + choriocarcinoma	1
YST + mature teratoma + immature teratoma embryonic carcinoma	1

[a] Hepatoid variant $n = 3$.

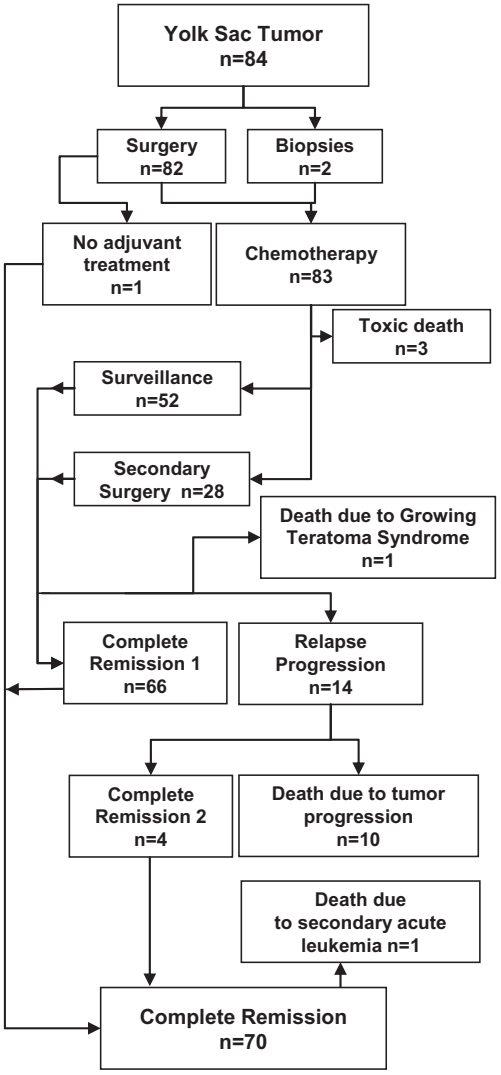

Fig. 1 – Flow of patient(s) treated for an ovarian yolk sac tumour.

Table 2 – Treatments (*n* = 84).

Surgery	84/84 (100%)
Radical surgery	28/84 (33%)
Fertility-sparing surgery	55/84 (66%)
Biopsies alone[a]	1/84 (1%)
Lumbar-aortic lymph node dissection	11/84 (13%)
Secondary surgery	28/84 (33%)
Initial chemotherapy[b]	83/84 (99%)
BEP	52/83 (62%)
EP	3/83 (4%)
PVeVB	10/83 (12%)
Other with CDDP	14/83 (17%)
Other without CDDP	4/83 (5%)

[a] One single patient with stage IIIc disease underwent peritoneal biopsies alone initially and died of septic shock during chemotherapy.

[b] One patient with stage Ia disease did not receive chemotherapy and never relapsed.

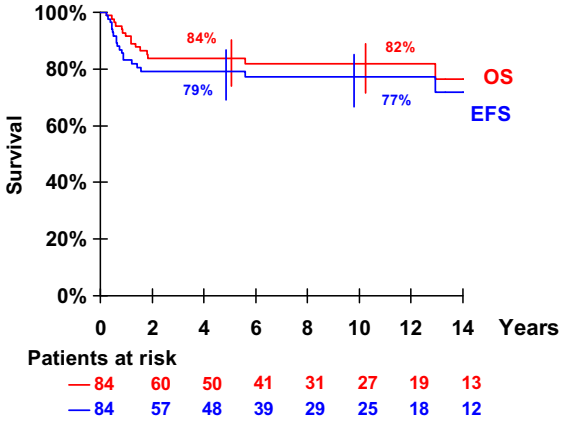

Fig. 2 – Kaplan–Meier estimates of overall survival (OS) and event-free survival (EFS).

Table 3 – Univariate analysis of 5-year OS and EFS (*n* = 84).

Variable	No of patients	OS (SD) (%)	*p*	EFS (SD) (%)	*p*
Stage					
IA	27	100	0.01	92% (6)	0.03
IC	15	87 (9)		87 (9)	
II–III–IV	42	73 (7)		69 (7)	
Stage					
IA	27	100	0.008	92 (6)	0.04
>IA	57	77 (6)		73 (6)	
Ascites at presentation					
No	54	96 (6)	<0.001	90 (4)	<0.001
Yes	30	63 (9)		60 (9)	
Postoperative AFP (ng/mL)					
⩽1000	32	93 (4)	NS	90 (5)	NS
>1000	41	79 (6)		75 (7)	
Pure OYST					
No	35	88 (6)	NS	88 (5)	NS
Yes	49	80 (6)		72 (7)	
Hepatoid appearance					
No	66	86 (4)	NS	85 (5)	0.05
Yes	18	76 (10)		60 (12)	
Lymphadenectomy					
No	73	81 (5)	NS	79 (5)	NS
Yes	11	100		82 (12)	
Fertility-sparing surgery					
No	29	75 (8)	0.05	69 (9)	0.03
Yes	55	88 (4)		85 (5)	
Treatment with BEP chemotherapy					
No	32	67 (9)	0.001	61 (9)	0.001
Yes	52	94 (3)		90 (4)	
Time to AFP normalisation					
⩽42 days	38	100	<0.001	100	<0.001
>42 days	35	70 (8)		65 (8)	
Serum AFP half-life (between C1 and C2)					
⩽10 days	55	92 (4)	<0.001	92 (4)	<0.001
>10 days	18	59 (12)		50 (12)	

SD: standard deviation.

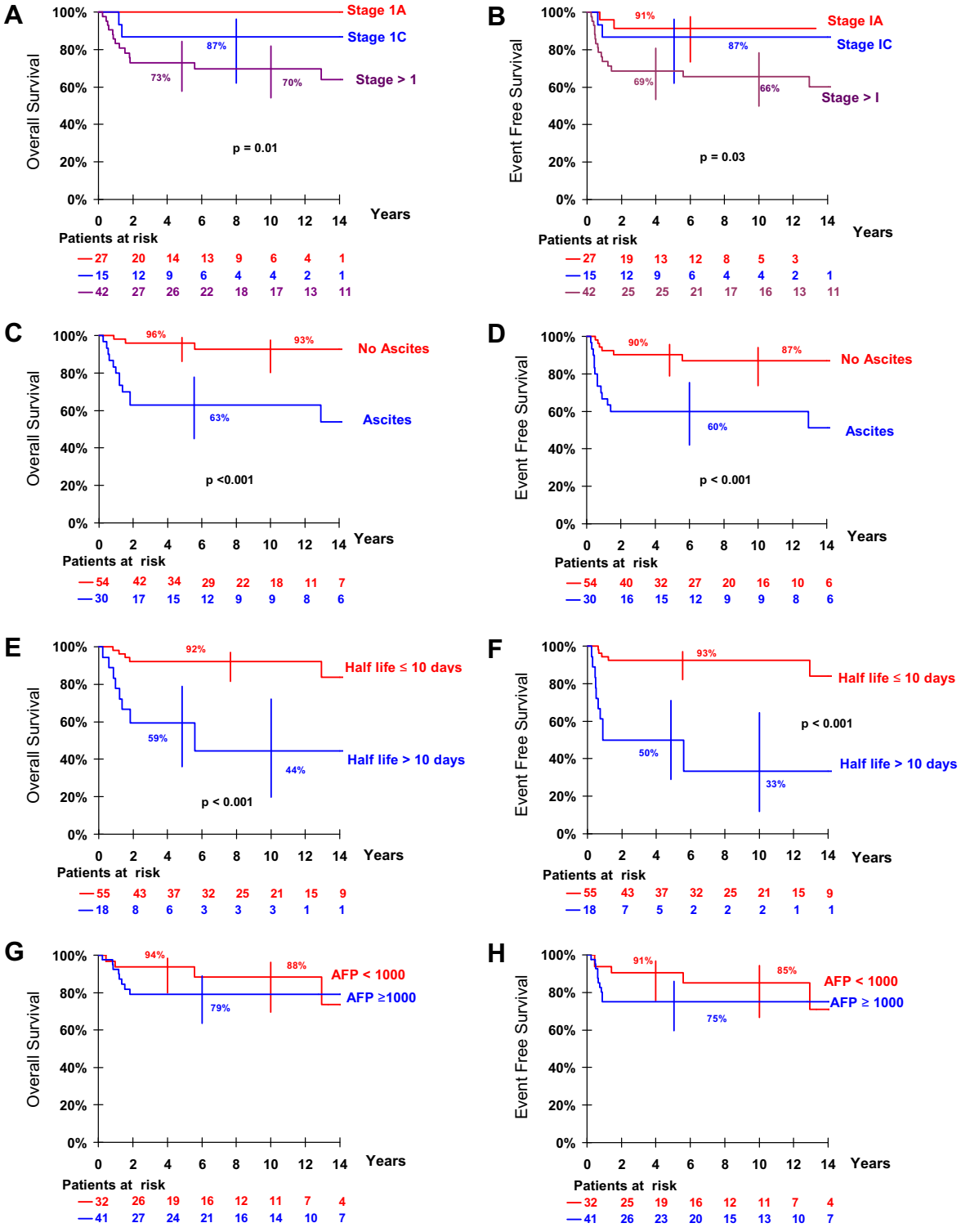

Fig. 3 – Kaplan–Meier estimates of some prognostic factors. (A and B) Overall and event-free survival by initial disease stage. (C and D) Overall and event-free survival according to ascites status. (E and F) Overall and event-free survival according to rate of decline in serum AFP. (G and H) Overall and event-free survival according to postoperative serum AFP.

3.3. *Serum AFP half-life*

Sufficient data were available to compute the serum AFP half-life in 73 patients. AFP normalised after surgical resection in 7 patients, who were classified in the good prognosis group. In 1 patient, AFP never declined and the patient was classified in the poor-prognosis group. The median serum AFP half-life was 7.2 days [2.3–787].

Table 4 – Multivariate analysis of 5-year OS and EFS (n = 84).

Prognostic variables	Overall survival		Event-free survival	
	Relative risk (CI 95%)	Relative risk adjusted on BEP (CI 95%)	Relative risk (CI 95%)	Relative risk adjusted on BEP (CI 95%)
Ascites	(p = 0.002)	(p < 0.02)	(p < 0.001)	(p < 0.02)
No	1	1	1	1
Yes	8.5 (2.3–32)	5.2 (1.3–21)	9.2 (2.5–34)	4.5 (1.4–15)
Half-life between C1 and C2	(p < 0.001)	(p < 0.001)	(p < 0.001)	(p < 0.001)
0	1	1	1	1
1	9.8 (2.9–34)	8 (2.4–27)	21 (5.6–82)	13.4 (4–44)
Stage	NS	NS	(p = 0.04)	NS
I			1	
>I			4.5 (2.5–34)	

3.4. *Prognostic factors*

The results of the univariate analysis are displayed in Table 3. The disease stage, presence of ascites at presentation, fertility-sparing surgery, BEP regimen, serum AFP half-life and the time to serum AFP normalisation were significantly predictive factors. No difference was found for the postoperative AFP level, pure ovarian YST, a hepatoid appearance or lymphadenectomy. Fig. 3 shows the most important prognostic factors. In the multivariate analysis (Table 4), only ascites at presentation and the serum AFP half-life were significantly predictive for OS and EFS. These factors remained significant after adjusting the model on the BEP regimen.

3.5. *Fertility outcome*

Table 5 shows fertility outcomes. Most of the patients treated with the current approach (conservative surgery followed by the BEP chemotherapy) were able to give birth to perfectly normal children.

Table 5 – Reproductive outcome after complete remission (n = 69).

Primary infertility before YST	2/69 (3%)
Infertile after surgery	20/69 (29%)
Potentially fertile	49/69 (71%)
Not attempting conception	28/69 (40%)
Age > 35	2
Previous children	3
Others	23
Attempting conception	21[b]/69 (30%)
Failures	5/69 (10%)
Tubal sterility[a]	3
Multiple uterine myomas	1
Partner's azoospermia	1
Patients achieving pregnancy	15/69 (21%)
With stage I disease	9
With stage IIIc disease	6
Total number of pregnancies	24
Normal pregnancy with normal child	21/24[c] (87%)

[a] N = 1 with additional endocrine dysfunction.
[b] The remaining patient; no specific reasons (lost to follow-up).
[c] Miscarriage (n = 2) and termination (n = 1).

4. Discussion

To our knowledge, we report herein the largest series of patients treated for an ovarian yolk sac tumour. It is very difficult to gather enough data to enable one to identify prognostic factors in such a rare tumour. All the previous published series were retrospective and included less than 80 patients.[11,12]

We show in our series that the long-term outcome of patients with OYSTs is good with 10-year OS attaining 82%. This may be related to the BEP or PVeVB regimens administered in the majority of our patients (75%).

In the univariate analysis, several factors were associated with a good prognosis: the BEP regimen, no ascites at presentation, stage I disease, <42 days to AFP normalisation, fertility-sparing surgery and a serum AFP half-life <10 days. Of note, lumbaraortic lymphadenectomy and postoperative AFP levels were not found to be significant prognostic factors. Lumbaraortic lymphadenectomy has been proposed by some authors to identify patients with a higher risk of relapse after surgery, in order to guide the choice of adjuvant chemotherapy.[11] This surgical procedure is associated with some morbidity. Furthermore, in our study, lymph node metastasis was found exclusively in 2 patients with stage IIIC peritoneal disease in whom chemotherapy is mandatory. No lymph node involvement was found in stage I disease. Early metastatic spread is different in ovarian tumours compared to testicular tumours, and occurs mainly in the peritoneal cavity like other ovarian cancers.

Thus, as in the paper by Kurman in stage I disease, we observed recurrences in the peritoneal cavity in 5/5 patients with stage Ia disease who did not receive immediate postoperative chemotherapy.[2,5] Thus, lumbaraortic lymphadenectomy aimed at avoiding adjuvant chemotherapy should not be systematically performed and needs to be carefully evaluated in a clinical trial. Adjuvant chemotherapy should remain the standard of care.

No prognostic difference was found between pure and mixed OYSTs, confirming that the prognosis is mainly dependent on the YST component. However, our study may lack the power to identify small differences amongst OYST histological subtypes, such as those exhibiting hepatoid features. For instance, in our series, the hepatoid subtype

carried a worse prognosis, although this was not statistically significant.

Only the absence of ascites at presentation and a serum AFP half-life below 10 days retained their statistical significance in the multivariate analysis. Ascites at presentation has been shown to be a strong prognostic factor in several retrospective studies.[11–13] It is noteworthy that this factor remained significant in the multivariate analysis whilst the staging did not.

A limitation of the serum AFP half-life calculation was the retrospective study performed on a limited number of time points. In addition, the 10-day cut-off was arbitrarily chosen before the analysis and may not be the best level for distinguishing two different prognostic groups. However, together with the presence of ascites, this is the only other prognostic factor in the multivariate analysis in our series. This finding may be important to identify patients with a poor prognosis. It is noteworthy that the decline in serum AFP has never been described in OYSTs, although this factor proved to be an independent prognostic factor in patients with poor prognosis non seminomatous germ cell testicular cancer.[14–16]

Overall, the prognosis of OYST seems to be similar to that observed in male patients with non seminomatous testicular cancers. Unfortunately, the International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic grouping classification for testicular cancer cannot be applied to ovarian germ cell tumours. Indeed, whereas visceral metastases are common in testicular cancer, it is rare to find extra peritoneal metastases and disease tends to remain confined to the peritoneal cavity in ovarian tumours.[2,5,6] Moreover, although high serum tumour markers (AFP or HCG) seem to be associated with a worse prognosis in MOGCTs,[17,18] no clear cut-off has been defined as in testicular cancer. In addition, all the studies specifically evaluating the significance of the AFP level in OYST series failed to demonstrate that this was a prognostic factor.[11–13]

Prospective early assessment of a decline in serum AFP between the first two cycles of chemotherapy may help clinicians select patients with a high risk of progression or relapse despite standard treatment. Current clinical research aims to improve outcomes in patients with poorprognosis tumours. In poorprognosis testicular non seminomatous germ cell tumours (NSGCT), an international phase III study (GETUG 13) addresses the issue of risk-adapted chemotherapy based on a decline in serum markers. If this study shows the superiority of the dose-dense chemotherapy experimental arms over the four courses BEP control arm, a careful assessment of the interest of adopting a dose-dense chemotherapy regimen in OYSTs with poor prognostic features (ascites at presentation and a low serum marker decline) need to be done. Indeed, due to the rarity of OYSTs, it is unlikely that a properly controlled study could be conducted to evaluate the benefit of such treatment.

Yet, it is important to identify patients with good prognostic factors in order to decrease the burden of chemotherapy. The issue of close surveillance instead of adjuvant chemotherapy for stage Ia OYSTs after adequate surgical staging has also been raised. This approach may be of interest in MOGCTs, although further studies are warranted.[19] In the specific context of OYSTs, the largest published series (71 women) showed that relapses occurred in the great majority (22 of 27) of resected stage I tumours when chemotherapy was not administered.[2] However, we would point out that this study was published in 1976 when the thoroughness of staging may well have been different. In a recent study, relapses occurred in 2 of 6 patients after conservative surgery and close surveillance of stage Ia OYSTs.[20] However, in another study, none of the three patients with a mixed stage Ia OYST relapsed after surgery alone.[18] In our patients, five women treated for a stage Ia OYST relapsed after surgery alone.[5] Although they all achieved a prolonged CR after BEP chemotherapy, watchful waiting after surgery for stage Ia disease should be carefully evaluated before it is adopted in routine clinical practise. Indeed, we wish to point out that although peritoneal relapses are successfully treated with chemotherapy, they may compromise fertility outcome due to the risk of invasion of the contralateral ovary. As most of the patients are young and nulligravida, fertility preservation is advocated as the most important secondary objective. In stage I non seminomatous testicular cancer, two adjuvant BEP cycles are enough to cure practically all patients. As long-term side-effects[21] and fertility impairment[22] increase with the dose of chemotherapy, we would propose that patients with stage Ia tumour may require only two BEP chemotherapy cycles. Still, this attitude must be evaluated in a clinical trial before being adopted in routine.

In our series, a substantial proportion of women treated with fertility-sparing surgery followed by chemotherapy were able to give birth. Even in patients with advanced-stage disease, conservative treatment does not seem to be associated with a poor outcome. These results are consistent with previous publications.[23,24]

In summary, this study showed that ascites at presentation and the serum AFP decline rate are independent prognostic factors in patients with OYSTs. This is relevant for the management of OYSTs because it could help identify patients who may require more intensive therapeutic strategies. However, this should not have an impact on treatment decision, at least currently. Further strategies should be explored in prospective trials aimed at proposing risk-adapted treatment in order to increase the cure rate in patients with a poorprognosis and to decrease toxicity in patients with a low risk of relapse.

Contributions of authors

Thibault de La Motte Rouge, Annie Rey and Catherine Lhommé were involved in the conception and design of the study. Thibault de La Motte Rouge and Catherine Lhommé wrote the manuscript.

Patricia Pautier, Pierre Duvillard, Philippe Morice, Christine Haie-Meder, Pierre Kerbrat, Stéphane Culine, Frédéric Troalen and Catherine Lhommé provided study material. Thibault de La Motte Rouge and Catherine Lhommé collected the data. Thibault de La Motte Rouge, Annie Rey and Catherine Lhommé analysed and interpreted the data. All authors validated the report.

Conflict of interest statement

None declared.

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