Low grade serous ovarian cancer: moving the needle

Molly Morton, David O'Malley

Gynecologic Oncology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA

Correspondence to
Dr David O'Malley, Gynecologic Oncology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA; David.O'Malley@osumc.edu

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Low grade serous carcinoma of the ovary represents a rare subset of epithelial ovarian cancer, with markedly divergent clinical behavior than high grade serous ovarian cancers.[1–3] Patients with low grade serous ovarian carcinoma tend to be younger, and often experience repeated exposure to ineffective and toxic therapies.[1] In this updated expert consensus report by Grisham et al, recommendations for the care of patients with low grade serous ovarian carcinoma and low grade serous carcinoma of the peritoneum are detailed, with special attention to emerging biomarker-driven therapeutic options and patient centered care.[2 4] The panel provides guidance for practitioners regarding the evidence based management of low grade serous ovarian carcinoma, and provides a timely summary of ongoing efforts to enhance our understanding of this rare disease. The authors should be commended for this comprehensive, collaborative effort and impactful contribution, as well as their collective work to date in low grade serous ovarian carcinoma.

The consensus presented by Grisham et al represents the second iteration of guidelines from a working group comprised of a panel of experts on low grade serous ovarian carcinoma, focused on critical updates on clinical management, translational and clinical research, pathology, and epidemiology.[2 4] A challenge in the treatment of low grade serous ovarian carcinoma is the limited efficacy of current treatments, including cytotoxic chemotherapy. The authors emphasize that low grade serous ovarian carcinoma is a distinct rare disease and is clearly differentiated by its clinical behavior and molecular pathways when compared with high grade serous ovarian carcinoma and other epithelial ovarian cancers. This is especially important when considering regulatory processes of the orphan drug designation pathway through the US Food and Drug Administration, and regulatory hurdles in the requirements for previous therapies have to be reconsidered (platinum resistance). Novel agents and innovative treatment strategies will be key to improving outcomes, but surgery, with attempt at complete gross resection, remains a mainstay of therapy in the primary and potentially recurrent settings. The importance of a maximal effort at cytoreduction, attempting to minimize the utilization of neoadjuvant chemotherapy, was emphasized by the authors, even in cases where complete resection cannot be obtained. Importantly, utilizing the expertise of gynecologic oncologists, as well as partnering with other surgical specialties (thoracic, hepatobiliary, and urology) is essential in achieving maximal cytoreduction.

Current therapeutic strategies and active clinical trials have focused on an evolved understanding of the unique tumor biology of low grade serous ovarian carcinoma to develop more effective treatment. In contrast with high grade serous ovarian carcinoma, there are markedly reduced objective response rates to first line platinum-based chemotherapy in patients with low grade serous ovarian carcinoma, although this remains a recommended regimen by the National Comprehensive Cancer Network and European Society for Medical Oncology/European Society of Gynaecological Oncology guidelines, and is affirmed by the panelists. Hormonal therapy is an area of active research, with the majority of tumors expressing estrogen and progesterone receptors. Although biologically plausible, no study has reliably demonstrated that estrogen receptor/progesterone receptor positivity is associated with response rates to endocrine therapy, and while stable disease rates are high, objective response rates are modest.[5–7] The best available evidence supports the use of aromatase inhibitors over tamoxifen from the cohort analysis in GOG-0281/LOGS.[5] The results of NRG-GY019 (NCT04095364), the LEPRE trial (NCT05601700), and MATAO trial (NCT04111978) are awaited to determine if letrozole may replace chemotherapy in the primary treatment setting, and determine if platinum based chemotherapy still provides additional benefit when incorporated into the primary treatment paradigm. Additionally, the authors describe the need for additional imaging compared with high grade serous ovarian carcinoma in the surveillance of patients with low grade serous ovarian carcinoma. It will be important for future consensus and guideline concordant therapy to reflect the need for additional imaging, rather than biomarker testing, in the surveillance of these patients.

The panel explored current therapeutic options for recurrent disease, including cytoreductive surgery,

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clinical trial enrollment, mitogen activated extracellular signal regulated kinase (MEK) inhibitor therapy, dabrafenib+trametinib (BRAF V600E positive tumors), hormonal therapy, or chemotherapy. In the recurrent setting, responses to cytotoxic chemotherapy based on GOG0281/LOGS and MILO/ENGOT-ov11 are noted at <15%.[5 8] Mitogen activated protein kinase (MAPK) pathway alterations (KRAS, BRAF) are present in approximately 50% of low grade serous tumors and portend a favorable prognosis, and alterations in this pathway may contribute to enhanced responses to MEK inhibitors. Although evidence supports improved objective response rates to MEK inhibitor therapy in those with MAPK pathway alterations, activity is observed in those without these alterations and the panel concludes that no optimal predictive biomarker for MEK inhibitor sensitivity exists.[5 8] GOG 0281/LOGS demonstrated that MEK inhibition provides significantly improved progression free survival compared with the physician's choice standard of care therapy, signaling the potential for targeted therapy in low grade serous carcinoma.[5] Given the rarity of this tumor type and the scarcity of effective therapy, the panel concludes that clinical trial enrollment should be considered for every patient with low grade serous ovarian carcinoma, providing access to exciting agents, many of which are biomarker driven.

Several trials are actively evaluating the activity of novel therapies, including GOG-3026 (letrozole+ribociclib, NCT03673124), BOUQUET (NCT04931342), and RAMP201/ENGOT-ov60/GOG3052 (avutometinib+defactinib, NCT04325270). Importantly, for clinical trial purposes, the panel consensus states that standard definitions of platinum sensitivity do not apply to low grade serous carcinoma, and the requirement for previous platinum based therapy for trial entry should be questioned. Further, the panel affirms recommendations for germline and somatic tumor testing in cases of low grade serous carcinoma. Clearly somatic testing should be performed in all patients with advanced and recurrent disease to identify potentially actionable mutations.

Finally, the consensus guidelines provide invaluable insight into the needs of patients with low grade serous ovarian carcinoma. Special attention to treatment toxicity and its early management is detailed given prolonged exposure to active agents, with particular attention paid to MEK inhibitor therapy. Using survey results from online communities, patients express needs for accurate information, emotional support, early discussion of fertility options, financial assistance, improved management of the treatment of side effects, and a better understanding of the characteristics of the disease. With regard to clinical trial participation, most indicated that the greatest factor influencing patient participation was being asked to participate. Concerns regarding finances, travel, appointment frequency, adverse events, and additional associated costs provide opportunities to better support patients who choose to enroll in clinical trials. These perspectives represent an essential step towards patient centered care in the field of gynecologic oncology, and their inclusion in these consensus guidelines demonstrates the commitment of the authors to these principles and should be commended.

In summary, the expert consensus guidelines presented by Grisham et al describe management strategies for low grade serous carcinoma, including novel therapeutic approaches utilizing an enhanced understanding of tumor biology. While surgical cytoreduction remains the mainstay of treatment, data from a number of clinical trials utilizing new treatment strategies are forthcoming and poised to alter the current treatment landscape for this disease. The inclusion of patient perspectives and timely management of toxicity in these guidelines should be applauded, and represents a commitment to patient centered care, quality of life, and clinical trial enrollment.

Twitter Molly Morton @mollyymorton

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