

OVARIAN CANCER IN FOCUS

Current Developments in the Management of Ovarian Cancer

Section Editor: Robert L. Coleman, MD

Management of Rare Epithelial Ovarian Cancers



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H&O What percentage of ovarian cancers are epithelial?

DG Approximately 90% of all invasive ovarian cancers are epithelial. The other 2 major categories of invasive ovarian cancers are germ cell tumors and sex cord stromal tumors, which account for approximately 5% each.

H&O What are the most and least common types of epithelial ovarian cancers?

DG The most common type by far is high-grade serous carcinoma, which accounts for approximately 70% of epithelial ovarian cancers. The remaining 30% of epithelial ovarian cancers are considered rare and fall into the categories of mucinous carcinoma, clear cell carcinoma, endometrioid carcinoma, or low-grade serous carcinoma.

The World Health Organization (WHO) classification also includes undifferentiated carcinoma as a type of epithelial ovarian cancer, although most people lump that into the high-grade serous category. The WHO classification formerly included transitional cell carcinoma, but most pathologists now consider this condition to be a variant of high-grade serous carcinoma, and it does not appear in the most recent update from 2014.

H&O How do the rare types of epithelial ovarian cancer differ from high-grade serous carcinoma?

DG Some pathologists classify ovarian epithelial tumors as type 1 and type 2, in which type 1 refers to the 4 rare subtypes and type 2 refers to high-grade serous tumors.

One argument in favor of this classification is that type 1 tumors usually have a precursor lesion, whereas high-grade serous carcinoma does not have a precursor lesion. I do not agree with the type 1/type 2 classification because the 4 rare subtypes have more differences than similarities. The molecular biology differs among the 4 subtypes, meaning that most of the mutations are different. As a result, the treatments that are in development also are different.

One major difference among the rare subtypes is that mucinous carcinoma, clear cell carcinoma, and to some degree endometrioid carcinoma typically present in the early stages—either stage I or II. In contrast, low-grade serous carcinoma is most likely to present in stage III or IV.

Differences in etiology also exist among the various subtypes. Clear cell and endometrioid carcinoma frequently develop from foci of endometriosis in the peritoneal cavity. Low-grade serous carcinoma may either occur de novo or stem from a serous borderline tumor. Our understanding of the pathogenesis of mucinous carcinoma is not as good as for the other types, but in at least some cases it develops from a borderline tumor.

Molecular characteristics also vary among the tumors. For example, mucinous tumors have a *KRAS* mutation in approximately 40% of cases and an amplification in human epithelial receptor 2 (HER2) in approximately 18% to 20% of cases. Clear cell tumors have a mutation in *ARID1A* in approximately 50% of cases and a mutation or aberration in the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway in approximately 30% to 40% of cases. Endometrioid carcinomas have an *ARID1A* mutation in approximately

30% of cases. Low-grade serous tumors have a mutation in *KRAS*, *NRAS*, or *HRAS* in approximately 20% to 40% of cases, and a mutation in *BRAF* in approximately 5% of cases.

In contrast, high-grade serous tumors tend to carry the *TP53* mutation. They may also have a homologous recombination deficiency; 18% to 20% of them have a mutation in *BRCA1* or *BRCA2*. Other mutations may exist, but the most consistent of these is *TP53*.

Another difference involves the aggressiveness of the tumors. Mucinous and clear cell carcinomas are very aggressive, whereas low-grade serous carcinoma tends to be indolent. For endometrioid carcinoma, the aggressiveness depends on the grade; grade 1 and 2 tumors tend to be more indolent, whereas grade 3 tumors behave similarly to high-grade serous carcinoma. As expected, the median overall survival is much better with low-grade serous carcinoma than with either mucinous or clear cell carcinoma. Overall survival also changes with the stage. Compared with high-grade serous carcinoma, the overall survival is similar in stage I or II mucinous and clear cell carcinomas and better in stage I or II endometrioid and low-grade serous carcinomas. That equation changes in stage III or IV disease, in which mucinous and clear cell carcinomas have significantly worse overall survival than high-grade serous carcinoma. Overall survival continues to be significantly better in stage III or IV low-grade serous carcinoma compared with high-grade serous carcinoma, and is approximately the same in advanced endometrioid carcinoma and high-grade serous carcinoma.

H&O Could you discuss treatment of the various types of epithelial ovarian cancer?

DG We used to treat the 4 rare subtypes exactly the same way as high-grade serous carcinoma until around 2005, when our approach began to change dramatically. Unlike the rare subtypes, which are often resistant to chemotherapy, high-grade serous carcinoma is typically sensitive to conventional chemotherapy agents such as carboplatin and paclitaxel because the tumor cells turn over fairly quickly. Chemotherapy may be used on its own or in combination with another agent, such as the anti-angiogenic agent bevacizumab. Poly(ADP-ribose) polymerase (PARP) inhibitors also may be used if evidence exists of a homologous recombination deficiency, which does not tend to occur in the rare subtypes. Immunotherapy also is being studied for use in high-grade serous carcinoma, but early results do not look very promising.

Mucinous tumors are microscopically very similar to tumors that arise in the gastrointestinal tract. For this reason, researchers have conducted some studies of regimens used in colorectal cancer, such as 5-fluorouracil/

leucovorin/oxaliplatin (FOLFOX) and capecitabine/oxaliplatin (XELOX). The phase 3 mEOC/GOG-241 trial (Carboplatin and Paclitaxel or Oxaliplatin and Capecitabine With or Without Bevacizumab as First-Line Therapy in Treating Patients With Newly Diagnosed Stage II-IV or Recurrent Stage I Epithelial Ovarian or Fallopian Tube Cancer; NCT01081262) randomly assigned patients with mucinous carcinoma to standard paclitaxel/carboplatin chemotherapy vs capecitabine/oxaliplatin, and also to bevacizumab vs no bevacizumab. Although this trial could not be completed because of the rarity of the tumor, regimens for gastrointestinal cancer continue to be studied in mucinous carcinoma.

As for clear cell carcinoma, clinical trials looking at the use of drugs to target *ARID1A* mutations have largely been disappointing. I expect that we will eventually find more effective therapies. One area that has garnered a great deal of interest in clear cell carcinoma is immunotherapy, and we have seen reported cases of patients with clear cell carcinoma responding very dramatically to immune checkpoint inhibitors.

Regarding endometrioid carcinoma, early-grade endometrioid tumors often respond to the same anti-estrogen agents used in low-grade serous carcinoma. Higher-grade endometrioid tumors are treated with chemotherapy, much like high-grade serous carcinoma, although a great deal of variation exists in how patients respond.

Low-grade serous tumors often respond to the anti-estrogen agents that are commonly used in breast cancer, including aromatase inhibitors, tamoxifen, and fulvestrant (Faslodex, AstraZeneca). Although these agents can be effective in the frontline setting—either as hormonal monotherapy or as maintenance therapy following primary chemotherapy—they are more of a mainstay in the recurrent setting. If a low-grade serous tumor has a *KRAS* or *BRAF* mutation, a targeted agent such as a MEK inhibitor or a BRAF inhibitor can be used. Although these agents have not been approved by the US Food and Drug Administration for use in ovarian cancer, clinical trials have shown that MEK inhibitors in particular are effective in some patients with low-grade serous carcinoma. Studies are continuing to look at the use of hormonal therapies and targeted agents in low-grade serous tumors.

H&O What other treatments are being used in these rare cancers?

DG We have some retrospective and prospective data supporting the use of bevacizumab in low-grade serous, clear cell, endometrioid, and possibly mucinous carcinoma. In some cases, bevacizumab is combined with chemotherapy, as is done in high-grade serous carcinoma.

H&O What recent advances have been made in our understanding of these rare cancers?

DG In low-grade serous carcinoma, which is my main area of focus, preliminary studies recently have shown that younger patients do not fare as well as older patients. Women with low-grade serous carcinoma have a worse prognosis if they are 35 years or younger at diagnosis than if they are older than 35 years at diagnosis, which is similar to what we see in estrogen receptor–positive breast cancer.

We also have preliminary evidence that women with low-grade carcinoma whose tumors contain a *KRAS* mutation—or less commonly, a *BRAF* mutation—seem to have a better prognosis than women whose tumors are wild-type. This observation needs to be confirmed in larger studies. Studies that have looked at these well-known mutations are just scratching the surface, however. We need to continue searching for other genetic or molecular abnormalities in these tumors. Through the use of studies that employ DNA copy number, next-generation sequencing, and whole-genome sequencing, researchers are working to understand the molecular biology of these tumors.

H&O Could you describe some additional ongoing studies in rare ovarian carcinoma?

DG A couple of studies are looking at the use of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors in low-grade serous and endometrioid carcinoma. For example, a phase 2 study from the Gynecologic Oncology Group called GOG-3026 (Ribociclib and Letrozole Treatment in Ovarian Cancer; NCT03673124) is looking at ribociclib (Kisqali, Novartis) plus the aromatase inhibitor letrozole in recurrent low-grade serous carcinoma of the ovary. This combination has already been proven effective in breast cancer.

I am also involved in a pilot study to test the use of hormonal therapy as neoadjuvant treatment in low-grade serous carcinoma. This trial is combining the anti-estrogen agent fulvestrant with the CDK4/6 inhibitor abemaciclib (Verzenio, Lilly). Chemotherapy is not very effective at shrinking tumors before surgery in these patients, so we want to see if hormonal therapy will be successful.

H&O What questions should future studies address?

DG The main focus should be on treatment, because we have barely begun to identify more-effective therapies for these rare subtypes. Also, as we are recognizing more and more, a big part of clinical trials should be patient quality of life. Of course, one of the problems we face when conducting research on rare tumors is accruing enough patients for a trial.

H&O What do you wish more physicians understood regarding these rare cancers?

DG Rare tumors can be easily misdiagnosed by general pathologists. I have seen many patients with low-grade serous carcinoma who were originally diagnosed with high-grade serous carcinoma. Should any question exist regarding the diagnosis, I recommend that the pathology sample be sent to an expert gynecologic pathologist for review.

A second opinion also may be warranted when it comes to treatment. Referring your patient to somebody who specializes in rare tumors is always a good idea, even if the goal is just to get a second opinion. We have initiated a program in the last year or so at MD Anderson whereby patients with rare gynecologic tumors who are referred to us for a second opinion or for treatment are triaged to one or more physicians who specialize in rare cases. This further develops the expertise of these physicians, so future patients benefit from even more knowledge. This approach also benefits research because identifying more people with the same rare subtype of a gynecologic cancer can make clinical trials possible.

Disclosures

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Suggested Readings

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