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Editorial

Toward Better Care of Rare Ovarian Tumors

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The ovary has a propensity to generate a greater variety of tumor types than any other organ. Tumors arise from the surface epithelium—which originates from the fetal coelomic epithelium, from the sex cord-stromal cells—which are composed of granulosa and theca cells, as well as germ cells. In this diversity of histologic types, non-epithelial ovarian tumors are the least frequently encountered tumor type. National Comprehensive Cancer Network (NCCN) guidelines define less common ovarian cancers (LCOC) as including carcinosarcoma (also known as a malignant mixed mullerian tumors (MMMTs)), clear cell carcinoma, mucinous carcinoma, low-grade (grade 1) serous/endometrioid epithelial carcinoma, borderline epithelial tumor, malignant sex cord-stromal tumor, and malignant germ cell tumor [1]. The prevalence of ovarian tumor histology varies widely by country and geographic region; for example, clear cell carcinoma accounts for 5.0% of ovarian cancers in the United States and 15.7% in Japan [2]. While there are international perspectives on what is considered a rare tumor type, LCOCs outlined above will be referred to as rare ovarian tumors in this paper. An overview of the current status of this tumor group and the problems will be presented.

In rare ovarian tumors, therapeutic development is not progressing at the pace observed for the development of therapeutics for common ovarian cancers. Prospective clinical trials are difficult to implement because of the small number of patients, and even if efficacy is confirmed in clinical trials, pharmaceutical companies will hesitate to commercialize a treatment for a disease with a small number of potential patients. Even in granulosa cell tumors (GCT), which are relatively frequent within LCOCs, retrospective cohort studies using nationwide, large-scale databases are the only source of available evidence [3,4]. We drawn the following conclusions regarding treating GCT based on our analysis of tumor registry data from the Japanese Society of Obstetrics and Gynecology (JSOG). Specifically, at the time of initial surgery, lymph node dissection can be omitted if the surgical findings are pT1 after a thorough intra-abdominal search. However, if tumors are staged at pT2 or higher, lymph node dissection should be considered. In addition, debulking is essential to minimize the chances of residual tumor following the initial surgery. In International Federation of Gynecology and Obstetrics (FIGO) stage I cases, fertility-sparing surgery can be considered, however, even in such cases, staging, including intra-abdominal examination and biopsy of the omentum and peritoneum, is necessary [4]. Chemotherapy for advanced GCT, although even less frequently encountered, could not be definitively determined. In the future, prospective studies using public registries outlining chemotherapeutic regimens will be required. The nationwide gynecological tumor case registration system, which as launched in 2023 jointly with the Japanese Society of Gynecologic Oncology (JSOG), and the Japan Society of Gynecologic and Obstetric Endoscopy and Minimally Invasive Therapy has great promise for accumulating detailed therapeutic data not previously available.

While there are difficulties in conducting clinical trials in patients with rare ovarian tumors, what about basic research into these tumors? Mutations in the *FOXL2* gene, a hallmark of GCT, were reported by Shah *et al*. [5] in 2009. *FOXL2* is a member of the forkhead-wing helix family of transcription factors, including a highly conserved DNA-binding forkhead domain [6]. One of the earliest markers of ovarian differentiation, *FOXL2* expression continues into adulthood and *FOXL2* is required for normal development of granulosa cells. Currently, mouse models have been created in which *FOXL2* mutations are introduced, and these mice form tumors similar to human GCTs [7]. For clinical applications, reports of *FOXL2* mutations and mutations in the *TERT* gene promoter are detected in cell-free DNA and are used to monitor disease [8]. While drug selection guided by molecular markers is a promising approach, predictive biomarkers for gauging responsiveness to checkpoint immunotherapy have been reported to be rare in molecularly defined GCT [9]. In addition to GCT, a recent report comprehensively reviewed molecular profiling of rare ovarian tumors [10]. Thus, along with elucidating molecular structures, the direction of utilizing them in diagnosis and treatment is an exciting avenue for investigation.

In regards to germ cell tumors exemplified by dysgerminomas and immature teratomas, evidence for chemotherapy is primarily based on the BEP (bleomycin, etoposide, and cisplatin) regimen that has been established, and the guidelines are written in an easy-to-understand manner. Nevertheless, there may be clinical situations where treating mature cystic teratoma with malignant transformation is challenging. This review suggests that tumors of this type are more common encountered in elderly patients, and that

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total hysterectomy and platinum-based chemotherapy are associated with improved prognosis; however, information is limited regarding such cases [11]. Addional studies are clearly needed in this area as well.

In summary, data on rare ovarian tumors is limited due, largely, to their infrequency, and prospective data may not be readily available. Clinical trials for eligible patients and individualized treatment plans for patients ineligible for clinical trials are the best approach to treating these patients at the present time. Also, as mentioned above, valuable information could be gleaned in geographic regions with high LCOC frequencies. Molecular biological research aimed at developing individualized treatment plans should also be carried out.

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References

[1] National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines ®) Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 2.2023. 2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf (Accessed: 16 June 2023).

[2] WHO Classification of Tumours Editorial Board. WHO Classification of Tumors. 5th Edition. WHO Press: Geneva, Switzerland. 2020.

[3] Seagle BLL, Ann P, Butler S, Shahabi S. Ovarian granulosa cell tumor: A National Cancer Database study. Gynecologic Oncology. 2017; 146: 285–291.

[4] Ebina Y, Yamagami W, Kobayashi Y, Tabata T, Kaneuchi M, Nagase S, *et al*. Clinicopathological characteristics and prognostic factors of ovarian granulosa cell tumors: A JSGO-JSOG joint study. Gynecologic Oncology. 2021; 163: 269–273.

[5] Shah SP, Köbel M, Senz J, Morin RD, Clarke BA, Wiegand KC, *et al*. Mutation of FOXL2 in granulosa-cell tumors of the ovary. The New England Journal of Medicine. 2009; 360: 2719–2729.

[6] Cocquet J, Pailhoux E, Jaubert F, Servel N, Xia X, Pannetier M, *et al*. Evolution and expression of FOXL2. Journal of Medical Genetics. 2002; 39: 916–921.

[7] Llano E, Todeschini AL, Felipe-Medina N, Corte-Torres MD, Condezo YB, Sanchez-Martin M, *et al*. The Oncogenic FOXL2 C134W Mutation Is a Key Driver of Granulosa Cell Tumors. Cancer Research. 2023; 83: 239–250.

[8] Groeneweg JW, Roze JF, Peters EDJ, Sereno F, Brink AGJ, Paijens ST, *et al*. FOXL2 and TERT promoter mutation detection in circulating tumor DNA of adult granulosa cell tumors as biomarker for disease monitoring. Gynecologic Oncology. 2021; 162: 413–420.

[9] Hillman RT, Lin DI, Lawson B, Gershenson DM. Prevalence of predictive biomarkers in a large cohort of molecularly defined adult-type ovarian granulosa cell tumors. Gynecologic Oncology. 2021; 162: 728–734.

[10] Takahashi N, Hatakeyama K, Nagashima T, Ohshima K, Urakami K, Yamaguchi K, *et al*. Characterization of rare histological subtypes of ovarian cancer based on molecular profiling. Cancer Medicine. 2023; 12: 387–395.

[11] Li C, Zhang Q, Zhang S, Dong R, Sun C, Qiu C, *et al*. Squamous cell carcinoma transformation in mature cystic teratoma of the ovary: a systematic review. BMC Cancer. 2019; 19: 217.