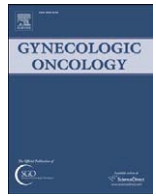




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Management of rare ovarian cancers: The experience of the French website «Observatory for rare malignant tumours of the ovaries» by the GINECO group: Interim analysis of the first 100 patients[☆]

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ABSTRACT

Background: Non-epithelial ovarian cancers are rare; their natural history is poorly understood and prognostic factors remain unclear. A French website (www.ovaire-rare.org) was developed to collect clinical cases and tumour samples in order to better define prognostic factors and develop specific trials. We report the results of the first 100 patients with germ cell (GCT) and sex cord-stromal (SCT) tumours.

Methods: All adult patients with histological evidence of GCT or SCT at diagnosis or first relapse were eligible.

Results: From 03/2002 to 06/2009, 180 patients were included; the first 100 were evaluated. Patient characteristics were: histology: SCT 61%, GCT 30%, others 5%; median age: 43 years; median tumour size: 12 cm; FIGO stages I–II: 83%, III–IV: 17%. Central pathology review (67 patients) differed from initial diagnosis in 37%. Fifty-six percent of the patients had initial conservative surgery and 10% lymph node dissection; 56 patients received chemotherapy. Eleven of the 78 first-line patients relapsed and 5 died; the 5-year OS rate was 94% and the median PFS 64 months.

Conclusions: This online observatory allows assessing medical practice for GCT and SCT in France. Histological discrepancies between diagnosis and second opinion confirm the need for systematic review before treatment. Extension to other rare gynaecologic malignancies is on-going.

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Introduction

Non-epithelial malignant tumours, mucinous tumours, clear cell carcinomas and Brenner tumours of the ovary are rare cancers; their natural history is poorly understood and prognostic factors remain to be clarified. Given the difficulties of accruing sufficient patients to conduct definitive clinical trials, the initial management of these rare tumours should be reorganized in order to optimize patient care, improve our biological knowledge of these diseases and develop specific clinical trials.

Adequate knowledge of these neoplasms is essential for accurate diagnosis and for the choice of surgical treatment, adjuvant therapy and efficient medical treatment in relapse [1,2]. To compensate for the rarity of these ovarian tumours, we have created a dedicated website (Fig. 1) allowing French physicians to ask for advice on the diagnosis and on the surgical and medical management of the patients through a discussion forum. The website also provides information for patients and families. The forum is accessible to all physicians in charge of these rare neoplasms, whether to ask for or to provide advice. Similarly, due to the diversity of these rare tumours (sex cord, germ cell, epithelial, urothelial, etc. origins), complete exploration was not immediately possible. In a first step, specific clinical research programs dedicated only to GCT and SCT were developed on the website in order to confirm the feasibility of this system, and to accumulate as much clinical and biological information as possible on the natural history and prognosis of these tumours.

[☆] Presented in part at the annual meeting of ESMO, Vienna in Sept 2004 and ECCO Stockholm in 2008.

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OVARIAN RARE MALIGNANT TUMOURS NATIONAL OBSERVATORY

Observatoire Francophone des Tumeurs Malignes Rares de l'Ovaire

Dialogue

- Information
- Patient inclusion
- List of patients included
- Management protocol
- Discussion forum

Management of the group

- Directory
- Meetings
- Slides available
- Annual report
- Policies and procedures

Inclusion count
52

Observatoire Francophone
des
Tumeurs Malignes Rares
de l'Ovaire

Welcome/Bienvenue/Bienvenido/Bienvenue

Public access

- Presentation of the group
- Information
- Bibliography
- Links
- Contact us

2067 visitors
7336 pages consulted

2010
Réalisation: teclinique

<http://www.ovaire-rare.org>

Display on-line

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Fig. 1. Picture of the website on rare ovarian cancers.

Actually, the group of sex cord-stromal (SCT) and germ cell tumours (GCT) includes a variety of histopathological subtypes which altogether account for approximately 15% of all ovarian neoplasms [3]. These 2 forms of gynaecological cancer have very different biological behaviours, with different management strategies and different curative potentials, stage for stage, and are therefore perfectly representative of the different rare tumours to be evaluated in terms of organization and management of care. Germ cell tumours are mostly curable, even in advanced stages, and radical pelvic surgery, possibly leading to infertility, can usually be avoided. Sex cord (commonly granulosa cell) tumours are much less chemosensitive, grow much more slowly, are best managed by repeat surgery and usually occur in a different age group. SCT and GCT of the ovary are rare, but they are histologically similar to other more common tumours of the testicle [4]. Many principles of treatment for these ovarian tumours have thus been derived from testicular cancer research [5,6].

To confirm the feasibility of this new internet tool and its contribution to the knowledge and the management of rare cancers, we have evaluated the results obtained in the first one hundred patients with GCT and SCT prospectively included in the dedicated clinical research program.

Patients and methods

In 2002, a French language website was created in order to inform patients and their families and keep an update of scientific and bibliographic knowledge of rare tumours of the ovary (Fig. 1). Information on the existence of such tool has been presented at

different French gynaecology/oncology meetings since 2002 and our project received financial support from the French government since 2005. In addition to offering French physicians best-practice advice on the diagnosis and the surgical and medical management of these patients, our objective was to develop a clinical research program with health professionals in order to accumulate clinical and biological information on the natural history and prognosis of these tumours. We also aimed to organize a central review of tumour samples. Finally, we initiated the study of long-term toxicities of chemotherapy and surgery and the monitoring of post-treatment fertility in these patients.

All cases of sex cord-stromal tumours, germ cell tumours, mesenchymal tumours or rare surface epithelial-stromal tumours such as mucinous, clear cell and transitional cell tumours can be referred to the website for advice. Shortly, physicians, identified by their registration number at the national Medical Association, register online and receive confidential login information to access the database. Then they can include rare ovarian cancer patients and enter information about these patients in the online expert advice forum. Brief information about patients characteristics, diagnosis and, if applicable, first surgery is collected and used for online expert advice. Before developing a complete database encompassing all these rare diseases, we have decided to limit our collection of biological information (tumour samples) and detailed clinical data firstly to SCT and GCT subtypes and then, in a second step, to broaden the scope to all rare ovarian tumours.

The study of SCT and GCT subtypes was performed according to good clinical practice guidelines, in accordance with the declaration of

Helsinki, and was approved by local ethics committees. Approval was gained from local review boards, and written informed consent was obtained from each participant before inclusion.

Pathological study

One of the main objectives of the present work was to evaluate the benefit of systematic central pathological review by national experts for patients diagnosed and included in the program. We aimed to compare the initial histological evaluation by the local diagnostic pathologist (generally not an expert in ovarian diseases) and the results from the central review by national experts. The expert panel was initially organized by I. Treilleux (Centre Léon Bérard, Lyon), P. Duvillard (Institut Gustave Roussy, Villejuif) and L. Frappart (Hôpital Edouard Herriot, Lyon), then new panellists were recruited: M. Devouassoux (Hôpital Croix Rousse, Lyon), F. Penault-LLorca (Centre Jean Perrin, Clermont ferrand), J.C. Sabourin (CHU Rouen) and M.C. Vacher-Lavenue (Hopital Cochin, Paris).

For each included patient, a copy of the original pathological report and a representative paraffin block were provided by the initial generalist pathologist to the expert panel group for systematic central pathological review.

Inclusion/exclusion criteria for subgroup study (SCT and GCT tumours)

Eligibility criteria were: age >18 years; histologically confirmed diagnosis of GCT or SCT of the ovary at initial diagnosis or first relapse, and patient's written informed consent. GCT also arise in young patients but, because of the organization of care in France, this health observatory only recruited young adults; actually, the management of GCT in adolescents is provided exclusively by paediatric oncologists who are not involved in this observatory and who generally enrol adolescents into clinical trials exclusively dedicated to the paediatric population. In addition, patients undergoing only surgery for initial management could be included at first relapse in order to explore the capability of "optimal" surgery and/or chemotherapy regimens to optimize the chance of cure in these patients.

Exclusion criteria were related to patients mentally unsuited for clinical research and those treated for more than one relapse of their disease or having received one line of chemotherapy prior to study entry.

After giving written informed consent, patients were entered in the study by the physician in charge (medical oncologist, general gynaecologist or gynaecologist specialized in oncology) who filled-out the inclusion form online. An e-mail was automatically sent to the data management centre in order to register the patient in the study.

Major patient management concerns for the subgroup study (SCT and GCT)

Clinical guidelines for the management of these rare ovarian cancers are available online and can be downloaded by investigators directly from the website. Surgical procedures are defined and recommended according to histological type, stage of disease, patient's age and desire for pregnancy. Depending on the surgical staging of the tumour, adjuvant chemotherapy is proposed, with 3 or 4 cycles of BEP (bleomycin, etoposide and cisplatin), regardless of histological type: GCT [5] or STC [7].

After completion of initial treatment, patients are evaluated. In case of a complete response, they are followed-up for 10 years with clinical examination, blood tests and radiological examination. In the absence of response to initial therapy or in case of a relapse, second-line therapy is individualized according to histologic type, patient's age and stage of disease.

Statistical analysis for subgroup study (SCT and GCT tumours)

Evaluation of response and survival

Procedures for disease evaluation included standard physical examination and marker level determination at each cycle (if relevant), as well as computed tomography scan of the abdomen and pelvis and two-view chest X-ray every two cycles. Objective response was evaluated using the Response Evaluation Criteria for Solid Tumours (RECIST) and reported by the investigator by completing the report form online [8]. In the absence of measurable disease, serologic response was determined if appropriate. Duration of response was measured as the time from initial documented response to the first sign of disease progression. Overall survival was evaluated by measuring the interval from the beginning of treatment to the date of last follow-up or date of death, whichever occurred first. Time to progression was defined as the time from the date of treatment to documentation of tumour progression.

Determination of toxicity

Toxicity was evaluated using the NCI-CTC scale, version 2.0. Haematological toxicity was evaluated weekly by complete blood count, while non-haematological toxicity was assessed before each treatment cycle.

Data were analysed using SPSS® 15.0 (Chicago: SPSS®, Inc. 2008). The prognostic factors studied on the first 100 patients enrolled included age, performance status, histology, LDH, AFP, HCG, inhibin and β HCG levels, decreased rate of tumour markers, site of metastasis, tumour size, presence of residual disease after initial surgery, and response to first and second-line chemotherapy [9].

Groups of patients were compared using Pearson's χ^2 test or Fisher's exact test. Quantitative data were analysed using Student's *t* test. Survival was analysed using the Kaplan–Meier method and survival curves were compared using the log-rank test. The chosen threshold for significance was $p=0.05$, all comparisons being two-sided.

The planned duration of the study was 10 years or more, depending on the inclusion rate.

Results of subgroup study (SCT and GCT)

Patient characteristics

Between March 2002 and June 2009, 180 patients from all over France were included in the SCT and GCT program (Fig. 2); for 25% of them a second opinion was sought from the online expert panel. Most patients were included by medical oncologists particularly involved in clinical trials ($n=84$) or not ($n=71$), or by surgeons ($n=25$). Clinical data were available for 100 of the 180 patients. Median age at diagnosis was 42 years (range 18–79). Sixty patients were less than 50 years old at the time of initial management. As shown in Table 1, a majority of patients had stage I disease, and the most frequent histologic type was SCT ($n=65$), with 41% of granulosa cell tumours. The main sites of metastasis were the liver and the lung. Preoperative markers (HCG, LDH, inhibin, α FP, CA19-9, and CA 125) were available for only 45 patients and were found increased in 12 (27%).

Histological panel review

Of the 100 patients initially screened and included, 23 (23%) were subsequently excluded, either because initial diagnosis had been established in a reference centre by one of the experts ($n=14$, 14%), or the initial histological report was not available at the time of analysis ($n=9$, 9%). Finally, 77 (77%) patients were eligible for second opinion. The central review of tumour samples by expert pathologists modified the diagnosis in 37% of patients (28/77). Discordance between initial diagnosis and review was essentially related to

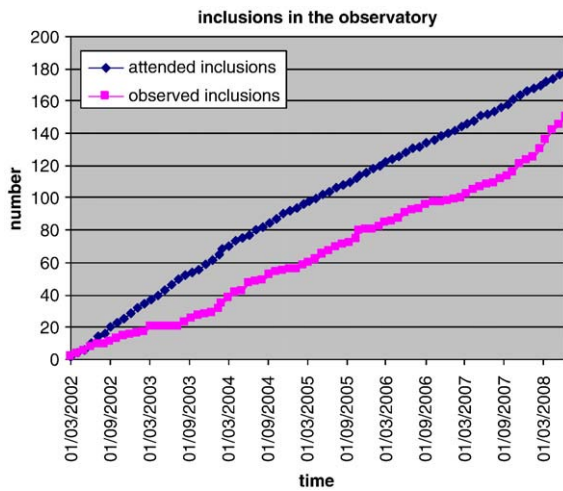


Fig. 2. Patient accrual.

grade, mitotic index and histological subtype (19 patients, 25%). Pathological diagnosis was revised for 8 patients: a granulosa cell tumour was finally classified as a small cell carcinoma, a Sertoli Leydig tumour as a benign tumour, 2 juvenile granulosa cell tumours as germ cell tumours, a Sertoli Leydig tumour as a synovial sarcoma (with confirmed SS18-SSX1 mutation), a teratoma as a carcinosarcoma, a dysgerminoma as an undifferentiated carcinoma, and a teratoma as a malignant neuroectodermal tumour. Finally, for 49 patients (63%)

Table 1 Patient characteristics (n = 100).

Characteristics	(%)	n
Age (years)		
Median		42
Range		18-79
Treatment at inclusion		
First line	78	78
First relapse	22	22
Stage at diagnosis		
I	73	73
IA	86	63
IB	3	2
IC	11	8
II	10	10
III	15	15
IV	2	2
Previous pregnancy (n = 91)		
Yes	64	58
No	36	33
Performance status		
0	89	89
≥ 1	11	11
Tumour size (mm)		
Median		120
Range		17-300
Diagnosis		
Sex cord tumours	65	65
Granulosa adult cell tumour	63	41
Granulosa juvenile cell tumour	5	3
Sertoli Leydig tumour	17	11
Fibrosarcoma	3	2
Fibrothecoma	2	1
Gynandroblastoma	2	1
Steroid cell tumour	3	2
Unclassified sex cord tumour	8	5
Germ cell tumours	30	30
Dysgerminoma	47	14
Yolk sac tumour	13	4
Immature teratoma	40	12
Germ cell + sex cord tumours	1	1
Others (clear cell, sarcoma, small cell carcinoma)	4	4

there was total concordance between initial pathological diagnosis and central review.

Surgical treatment

In this cohort, most patients (n = 72) had received conservative surgery (unilateral annexectomy or tumorectomy); of these, 58 (80%) were less than 50 years old at diagnosis. Of the 28 patients treated with radical procedures (bilateral annexectomy, total hysterectomy, peritoneal biopsies ± omentectomy), 20 (71%) had localized stage disease. The clinical guidelines for the management of these patients do not recommend systematic lymph node sampling [10], so only 11% of the patients underwent node dissection at initial management. At first-line treatment, majority of the patients (72%) received one surgical procedure; only 17 patients had two and one had three. Fifteen patients had macroscopic residual disease after initial surgery.

The details of patient management are reported in Table 2.

Chemotherapy

The observatory recommended the use of adjuvant chemotherapy for patients with stage I-IV GCT, except dysgerminoma (stages IA-IB) and immature teratoma grade IA. For SCT, chemotherapy was proposed for patients with at least stage IC.

Fifty-six patients received chemotherapy with BEP as recommended (3 or 4 cycles, depending on whether the patient had residual tumour or not after surgery). Of the 15 patients with residual tumours, 14 received 4 cycles of BEP. Three patients received adapted chemotherapy (2 had carboplatin-paclitaxel and one had etoposide-cisplatin because of cardiac or pulmonary deficiency). A total of 189

Table 2 Management at diagnosis.

Surgery	N (%)
Radical	28 (28)
Stages I-II (n = 83)	20 (25)
SCT subgroup	18 (90)
GCT subgroup	2 (10)
Stages III-IV (n = 17)	8 (50)
SCT subgroup	8 (100)
GCT subgroup	0 (0)
Conservative	72 (72)
Stages I-II (n = 83)	63 (75)
SCT subgroup	39 (62)
GCT subgroup	24 (36)
Stages III-IV (n = 17)	9 (50)
SCT subgroup	3 (33)
GCT subgroup	6 (77)
Lymph node sampling	11 (11%)
Stages I-II (n = 83)	9 (12)
SCT subgroup	5 (55)
GCT subgroup	4 (45)
Stages III-IV (n = 17)	2 (12)
SCT subgroup	0 (0)
GCT subgroup	2 (100)
Adjuvant treatment	
None	42 (42)
SCT subgroup	18 (57)
GCT subgroup	24 (43)
Chemotherapy	56 (56)
SCT subgroup	35 (63)
GCT subgroup	21 (37)
3 BEP	39 (70)
4 BEP	14 (25)
Other	3 (5)
Radiation therapy	4 (4)
SCT subgroup	0 (0)
GCT subgroup	4 (100)

SCT group: sex cord tumours (+ 1 mixed tumour (SCT + GCT)); GCT group: germ cell tumour.

chemotherapy cycles were administered to the 56 enrolled patients (median 3; range 2–6). Haematological side effects represented the main toxicity of the BEP combination. Severe haematological and non-haematological toxicities (grades 3–4) were registered (Tables 3 and 4). Blood transfusions were required in six patients (11%) and platelet transfusions in two. Ten patients (20%) were treated with epoetin. Systematic granulocyte-colony stimulating factor (G-CSF) administration was recommended and was used for all patients.

No grade 4 non-haematological toxicity was observed. Neuropathy occurred in 7 patients, but was not so severe as to compromise daily activities. Alopecia was not evaluated since most of the patients presented with this complication. There were no unexpected non-haematological toxicities.

Of the 56 patients receiving chemotherapy, 38 (68%) were treated at initial diagnosis whereas 18 (32%) received first-line chemotherapy at the time of first relapse. The overall response rate at the end of treatment (3 or 4 cycles) was 84% (n=32) in first line and 50% (n=9) when chemotherapy was given at first relapse.

Patient survival

With a median follow-up of 50 months, the median progression-free survival (PFS) for the whole group was 62 months (range 2–150), and the overall survival rate at 5 years was 94%. PFS according to histological subgroup was 65 months (IC 95%, 60–68) for patients with SCT (n=70) and 87 months (IC 95%, 77–89) for those with GCT (n=30). Overall survival rates at 5 years were respectively 87% and 96% for SCT and GCT. In univariate analysis, independent prognostic factors for PFS were age over 60 years (median PFS 57 vs. 70 months, p=0.02); tumour size over 100 mm (median PFS 62 vs. 124 months, p=0.01); and FIGO stages III–IV vs. I–II (median PFS 26 vs. 65 months, p=0.008). Fig. 3 reports disease-free survival by stage and histological subgroup.

Discussion

This first analysis confirms several important hypotheses concerning the management of rare ovarian cancers. Firstly, with 37% of discrepancies between initial diagnosis and second opinion, our results demonstrate that the pathological diagnosis of these rare entities requires expertise and centralized review. Secondly, the subgroup analysis of SCT and GCT patients registered to the website confirms that stage, tumour size and age are the most important clinical prognostic factors for overall and disease-free survival. Since 1980s, all reports of patients diagnosed with ovarian GCT or SCT have been retrospective analyses spanning periods longer than 10 years and including less than 300 patients [11–18]. The patients in these reports often have had different surgical procedures, even for the same stage of disease, different chemotherapy regimens in first line

Table 3
Major grade III/IV toxicities, and treatments (n=49)*.

	NCI-CTC grades 3–4	
	% Cycles	% Patients
Leucopenia	20	34
Neutropenia	33	42
Thrombocytopenia	6	19
Anaemia	8	11
Febrile neutropenia	15	19
Digestive reaction	25	31
Pulmonary reaction	4	1
Asthenia	3	8
Peripheral neuropathy	1	8
Allergy	4	14
G-CSF requirement	80	100
EPO requirement	ND	20

NCI-CTC, National Cancer Institute Common Toxicity Criteria.

Table 4
Non-haematological toxicities.

Toxicity	NCI-CTC grade (% patients)			
	1	2	3	4
Nausea/vomiting	28	25	7	–
Mucositis	10	8	4	–
Constipation	11	12	–	–
Diarrhoea	9	3	–	–
Infection	5	11	2	–
Neuropathy	21	6	1	–
Asthenia	26	33	8	–
Hypersensitivity	0	0	2	–

NCI-CTC, National Cancer Institute Common Toxicity Criteria.

and notably in second line, and their 10-year survival rate is rather high; consequently, interpretation of such data is hazardous. Indeed, because the number of events (relapses or deaths) at 10 years is small and the patients are young at the time of diagnosis, the number of patients lost to follow-up is high, which somewhat alters the significance of statistical analyses. Our prospective cohort of patients with GCT and SCT confirms the reliability of the dedicated website for exploring survival and prognostic factors in such patient populations.

As regards medical practice, we surprisingly observed 25% of patients undergoing radical surgery for localized stage tumours and, conversely, 50% receiving conservative surgery for advanced or metastatic stages. As patients could be included at relapse, it is possible that these inappropriate surgical procedures had been performed before inclusion of the patients in the observatory. This needs to be explored more systematically (analysis of detailed surgical reports in patient charts is on-going) and in a larger cohort of patients in relation to histological subtype (GCT vs. SCT). Similarly, whether the proper concept of a website dedicated to rare tumours can improve medical practice or just be used to collect patient cases remains to be clarified. Indeed, 50 patients by subgroups are warranted to explore medical practices at a national level [19]. This opens the debate between pros and cons of the website: pros suggest that more information can be conveyed to practitioners for better patient management, whereas cons maintain that more support should be given to some specialized centres to significantly improve the efficiency of clinical management... Again, it seems too early to gain conclusive evidence from this study.

By nature, studies of rare tumours are often hampered by limited or non-uniform data because they encompass multiple histologic subtypes and multiple medical strategies. As a result, making firm recommendations based on the findings of such studies can be

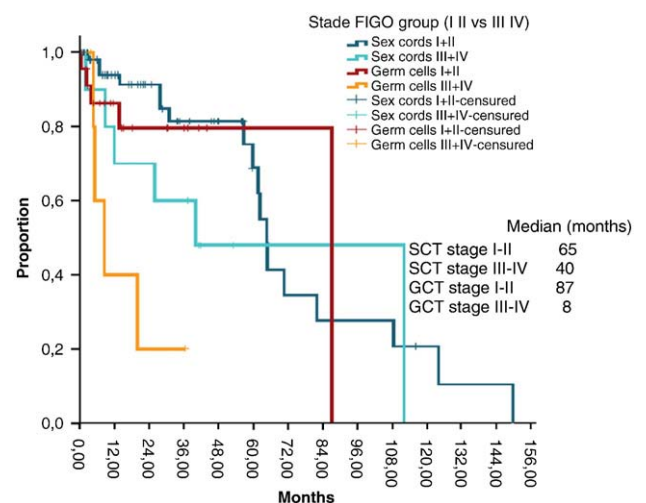


Fig. 3. Progression-free survival by histological group and FIGO stage.

difficult [6]. The present study highlights the ability of the website observatory to serve as a basis for developing biological and clinical research trials on rare tumours and establish adapted clinical guidelines. For example, biological or immunohistochemical factors are under study, notably for SCT. Granulosa cell tumours of the ovary arise from granulosa cells of the ovary and can be identified based on morphological, biochemical and molecular criteria [20]. In order to understand the molecular pathogenesis of these tumours, different activating mutations of the signalling pathways are under consideration using tumour samples (n=100) collected within the clinical research program from our website. These samples represent a unique opportunity, since the diagnosis of granulosa cell tumours has been confirmed and all patients have received similar management (adapted to disease stage and other prognostic factors) and appropriate follow-up allowing comprehensive analysis of biological factors. A better characterization of signalling pathways known to be important in the regulation of granulosa cell growth and differentiation could lead to the identification of new targets for treatment and, consequently, new opportunities of targeted treatment for these rare tumours. Accordingly, the need for prospective data allowing reproducible research work is important.

The rate of study inclusions after 5 years seems to confirm the website's ability to help organizing clinical research on rare tumours at a national level and stimulate patient recruitment. In addition to firm clinical data on prognosis and management, physicians need rapid answers to the questions they are faced with when dealing with these patients, especially young patients with good prognosis and a desire of preserving fertility. The website, which provides accurate online information and a bibliography and runs a discussion forum dedicated to these tumours, appears relevant to this particular issue. While providing both patients and physicians with rapid access to information on these rare neoplasms, this experience also enables the progression of clinical research and the centralized accumulation of data with the aim to further improve the management of these young patients. However the question remains of whether the website can help improve medical practice for these particularly rare cancers and hence whether it can be used as a tool to better organize clinical management and provide expert advice to the physicians and the patients. Indeed, most inclusions were made by specialized units involved in clinical trials. Research in the near future will test the concept that new tools such as our dedicated website can be of major clinical importance for patients with rare tumours.

Given the rapid success of this experience with patients and physicians, in 2008 the scientific board decided, with a substantial financial support from the French Cancer Institute (Inca), to broaden the scope of the website and to offer information and develop a database on other rare ovarian tumours such as borderline carcinoma, small cell carcinoma, mucinous and clear cell carcinoma and other very rare tumours. The goals remain the same, namely the provision of a helpful tool for diagnosis and treatment and the development of specific clinical and biological trials for these rare tumours. Finally, there remains the problem of the availability of new drugs for these patients (not only in first line but also at relapse). In Europe, accrual in phase II or III trials conducted at the national level might not be high enough to confirm clinical benefits in patients with rare tumours. International studies should be developed to enhance patient accrual and improve both clinical knowledge and management.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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