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ORIGINAL ARTICLE

Networking for ovarian rare tumors: a significant breakthrough improving disease management

N. Chiannilkulchai[1], P. Pautier[2], C. Genestie[3], A. S. Bats[4], M. C. Vacher-Lavenu[5†], M. Devouassoux-Shisheboran[6], I. Treilleux[7], A. Floquet[8], S. Croce[9], G. Ferron[10], E. Mery[11], C. Pomel[12], F. Penault-Llorca[13], C. Lefeuvre-Plesse[14], S. Henno[15], E. Leblanc[16], A. S. Lemaire[17], G. Averous[18], J. E. Kurtz[19] & I. Ray-Coquard[20*]

[1]ARCAGY-GINECO, Centre Cancers de la Femme et Recherche Clinique, Paris; Departments of [2]Cancer Medecine; [3]Biopathology, Gustave Roussy, Villejuif; [4]Departments of Gynecological Surgery, Hôpital Européen Georges Pompidou; [5]Pathology, Hôpital Cochin, AP-HP, Faculté deMédecine, Université Paris-Descartes, Paris; [6]Department of Pathology, University Hospital, Lyon; [7]Department of Pathology, Centre Léon-Bérard, Lyon; Departments of [8]Oncology; [9]Pathology, Institut Bergonié, Bordeaux; Departments of [10]Onco-Surgery; [11]Pathology, Institut Claudius Regaud, Toulouse; Departments of [12]Gynecological Surgery; [13]Pathology, Centre Jean Perrin, EA 4677, University of Auvergne, Clermont-Ferrand; [14]Department of Oncology, Centre Eugène Marquis, Rennes; [15]Department of Pathology, University Hospital, Rennes; [16]Departments of Gynecological Oncology; [17]Pathology, Centre Osacar lambret, Lille; Departments of [18]Pathology; [19]Oncology and Hematology, Hôpitaux Universitaires de Strasbourg, Strasbourg; [20]Department of Adult Medical Oncology, Centre Léon-Bérard & University Claude Bernard Lyon I, Lyon, France

Correspondence to: Dr Isabelle Ray-Coquard, Department of Adult Medical Oncology, Centre Léon-Bérard, 28, rue Laennec, F-69008 Lyon, France. Tel: +33-478-78-28-88; E-mail: isabelle.ray-coquard@lyon.unicancer.fr

[†]On behalf of the PathGyn Group.

Background: Rare ovarian tumors represent >20% of all ovarian cancers. Given the rarity of these tumors, natural history, prognostic factors are not clearly identified. The extreme variability of patients (age, histological subtypes, stage) induces multiple and complex therapeutic strategies.

Methods: Since 2011, a national network with a dedicated system for referral, up to 22 regional and three national reference centers (RC) has been supported by the French National Cancer Institute (INCa). The network aims to prospectively monitor the management of rare ovarian tumors and provide an equal access to medical expertise and innovative treatments to all French patients through a dedicated website, www.ovaire-rare.org.

Results: Over a 5-year activity, 4612 patients have been included. Patients' inclusions increased from 553 in 2011 to 1202 in 2015. Expert pathology review and patients' files discussion in dedicated multidisciplinary tumor boards increased from 166 cases in 2011 (25%) to 538 (45%) in 2015. Pathology review consistently modified the medical strategy in 5–9% every year. The rate of patients' files discussed in RC similarly increased from 294 (53%) to 789 (66%). An increasing number (357 in 5 years) of gynecologic (non-ovarian) rare tumors were also registered by physicians seeking for pathological or medical advice from expert tumor boards.

Conclusion: Such a nation-wide organization for rare gynecological tumors has invaluable benefits, not only for patients, but also for epidemiological, clinical and biological research.

Key words: ovarian rare tumors, national network, reference centers, clinical practice guidelines, gynecological rare cancers

Introduction

Rare tumors are defined by an incidence of less than six per 100 000 per year. With an incidence of 16.1/100 000 cases in Europe, the sum of all rare gynecological tumors, including ovarian, fallopian, uterine, cervix, vaginal, and vulvar cancers, represents >50% of all gynecological cancers [1]. Adequate knowledge of these neoplasms is crucial for diagnosis and initial treatment, and management of relapse.

Histological review by pathologist experts is a corner stone for the diagnosis of uncommon tumors, which most of pathologists

are unfamiliar with [2]. Molecular characterization is helpful both for the diagnosis accuracy and for relevant targeted therapies [3–8]. For adequate initial management, if guidelines are of outstanding importance for frequent cancers, this is from far less clear for rare tumors [9–12].

In 2004, to compensate for the rarity of non-epithelial ovarian tumors, we have set-up a website allowing French physicians to seek for advice on diagnosis and care through a discussion forum [13]. Given the rapid success of this experience, the initial website has been broadened to offer more information and access to dedicated multidisciplinary tumor boards for patient management on all rare ovarian tumors. It is now clear that some epithelial subtypes have distinct pathological behavior patterns, thus now classified as rare [14–16].

In this article, we present the rare ovarian tumors network activity and potential benefits of such a nation-wide organization for patients, physicians and health care system.

Patients and methods

TMRO network and reference centers

The national network for rare ovarian cancers (TMRO) was officially recognized by national authorities in 2011 comprising a 3-site national expert center and 22 regional reference centers (RC), covering the French territory. Altogether, 25 RCs have involved physicians from 15 comprehensive cancer centers, 7 university hospitals, 4 private structures, and 29 pathologist referee experts (supplementary Figure S1, available at *Annals of Oncology* online). Each RC organizes a regional referral multidisciplinary tumor board (MTB), with pathological review facilities. It is also active in healthcare professionals' medical education, and in clinical trials dedicated to rare ovarian tumors. National expert centers have the role of regional RC in their region.

Rare ovarian tumors in the network (inclusion/exclusion criteria)

Rare ovarian tumors considered in this network are, sex cord-stromal (SCT), germ-cell tumors, small cell carcinoma, and rare epithelial cancers, such as mucinous, clear-cell, carcinosarcoma, malignant Brenner tumors and low-grade serous carcinomas. All non-serous, and serous borderline tumors with peritoneal implants and/or with micro papillary aspects, were also included. Clearly excluded from our scope were high-grade serous and endometrioid ovarian cancers, ovarian metastases from other primaries, and the most frequent low-risk serous borderline tumors (no implant, no micro papillary or micro invasion) [17].

Process to include patient

After patient's agreement, only physicians, preliminarily identified by their registration number at the National Medical Association, can enroll patients into the database. Patients can only be registered or registered with an MTB advice and diagnosis review. As diagnosis review is mandatory, either the initial pathologist, the clinician in charge of the patient, or the MTB, can ask for the diagnosis review. The minimal itemized information registered in the database are patients' name initials, date of birth, initial histological diagnosis, and FIGO stage.

For discussion within the MTB, a brief relevant patient history, along with surgery and histopathological reports, is required. All anonymized documents are available via the website (downloaded by the physician after patient's agreement). Patients can themselves ask via their own practitioner for a second opinion through the system.

Diagnosis review

All cases of rare ovarian tumors had to be histologically confirmed owing to a systematic review either by a network expert pathologist or upon request by clinicians or initial pathologists. Discrepancies between initial diagnosis and second lecture were retrospectively analyzed in the setting of the systematic review organized in the five top-recruitment centers. Diagnosis was qualified as either in *full agreement*, or *partial agreement* (discrepancy but no change in patient management), or *no agreement* when diagnosis requalification induced a significant modification of patient care, according to the national guidelines.

Dedicated multidisciplinary tumor board

Multidisciplinary tumor boards, gathering gynecological surgeons, gynecologists, medical oncologists, radiologists, pathologists and fertility specialists, are organized in RC to recommend patients' management according to the national guidelines. In the setting of complex cases requiring additional expertise, regional RCs can refer the patients' files to one of the three expert centers which are Centre Léon Bérard, Gustave Roussy and Assistance Publique-Hôpitaux de Paris (AP-HP).

National clinical practice guidelines

Clinical practice guidelines for rare ovarian tumors have been established since 2008 for sex-cord, germ-cell tumors, clear-cell carcinoma, mucinous, small cell carcinomas, and borderline tumors. First line and relapse management were proposed for these subtypes. All the guidelines were internally (all members of the network) and externally (all members of the GINECO group) validated with systematic review in annual meetings. Guidelines for ovarian carcinosarcoma and low-grade serous tumors were added in 2013. Eight yearly updated guidelines are available on the website [18]. In 2014, the Gynecologic Cancer InterGroup (GCIG) rare tumor committee published 20 clinical guidelines for rare gynecological tumors after validation by the 28 GCIG national group members [19]. All the French national guidelines were consequently revised in accordance with the international guidelines.

Ethical considerations

The website with the data basis created to improve management of women with rare gynecological malignant tumors cohort was endorsed by the French authorities ('Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé' (CCTIRS) authorization numbers 09.342 and 09.342bis, and 'Comité National Informatique et Liberté' (CNIL) authorization number 909454), for registration of adult patients. Further notification was formally done to the CCTIRS for patients over 15 years old in 2014. The complete organization including database, MTB was also endorsed and labeled by the National Cancer Institute in 2011 then 2014. Follow up and creation of a database dedicated to rare cancer are missions asked by the French authorities via Plan Cancer 2009–2013 [20]. According to the French law, all patients are informed by their physicians about the network goals as a centralized platform dedicated to rare gynecological cancers management. Implicit agreement is part of patients' management, otherwise a patient signed documented refusal is required for her opposition to be registered in the database. Multidisciplinary tumor board for cancer management (of initial treatment and at each relapse) is now required by law in France (Plan Cancer 2003–2007, [20]). So, the recommendation to discuss rare ovarian tumor via our dedicated MTB is directly in accordance with French legacy. For specific biological research purposes, patients can sign the institutional informed consent, as well as the specific informed consent for rare ovarian tumors, both are equally considered effective for further studies on biological samples.

Results

Data and incidence rate

Since 2011, nearly 5000 cases have been registered in the database with a yearly progression of registration incidence for rare tumors (Figure 1). Table 1 reports 4612 patients with rare ovarian tumors included from 2011 to 2015, grouped by histological subtypes.

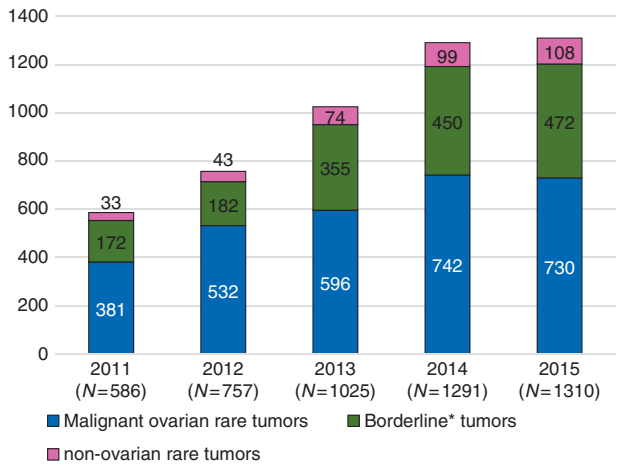

Figure 1. Yearly new cases of malignant ovarian rare, borderline* (all non-serous, and serous borderline tumors with peritoneal implants and/or with micro papillary aspects), and gynecologic (non-ovarian) rare tumors.

Incidence has seemingly neared the plateau for most, except for low-grade serous tumors, which were later included in the database. Patients' age (ranges and median), at initial diagnosis, confirmed its large scope according the wide spectrum of pathologic subtypes (Table 1). Altogether, the median age at diagnosis was 50 years old (range 15–92).

Over these 5 years, some other gynecological rare tumors ($n = 357$) were registered for second opinion and MTB advice (supplementary Table S2, available at *Annals of Oncology* online).

Second opinion on diagnosis and molecular characterization

Regarding ovarian rare tumors, 561 (12%) cases were initially diagnosed by TMRO referee pathologist and 825 (18%) remained non-reviewed by any TMRO expert pathologist. Three thousand two hundred and twenty-six (70%) cases were systematically analyzed by at least two pathologists, i.e. the first pathologist addressing the tumor block for a systematic review ($n = 2601$) or for a second opinion ($n = 625$), and one TMRO referee pathologist.

Over the 5-year activity, 260 (10%, out of 2601 cases) were classified with 'partial agreement' and 175 (7%) having 'no agreement'. Details of diagnoses with no agreement are presented as supplementary data (supplementary Table S3, available at *Annals of Oncology* online).

To better determine the diagnosis of some rare ovarian tumors, molecular characterization in diagnostic algorithms is implemented. Indeed, DICER1 and FOXL2 mutational status have been analyzed in SCT in 195 and 440 of cases, respectively [3, 21]. Similarly, SMARCA4 mutational status, implemented in 2013

Table 1. Incidence from 2011 to 2015, minimum, maximum and median age at diagnostic for ovarian rare tumors (confirmed diagnosis)

Histology (subtotal)	Subtypes	Year						Age at diagnosis		
		2011	2012	2013	2014	2015	Total	Min	Max	Median
Sex cord-stromal tumor ($n = 972$)	Adult granulosa cell tumor	83	141	128	163	150	665	17	90	54
	Juvenile granulosa cell tumor	7	12	3	6	4	32	16	67	22
	Sertoli±Leydig cell tumor	18	33	26	30	40	147	16	77	60
	Other sex cord-stromal tumor	20	16	34	36	22	128	19	75	51
Germ cell tumor ($n = 528$)	Dysgerminoma	23	15	21	19	13	91	16	50	24
	Yolk sac tumor	11	8	15	9	22	65	15	71	28
	Immature teratoma	18	26	36	29	27	136	16	82	28
	Teratoma with malignant transformation	9	24	16	50	43	142	18	85	51
	Other germ cell tumor	34	20	14	6	20	94	17	84	26
Small cell carcinoma ($n = 41$)	Small cell carcinoma	6	8	8	12	7	41	17	86	31
Carcinosarcoma ($n = 200$)	Carcinosarcoma	30	42	50	42	36	200	25	92	66
Low-grade serous tumor ($n = 135$)	Low-grade serous tumor	2	13	14	36	70	135	19	82	55
Clear cell carcinoma ($n = 430$)	Clear cell carcinoma	42	77	83	105	123	430	18	89	58
Mucinous carcinoma ($n = 475$)	Mucinous carcinoma	41	83	117	109	123	473	18	89	50
	Seromucinous carcinoma	na	na	na	na	2	2	57	73	65
Borderline tumor ($n = 1631$)	Serous with implants	108	13	133	187	175	616	18	86	48
	Mucinous	57	154	193	219	262	885	16	91	48
	Seromucinous	1	4	3	na	21	29	23	83	51
	Other	6	11	26	44	14	101	18	83	54
Other ($n = 200$)	Malignant Brenner tumor	9	3	5	6	9	32	46	86	63
	Other rare tumor	28	11	26	84	19	168	18	85	57
Total 2011–2015 ($n = 4612$)		553	714	951	1192	1202	4612	15	92	50

contributed to the diagnosis of 16 SCCOHT patients. Finally, cMET IHC and FISH ($n = 98$ and 99, respectively), and KRAS and BRAF ($n = 19$) mutations characterization were performed on rare epithelial cancers for enrollment into the basket trial 'AcSé program' [22].

Reference center MTBs and integrative medical decision

Out of all ovarian rare tumor cases, 2852 patients (62%) were discussed in RC MTB at the regional or national level. Typically, 50 (6%) cases per year were discussed at the regional, then national level. The numbers of patients who were reviewed for diagnosis, care management, or both from 2011 to 2015 appear in Figure 2. Interestingly, the number of patients having benefited from both MTB and histological second opinion increased over time from 25% to 45%.

Ovarian rare cancer clinical trials

Owing to this unprecedented nation-wide network, clinical trials specifically aiming to rare ovarian cancers are now possible. The first contribution of the network was in 2010 with the COCCINELLE study, a randomized phase-III study on first-line chemotherapy for clear cell carcinoma (GINECO-OV114, EUDRACT-2007-007849-13). Twelve French patients, with rapid confirmed diagnosis prior to randomization, were included alongside 652 in Japan, where this tumor is not so rare [23]. In the ALIENOR trial, focusing onto relapsed-SCT patients (GINECO-OV222, EUDRACT-2012-002841-39), the network facilitated recruiting 38 patients out of a target of 60 achieved within <4 years. Similarly, 25 French patients with relapsed low-grade serous tumor were enrolled in the MILO study (GINECO-OV233, EUDRACT-2013-000277-72) within 16 months, among 332 included by 140 centers worldwide. Finally, a randomized phase II study of Nintedanib compared with chemotherapy in patients with recurrent clear-cell carcinoma of the ovary or endometrium (NiCCC, GINECO-OV226, EUDRACT-2013-002109-73) is now recruiting.

Patient advocacy group

Since 2013, we have supported the first French patients' advocacy group for gynecological cancers, IMAGYN. Patients in ovarian rare tumors are willing to contribute to the network activity. A number of issues towards patients' needs and care will certainly be addressed from a close collaboration between physicians and the IMAGYN group in future studies [24].

National recognition

Owing to the TMRO database and the website, both French-speaking patients and healthcare professionals have access to valuable information. Indeed, 69 cases from European and North African countries have been taken into care by the network. The TMRO network has been officially acknowledged in 2014, among 18 rare cancer networks, for its organization and performance by the INCa. An application is already approved by the EU authorities as partner of the European Reference Networks on rare cancers (EURACAN).

Discussion

Given the lack of information on rare ovarian cancers, given the limited information amount about ovarian rare tumors in the past, organization with centralized expertise has eventually constituted a momentum for further studies. The organization has been proficient to rally expertise at the national level for patient and research benefits. Owing to the network, we can provide diagnostic expertise, which is the corner stone for further relevant care, as previously shown for French Sarcoma RC [25].

Over the 5-year activity, 175 patients (7%) benefited from the expert pathology review by having their initial diagnosis substantially modified. Mucinous carcinoma and BOL tumors are the most frequent histological subtypes where complete discordances were reported, underlining the systematic review importance (see supplementary Table S3, available at *Annals of Oncology* online).

Besides diagnosis accuracy, the network also aims to improve the care of patients with these rare tumors, thanks to the diffusion of the aforementioned GCIG guidelines, and the referral multidisciplinary tumor boards. Combining accurate diagnosis with adequate patient management is crucial for establishing a long-lasting, high-quality level of care, thus supporting a favorable

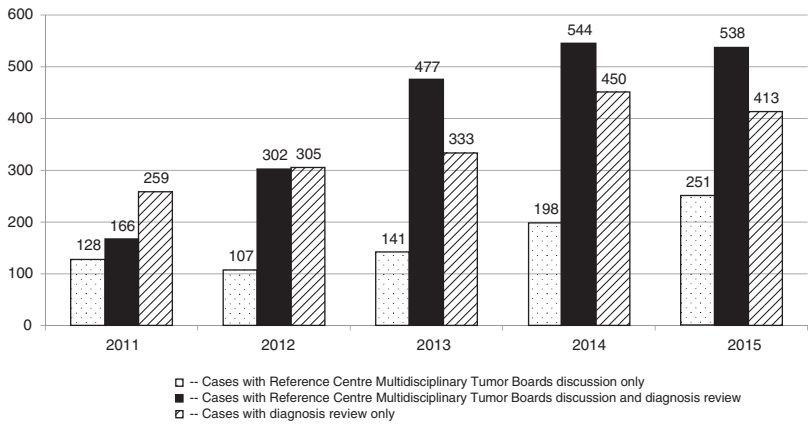

Figure 2. Distribution of rare ovarian tumor according to their management on yearly basis.

cost/benefit ratio for the network. Subsequent analyses for, conformity management with guidelines and their outcome analysis, though highly time-consuming and scarcely funded, are already planned for mucinous, sex cords and BOL subgroups.

Rare tumors management and international collaborations

Trials in first-line chemotherapy for ovarian mucinous carcinoma (NCT01081262, [26]) or relapsed low-grade serous tumors (EUDRACT-2013-000277-72) were unfortunately prematurely closed due to, respectively, insufficient recruitment and toxicity. The network organization has demonstrated the feasibility of trials dedicated to only rare cancers as shown in the ALIENOR study [27]. Indeed, the study recruited 60 targeted patients in 4 years owing to both the French network-based recruitment, and a successful international effort.

This international collaboration is undoubtedly in progress, as GCIG guidelines for 20 rare gynecologic cancers were recently coordinated by the GINECO and published in 2014 [19]. The 'rare tumors' topic was discussed, for the first time, in a cancer consensus conference at the fifth Ovarian Cancer Consensus Conference in 2015 [28].

Interestingly, germ cell, juvenile granulosa cell and small cell tumors, which affect children, teens and young adults, also benefit from pediatric oncology expertise. Currently all patients >15 years old can be included in the present network. Unfortunately, mixed expertise is rarely proposed for young adult and adolescent patients. Within the network, including pediatricians in some (not all) MTB, we anticipated more effective interaction and so improvement at the end for global management of young patients. In the view of patients' young age and favorable long-term prognosis in most pathologic subtypes, special attention towards hormonal function and fertility preservation has been identified for future national recommendations (on preparation) and studies within the network.

Finally, this momentum towards a better knowledge of rare ovarian tumors will benefit for both patients and healthcare professionals. For the latter, this is reflected by the growing number of new user's subscriptions every year, as by the spontaneous requests for expertise in non-ovarian rare gynecological tumors. This work has to be developed, in the view of practice evaluation, education and further harmonization. One must acknowledge that nothing would have been possible without patients' support, commitment, and participation to clinical and biological research.

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Disclosure

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