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## Potential histological discordance revealed by second review in the national rare gynecological cancer network (TMRG)

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## **ABSTRACT**

*Introduction:* Since 2010, the network of rare malignant tumors of the ovary (TMRG) was developed to optimize the management of patients, also allowing a histological second opinion of rare ovarian tumors. The aim of this work was to study the contribution of second opinion to improve histological diagnostic accuracy on ovarian rare malignant tumors included in the TMRG database.

*Material and Methods:* Histological data of patients diagnosed with a rare ovarian tumor included in TMRG network over a one-year period (2018) were collected. Initial diagnoses were compared with second opinion from national gynecological pathologist experts. The modalities of histological second opinion requests were studied, as well as the histological characteristics of the tumors. The discordances were classified as minor (if the modification of histological diagnosis did not change patient management) and major (if the patient management can be modified).

*Results:* Of 1185 included patients, 937 matched the inclusion criteria. Full concordance between primary diagnosis and expert second opinion was reached in 611 cases (65,3%), minor discordance was seen in 114 (12,2%) and major discordance in 209 (22,3%) of cases. In systematic review requested by the network, 26% (n =137) of cases were reported with a change in histological diagnosis, while the change concerned 44% (n=186) of cases for a second opinion spontaneously requested by the initial pathologist. The discrepancies concerned all categories of ovarian tumors, with a majority of mucinous tumors (43% of major discordances), followed by stromal and sex-cord tumors (13.8% of major discordances) and clear cell tumors (12,4% of major discordances).

*Conclusion:* This analysis confirms the diagnostic difficulty of ovarian tumors, due to their rarity and morphological heterogeneity. French pathologists are aware of these difficulties and

spontaneously refer ovarian tumors with unusual histology for a second opinion and collaborate with rare tumor networks for systematic review.

**Key Words** : ovarian tumor, rare ovarian tumor, network, pathological review, pathological discordance, concordance evaluation

## **INTRODUCTION**

Ovarian tumors are rare neoplasms and most are benign. Malignant ovarian tumors ranked as the eight most common cancer diagnoses in the world and the most frequent histological type is high-grade serous carcinoma, accounting for 60-70% of ovarian cancers [1]. The remaining 30% are subdivided into more than 30 histological subtypes according to WHO classification 2020 [2]. Given the rarity of these tumors, accurate histological diagnosis as well as clinical management is difficult for non specialized pathologists, surgeons and oncologists. We therefore created a dedicated national network (TMRG) allowing French physicians to ask for advice on the diagnosis and surgical and medical management of the patients through a dedicated multidisciplinary tumor board (MTB) (regional and national) via a website platform ([www.ovaire-rare.org](http://www.ovaire-rare.org)) [3]. In addition to the MTB advice for management, a systematically histological review by one of the expert pathologists of the network is promoted. The pathologists experts panel is organized around three national centers in Lyon (MDS, IT), Paris (PAJ, MALB) and Gustave Roussy (CG) and 15 regional centers covering French national territory [3-8].

The network also included cases referred to expert pathologists for second opinion, spontaneously from a generalist pathologist, even though the physician in charge of the patient did not asked for therapeutic advice. All patients have consented to be included into the website and cases appear as anonymous without patient's entire name and identity.

The aim of the present work was to evaluate the benefit of systematically pathological review or second opinion by a pathologist expert for rare malignant ovarian tumors.

## **MATERIAL AND METHODS**

We retrospectively studied the histological diagnosis of all cases of rare malignant ovarian tumors included into the French website (TMRG) during one year-period in 2018. We

aimed to compare the initial histological diagnostic of local pathologist to that made by the TMRG expert gynecological pathologist. All cases from the database that have been initially diagnosed by one of the expert pathologists were excluded. For each included patient, a copy of the original pathological report and representative HES slides and paraffin blocks were provided by the initial generalist pathologist to the expert TMRG pathologist for pathological review. Cases were subdivided into 1) systematic histological review (SR) (when the tumor board requested a histological review) and 2) histological second opinion (SO) initiated spontaneously by the local pathologist in challenging cases because of difficulties on histological analyses. The goal of this subdivision was to explore the added value of the TMRG network (mandatory SR) and the role of standard organization of pathologists (SO).

Only cases with one single proposed diagnosis from the local pathologist were included (exclusion of cases sent without a definitive diagnosis or with several proposed diagnoses from the initial pathologist). After comparison of the first (initial pathologist) and the second (expert pathologist) diagnosis, cases were classified as 1) concordant (total agreement) when both diagnoses were identical, as 2) minor discordance when the histological modification of the diagnosis did not modified the clinical management of the patient and as 3) major discordance when the review diagnosis conducted to a major change in the patient's management (either changes in the treatment strategy or in the surveillance scheme and prognosis).

Rare ovarian tumors that can be included in the website are listed in table 1.

Among 1287 cases included in the TMRG database in 2018, 1185 concerned rare malignant ovarian tumors as listed in table 1. The number of cases reviewed by each expert pathologist varied from 11 to 197.

Several cases were excluded (20%) including one hundred and ten (9%) cases initially diagnosed by one of the expert pathologists, 59 (5%) due to missing data about the goal of the

review (SO or SR), cases (n =23) without proposed diagnosis from the initial pathologist and 56 cases with several potential histological diagnostic proposed.

At the end, the analysis on histological discrepancy was conducted on 937 cases in which one diagnosis and the goal of the histological review (SO or SR), were mentioned by the initial pathologist.

Among 937 cases (420 (45%) and 517 (55%) were SO and SR respectively), the majority were epithelial tumors (n = 672;71.7%) followed by gonadal stromal and sex cord tumors (n = 164;17.5%) and germ cell tumors (n = 73;7.8%). Among epithelial tumors, mucinous variant were the most frequent in this study (n = 349;52%), and among non epithelial category, adult granulosa cell tumors predominated (n = 118;72%).

## RESULTS

On the final 937 analyzed cases, the overall agreement rate between original and review diagnoses reached 65,3% (n = 611). A disagreement was observed in 326 cases (34.7%), including 22,3% of major discordances and 12,2% of minor discordances respectively.

Among 323 discordant cases (3 cases were excluded due to incapacity of their classification as minor or major discordances), 64.7% were major (209 total disagreement) and 35.3% were minor discordances (114 partial disagreement).

As anticipated, the majority of discordances concerned SO (186/420 (44%)), including 16% (n =67) minor and 28% (n =119) major discordances. In contrast, among the SR group, 137/517 (26%) were discordant, with 9% (n =47) minor and 17% (n =90) major discordances. Among the major discordances, 13 of 209 cases (6.2%) were due to a change in histology category (epithelial *versus* sex cord *versus* germ cell tumors), 58 cases were a modification from borderline to invasive carcinoma and *vise et versa* (27.8%), 23 cases (11%) were



changes in borderline *versus* benign tumors, 14 cases (6.7%) benign *versus* malignant tumors, while 12 cases (5.7%) concerned primary *versus* metastatic localization from other tumors. Major disagreements by histological subgroups are detailed in table 2.

## DISCUSSION

The pathological diagnosis of most ovarian tumors is mainly based on morphological findings with very few ancillary techniques available for difficult cases. This subjective morphological interpretation of microscopic findings along with the rarity of ovarian tumors, explain inevitable diagnostic errors. The TMRG network was implemented in France in 2010 to help a pathologic review in diagnostically challenging tumors as well as offering best-practice advice on the surgical and medical management or surveillance of the patients presenting with rare malignant ovarian tumors [3-8]. This study investigated the impact of pathological review of cases included in TMRG network during a one-year period in 2018. To best of our knowledge, this is the first study evaluating pathological discordances in the routine practice, since the material is not based on a clinical trial cohort nor specific inter-observer series. The study found a total agreement between the initial and expert pathological diagnosis in the majority of cases (65,3%) and major discordances achieving a modification in the management of patients were seen in 22,3% of all cases. The total disagreement rate (22,3%) is higher in this study compared to Kommos et al study (6,8%) where they compared original and review pathological diagnosis of AGO study cohort [9]. We have included in this study cases that have been reviewed systematically upon a demand from the tumor board (SR) (55%) and cases sent to one of the expert pathologist of TMRG spontaneously by the initial pathologist as histological second opinion (SO) (45%). Importantly, the discordances rate is 44% in the SO group and 26% in the SR group. The SR group is more comparable to Kommos et al study [9], since they have systematically

reviewed the slides from a clinical trial. In fact the rate of major discordances in SR cases (17%) is higher than anticipated and highlights the difficulties to diagnose such rare entities, supporting the beneficence of systematic review. Also, the level of discordances in SO group in the current study (44%) illustrates how the vast majority of generalist French pathologists are aware of diagnostic difficulties in ovarian tumors and spontaneously ask for an expert second opinion.

The majority of total disagreement concerned epithelial tumors (76%), with first mucinous tumor (all categories (benign, borderline, expansile or infiltrative and metastatic carcinomas from other localizations) are involved) followed by clear cell carcinomas. In Barnard et al study, the majority of discordances also concerned non serous variant of ovarian carcinomas [10]. The diagnosis of mucinous tumors in the ovary is one of the most difficult and essentially based on morphological analyses. A limited panel of immunohistochemical markers may help in distinguishing primary from metastatic tumors, essentially from colorectum and appendix [11]. However, pancreato-biliary primaries do not have specific markers except loss of SMAD4 in less than 50% of cases using an antibody with many technical difficulties [12]. In Kommos et al study, ovarian metastases constituted the second most frequent misdiagnosis [9]. In our study, only 12 cases initially diagnosed as primary mucinous ovarian tumors were in fact metastases (8 proven cases originated from gastro-intestinal tract and 4 suspected cases). It is important to exclude an occult gastrointestinal primary cancer with a comprehensive clinical, radiologic and endoscopic workup, when dealing with ovarian mucinous tumors, especially if the tumor is < 10 cm, bilateral or with peritoneal spread [13]. This recommendation included in our French algorithms also explain the potential difference between our results and those of Kommos et al [9]. The distinction of benign from borderline and carcinoma expansile *versus* infiltrative type is only based on morphological findings, with a lack of reproducibility of the current histological criteria and the absence of alternative or

additional tools for classification, including immunohistochemical and molecular markers. In a recent study on mucinous ovarian tumors, the concordance between two expert gynecological pathologists remains quite low with a  $k$ : 0.78 and using *KRAS* or *TP53* mutations is not useful in the differential diagnosis [14]. The major difficulty (major discordances) in mucinous tumors concerned the distinction between borderline tumor and expansile type invasive adenocarcinoma (31 cases: 14.8%), followed by borderline tumor and infiltrative type adenocarcinoma (9 cases: 4.3%) and infiltrative *versus* expansile type adenocarcinoma (7 cases: 3.4%). Also, three cases of mucinous adenocarcinoma were classified as major discordances, because the pattern of invasion (expansile *versus* infiltrative) was not indicated in the initial pathologic report. This distinction is of major clinical importance since stage I expansile type of invasive adenocarcinoma and borderline tumors in young patients can be managed more conservatively than the infiltrative type mucinous adenocarcinoma [13, 15].

The diagnosis of ovarian clear cell carcinomas is also mainly based on the morphological analyses. A panel of immunohistochemical study may help distinguishing clear cell carcinomas from other subtype of carcinomas with clear cell changes [16]. However, a thorough sampling of a clear cell tumor is usually necessary to separate a borderline from a carcinoma, since the diagnosis is based only on morphological analyses. The presence of papillae and back to back tubulo-cystic patterns are features that should be searched in adenofibromatous clear cell tumors, helping to classify the tumor as clear cell carcinoma rather than borderline tumor [2]. The diagnosis of clear cell carcinoma has therapeutic implications with the possible use of immunotherapy and ATR inhibitors since *ARID1A* mutations or *PIK3CA* alterations are frequent [17].

Major discordances were lower in this study for serous type tumors, since high grade serous carcinomas and classic serous borderline tumors without peritoneal implants are not part of

tumors included in our TMRG database. However, 8 cases of major discordances between low and high grade serous carcinomas (3,8%) were reported. The use of P53 immunostaining is a real help in these cases, since P53 shows a wild type pattern of staining in low grade and an aberrant pattern of staining in high grade serous carcinomas [2]. In 10 cases, the major discordance concerned serous borderline tumor *versus* invasive low grade carcinoma (4,8%). The rate of 4.8% is much lower than previously reported in the literature where 29,3% [18] to 42,2% [19] of cases initially diagnosed as invasive serous carcinoma were reclassified as serous borderline tumors, as they also included high grade serous carcinomas in their studies. Of interest, very few cases (n = 2) of peritoneal implants in serous borderline tumors were misclassified in the current study (invasive *versus* non invasive). Invasion in a serous borderline tumor or its peritoneal implant shows a destructive stromal and adipose tissue invasion and infiltrative process with typical patterns of invasive serous carcinomas [2].

Difficulties in histological diagnosis of sex cord stromal tumors are often reported in the literature [20]. In our study, 38 cases showed discordances, of which 29 concerned granulosa cell tumors, with major discordances in 26 cases (12,5%). The distinction between sertoli-leydig cell and granulosa cell tumors has important clinical implications [21], and concerned 11 cases in our study. Also, the distinction between fibroma/thecoma and adult type granulosa cell tumor in its solid variant seen in 6 cases in this study may be difficult but is crucial for patient's management [22]. We have published an algorithm stipulating that the presence of somatic *FOXL2* mutation favors an adult granulosa cell tumors, since this mutation is usually not seen in other sex cord stromal tumors including juvenile granulosa cell tumors [23, 24, 25].

The lowest rate of histological discordances in the present study concerned germ cell tumors (21 cases) of which 16 were reported with a total disagreement. Non teratomatous malignant germ cell tumors (dysgerminomas, yolk sac tumors, mixed germ cell tumors) were

all correctly diagnosed. This is essentially due to the availability of many immunohistochemical and serum markers that help both pathologists and oncologists in making the correct diagnosis [26]. All 16 cases of major discordances in the germ cell tumor category were seen with immature teratomas, either low *versus* high grade (3,4%), or immature teratoma *versus* carcinosarcoma (1,4%) or *versus* other type of tumors (2,9%). The grade of immature teratomas in the ovary has therapeutic implications since chemotherapy may be used in high grade tumors only [27].

Three cases of small cell carcinomas of hypercalcemic type were misdiagnosed in our series. The loss of BRG1 (SMARCA4) immunostaining is a useful tool and should be performed in undifferentiated tumors of young patients [28]. This is a highly malignant and rapidly progressing neoplasia that needs a rapid and specific chemotherapeutic regimen [29]. Finally, the second opinion also permit to well conduct clinical trials as Alienor, a randomized study dedicated to sex cords [30] or the Bouquet trial (NCT04931342) including only rare ovarian cancer reporting molecular abnormalities and where currently 100% of complete concordance with central review is already observed for French patients (data not shown).

In conclusion, this study reports, despite the rarity of malignant ovarian tumors, 66% of cases are correctly diagnosed by the initial pathologists, thanks to many French and international post graduate courses and training programs. However, still 22% of major discordances with therapeutic and prognostic implications are detected when a histological review is performed by expert gynecological pathologists, either spontaneously as a demand from the initial pathologist or systematically requested by a tumor board. These findings provide an incentive for pathologists to send out their difficult cases of ovarian tumor for a second opinion, and also support systemic review, avoiding inadequate treatments for a number of patients. Furthermore, pathologic review may increase the rigor of clinical research and trials.

### **Author contributions**

Data analysis, writing of the original article: S. Henno, C. Jeanne, M. Devouassoux-Shisheboran, I. Ray-Coquard.

Contribution to the clinical aspects: T. De La Motte Rouge, I. Ray-Coquard.

Critical review: I. Ray-Coquard, M. Devouassoux-Shisheboran.

Database contribution: S. Henno, C. Jeanne, C. Genestie, I. Treilleux, S. Croce, PA. Just, MA. Le Frere-Belda, E. Guinaudeau, F. Penault-Llorca, L. Arnould, E. Mery-Lamarche, A. Leroux, AS. Lemaire, G. Averous, O. Renaud, E. Charafe-Jauffret, C. Bonneau, C. Leaha, M. Devouassoux-Shisheboran.

### **Declaration of interest**

The authors declare no conflict of interest

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### **Table/figure legends**

**Table 1:** rare malignant ovarian tumors that can be included in TMRG network

**Table 2:** Histological characteristic of major disagreements

<b>Borderline and malignant epithelial tumors</b>
Serous borderline tumor with peritoneal implant
Micropapillary serous borderline tumor
Low grade serous carcinoma
Borderline sero-mucinous, endometrioid, tumors
Borderline and malignant mucinous tumors
Borderline and malignant clear cell tumors
Borderline and malignant brenner tumors
Carcinosarcoma
Indifferentiated/dedifferentiated carcinoma
<b>Sex cord stromal tumors</b>
Fibrosarcoma
All sex cord tumors including granulosa and sertoli-leydig
<b>Malignant germ cell tumors</b>
Dysgerminoma
Yolk sac tumor
Embryonal carcinoma and non gestational choriocarcinoma
Mixte malignant germ cell tumors
Immature teratoma
Teratoma with somatic malignancy
<b>Small cell carcinoma of hypercalcemic type</b>

**Table 1:** rare malignant ovarian tumors that can be included in TMRG network

<b>major disagreements (n=209)</b>		
	<b>n</b>	<b>%</b>
<b>Epithelial tumors</b>	<b>159</b>	<b>76%</b>
Serous carcinoma : Low grade versus high grade	8	3,8%
Serous tumor: Benign versus borderline	3	1,4%
Serous borderline tumor: classic versus micropapillary	10	4,8%
Serous tumor : Borderline versus invasive low grade carcinoma	10	4,8%
Clear cell carcinoma versus other diagnosis	26	12,4%
Mucinous tumor : benign versus borderline	17	8,1%
Mucinous : expansile carcinoma versus borderline tumor	31	14,8%
Mucinous : infiltrative carcinoma versus borderline tumor	9	4,3%
Mucinous : expansile versus infiltrative carcinoma	7	3,4%
Mucinous : primary versus metastatic tumor	8	3,8%
Mucinous carcinoma versus other type primitive tumor	7	4,3%
Borderline tumor : serous versus mucinous	5	2,4%
<b>Sex cord tumors</b>	<b>29</b>	<b>13,8%</b>
Granulosa adult versus Sertoli-Leydig	11	5,3%
Granulosa adult versus fibroma/thecoma	6	2,9%
Granulosa adult versus FATWO	3	1,4%
<b>Germ cell tumors</b>	<b>16</b>	<b>7,6%</b>
Immature teratoma : low versus high grade	7	3,4%
Immature teratoma versus carcinosarcoma	3	1,4%
Immature teratoma versus other diagnosis	6	2,9%
<b>Others</b>	<b>5</b>	<b>2,4%</b>
Small cell hypercalcemic type carcinoma versus other diagnosis	3	1,4%

**Table 2:** Histological characteristic of major disagreements