Low-grade serous carcinoma of the ovary or peritoneum

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Over the past decade, the strategy for clinical trial design in making progress against epithelial cancers of the ovary/peritoneum/fallopian tube has changed dramatically. The NRG (GOG) Rare Tumor Committee has been a leader in this transformation. No longer does ‘one size fit all’. Rather, separate clinical trials for rare subtypes have been developed and, in some cases, completed. An enhanced understanding of their pathologic diagnosis, molecular biology, and clinical behavior has galvanized this change. Low-grade serous carcinoma may occur de novo or following an initial diagnosis of serous tumor of low malignant potential. It is characterized by young age at diagnosis, relative chemoresistance, and prolonged survival compared with high-grade serous carcinoma. Historically, conventional chemotherapy has demonstrated very limited activity in this subtype. Hormonal therapy may provide benefit in this subtype. Preclinical studies have identified and elucidated genes and pathways—MAP kinase pathway, IGF1-R, the angiogenesis pathway, and possibly, the PI3K/AKT/mTOR pathway in low-grade serous carcinoma. To date, clinical evidence supports the activity of MEK and BRAF inhibitors and bevacizumab. Further pursuit of targeted therapy trials is clearly warranted.

**Key words:** ovarian cancer, low-grade serous carcinoma, targeted agents, chemotherapy, hormonal therapy

**introduction**

Historically, all women with epithelial ovarian cancer or primary peritoneal cancer, regardless of their tumor’s histologic subtype, have been treated similarly within single-institution, investigator-initiated, or cooperative group trials. However, within the past few years, based on our enhanced understanding of the heterogeneity of ovarian or peritoneal cancer related to refinement of pathologic criteria, elucidation of molecular biology, and reports of clinical behavior, separate clinical trials for specific subtypes have been developed and conducted. One of the leaders in this transformation has been the Rare Tumor Committee of the Gynecologic Oncology Group (GOG), which was established in 2005. In 2014, the GOG merged with other cooperative groups to form the new NRG Oncology cooperative group. Since 2005, several clinical trials for rare ovarian/peritoneal cancer subtypes—clear cell carcinomas, mucinous carcinomas, and low-grade serous carcinomas, and non-epithelial tumors—have been activated. This review will focus on one of those cell subtypes—low-grade serous carcinoma.

**pathology**

After over a decade of experience using a binary grading system rather than that of the International Federation of Gynecology and Obstetrics (FIGO) for serous carcinoma, the findings were reported in 2004 [1]. This seemingly trivial proposal for replacement of the time-honored three-tier grading system (grade 1–3) with the two-tier system (low grade and high grade) actually galvanized the medical community to seriously study the significant differences between low- and high-grade serous carcinoma in terms of molecular biology and clinical behavior.

The binary grading system for serous carcinoma is based primarily on the assessment of nuclear atypia with the mitotic count used as a secondary criterion [1]. In comparison with the FIGO grading system, all but one of the 36 FIGO grade 1 cases were classified as low grade, and all of the 11 FIGO grade 3 cases were classified as high grade. However, of the 53 FIGO grade 2 cases, 15 were classified as low grade and 38 as high grade. The results of this study simply underscore the confusion surrounding the FIGO grade 2 category and why converting to a two-tier grading system makes so much sense. A further important finding of this study was the coexistence of serous tumor of low malignant potential and low-grade serous carcinoma in 60% of cases. Subsequent reports only further strengthened the observation that the FIGO grading system is flawed and the wisdom surrounding dichotomization of the grading system for serous carcinoma [2–8]. For instance, in the study of Bodurka et al., there was no difference in the clinical outcome in patients with grade 2 or 3 tumors in multivariate analysis [6].

**molecular biology**

Molecular and genetic investigations over the past decade have brought the biology of low-grade serous carcinoma into much sharper focus. Based on available evidence, we currently believe that low-grade serous carcinoma may arise following an initial diagnosis of serous tumor of low malignant potential or de novo [9–14]. In concordance with these observations, genomic profiling studies have demonstrated that low-grade serous carcinomas
SEGREGATE FROM HIGH-GRADE SEROUS CARCINOMAS BUT ARE SIMILAR TO SEROUS TUMORS OF LOW MALIGNANT POTENTIAL [15, 16]. COMPARED WITH HIGH-GRADE SEROUS CARCINOMAS, LOW-GRADE SEROUS CARCINOMAS HAVE A MUCH LOWER FREQUENCY OF P53 MUTATIONS OR P53 EXPRESSION [17, 18], GREATER EXPRESSION OF ESTROGEN RECEPTOR (ER) AND PROGESTERONE RECEPTOR (PR) [19], GREATER EXPRESSION OF PAX2 [20], OVEREXPRESSION OF ANTERIOR GRADIENT HOMOLOG 3 (AGR3) [21], AND OVEREXPRESSION OF INSULIN-LIKE GROWTH FACTOR 1 (IGF-1) [22]. ALTHOUGH GERMINE BRCA MUTATIONS OCCUR IN A RELATIVELY HIGH PROPORTION OF WOMEN WITH HIGH-GRADE SEROUS CARCINOMA, LOW-GRADE SEROUS CARCINOMA DOES NOT APPEAR TO BE PART OF THE HEREDITARY BREAST–OVARIAN CANCER SYNDROME [23, 24].

THE WEIGHT OF EVIDENCE FURTHER SUGGESTS THAT THE MITOGEN-ACTIVATED PROTEIN KINASE (MAPK) PATHWAY PLAYS A PROMINENT ROLE IN THE PATHOGENESIS OF BOTH SEROUS TUMORS OF LOW MALIGNANT POTENTIAL AND LOW-GRADE SEROUS CARCINOMAS. IN 2003, SINGER ET AL. [25] REPORTED THEIR STUDY OF 182 OVARIAN TUMORS, INCLUDING 51 SEROUS TUMORS OF LOW MALIGNANT POTENTIAL AND 21 LOW-GRADE SEROUS CARCINOMAS. KRAS MUTATIONS WERE REPORTED IN 33% OF SEROUS TUMORS OF LOW MALIGNANT POTENTIAL AND IN 35% OF LOW-GRADE SEROUS CARCINOMAS, AND BRAF MUTATIONS WERE FOUND IN 28% AND 33%, RESPECTIVELY. SUBSEQUENT REPORTS OF LOW-GRADE SEROUS CARCINOMA, HOWEVER, SEEMED TO CONFIRM A 20%–40% FREQUENCY OF KRAS MUTATIONS BUT A MUCH LOWER FREQUENCY OF BRAF MUTATIONS—2%–6% [26, 27]. BASED ON THEIR FINDINGS, WONG ET AL. [26] CONCLUDED THAT THE LOW FREQUENCY OF BRAF MUTATIONS IN ADVANCED STAGE LOW-GRADE SEROUS CARCINOMAS COMPARED WITH SEROUS TUMORS OF LOW MALIGNANT POTENTIAL SUGGESTED THAT THE FORMER ARE MORE LIKELY DERIVED FROM SEROUS TUMORS OF LOW MALIGNANT POTENTIAL WITHOUT BRAF MUTATIONS. A MORE RECENT STUDY APPEARED TO CONFIRM THESE OBSERVATIONS [28]. IN OTHER WORDS, THE PRESENCE OF A BRAF MUTATION IN AN ADVANCED STAGE SEROUS TUMOR OF LOW MALIGNANT POTENTIAL MAY SOMEHOW PROTECT AGAINST THE DEVELOPMENT OF A SUBSEQUENT LOW-GRADE SEROUS CARCINOMA. IN A STUDY OF 23 PATIENTS WITH AN ORIGINAL DIAGNOSIS OF SEROUS TUMOR OF LOW MALIGNANT POTENTIAL WHO SUBSEQUENTLY RECURRED WITH LOW-GRADE SEROUS CARCINOMA, PATIENTS WITH KRAS G12V MUTATIONS HAD SHORTER SURVIVAL TIMES THAN THOSE WITH EITHER KRAS G12D, WILD-TYPE, OR RARE KRAS VARIANTS (HR = 4.77; P = 0.023) [29]. IN A STUDY OF OVER 1200 CASES OF OVARIAN CANCER, EMANUEL ET AL. [30] IDENTIFIED 102 CASES OF SEROUS CARCINOMAS WITH ADJACENT REGIONS OF SEROUS TUMOR OF LOW MALIGNANT POTENTIAL, AND THEY FOUND A 9% FREQUENCY OF NRAS MUTATIONS. THEY CONCLUDED THAT NRAS MAY BE AN ONCOGENIC DRIVER IN SEROUS CARCINOMAS. ALTHOUGH CUMULATIVE EVIDENCE STRONGLY IMPLICATES ACTIVATION OF THE MAP KINASE PATHWAY IN LOW-GRADE SEROUS CARCINOMA, THE PRECISE MECHANISMS INVOLVED REMAIN SOMEWAT ELUSIVE AND REQUIRE CONTINUED STUDY (SEE BELOW).

IN ADDITION, ALTHOUGH IT APPEARS THAT ABERRATIONS OF THE PI3K/ AKT/mTOR PATHWAY ARE RELATIVELY RARE IN LOW-GRADE SEROUS CARCINOMA [31], THERE IS SOME EVIDENCE THAT DUAL BLOCKADE OF THE MAP KINASE AND PI3K/ AKT/mTOR PATHWAYS MAY BE ASSOCIATED WITH ENHANCED ACTIVITY COMPARED WITH MAP KINASE PATHWAY BLOCKADE ALONE (SEE BELOW).

TREATMENT AND CLINICAL BEHAVIOR

PRIMARY TREATMENT

SURGERY IS A MAJOR MODALITY OF TREATMENT IN LOW-GRADE SEROUS CARCINOMA, AS IT IS IN ALL HISTOLOGIC SUBTYPES. FOR MOST PATIENTS, PRIMARY SURGERY, INCLUDING SURGICAL STAGING FOR PATIENTS WITH APPARENT EARLY-STAGE DISEASE AND CYTOREDUCTIVE SURGERY FOR THOSE WITH METASTATIC DISEASE, IS THE INITIAL TREATMENT. FERTILITY-SPARING SURGERY IS AN OPTION FOR SELECTED YOUNG PATIENTS. FOR SELECTED WOMEN WITH EXTENSIVE METASTATIC DISEASE OR SIGNIFICANT CO-MORBIDITIES, NEOADJUVANT CHEMOTHERAPY WITH INTERVAL CYTOREDUCTIVE SURGERY MAY BE RECOMMENDED. IN SUCH CASES, EITHER FINE NEEDLE ASPIRATION/CORE BIOPSY OR A MINIMALLY INVASIVE SURGICAL PROCEDURE TO ESTABLISH AN ACCURATE DIAGNOSIS IS CARRIED OUT BEFORE STARTING CHEMOTHERAPY. AT THIS WRITING, SELECTION OF PATIENTS FOR NEOADJUVANT CHEMOTHERAPY REMAINS CONTROVERSIAL AND IS CONTINUING TO Evolve IN TERMS OF CRITERIA FOR SELECTION—DEMOGRAPHIC, CLINICAL, SURGICAL, ETC.

SEVERAL PROMINENT THEMES HAVE EMERGED FROM STUDIES OF THE CLINICAL COURSE OF LOW-GRADE SEROUS CARCINOMA OF THE OVARY OR PERITONEUM. IN AN ANCILLARY STUDY OF GOG PROTOCOL 182, FADER ET AL. [32] REPORTED THE DETAILS REGARDING 189 PATIENTS WITH FIGO GRADE 1 SEROUS CARCINOMA (A SURROGATE FOR LOW-GRADE SEROUS CARCINOMA). ON MULTIVARIATE ANALYSIS, ONLY RESIDUAL DISEASE STATUS FOLLOWING PRIMARY SURGERY WAS SIGNIFICANTLY ASSOCIATED WITH OVERALL SURVIVAL (OS). PATIENTS WITH MICROSCOPIC RESIDUAL DISEASE HAD A SIGNIFICANTLY LONGER MEDIAN PROGRESSION-FREE SURVIVAL (PPS) (33.2 MONTHS) AND OS (96.9 MONTHS) COMPARED WITH THOSE WITH RESIDUAL 0.1–1.0 CM DISEASE (14.7 AND 44.5 MONTHS, RESPECTIVELY) AND >1.0 CM OF RESIDUAL DISEASE (14.1 AND 42.0 MONTHS, RESPECTIVELY). THE OVERALL PATTERN OF THESE RESULTS CLOSELY RESEMBLES THAT OF EPITHELIAL OVARIAN CANCER IN GENERAL. IN A SECOND STUDY FROM THE SAME DATASET, SERUM CA 125 VALUES WERE ANALYZED [33]. ALTHOUGH PRE-TREATMENT CA 125 WAS NOT PROGNOSTIC OF THE OUTCOME, PATIENTS WITH CA 125 LEVELS THAT NORMALIZED AFTER 1–3 CYCLES OF CHEMOTHERAPY WERE 60%–64% LESS LIKELY TO EXPERIENCE DISEASE PROGRESSION WHEN COMPARED WITH THOSE WHOSE CA 125 LEVELS NEVER NORMALIZED OR NORMALIZED AFTER FOUR CYCLES (P ≤ 0.024). NORMALIZATION OF CA 125 LEVELS BEFORE THE SECOND CYCLE WAS NEGATIVELY ASSOCIATED WITH DEATH, WITH AN HR OF 0.45 (P = 0.025).

PREVIS ET AL. [34] REPORTED THE DUKExperience with 81 women with low-grade serous carcinoma of the ovary. ON MULTIVARIATE ANALYSIS, OBESITY (HR = 2.8) AND OPTIMAL TUMOR DEBULKING (HR = 0.05) WERE SIGNIFICANT PREDICTORS OF OS. ADDITIONALLY, OBESITY WAS NOT ASSOCIATED WITH WORSE DISEASE-SPECIFIC SURVIVAL, SUGGESTING THAT MORTALITY OF OBSE Vogue patients may have been attributable to other comorbidities.

IN THE INITIAL SYSTEMATIC STUDY OF 112 WOMEN WITH STAGE II–IV LOW-GRADE SEROUS CARCINOMA OF THE OVARY, MAJOR FEATURES, COMPARED WITH HISTORICAL EXPERIENCE WITH HIGH-GRADE SEROUS CARCINOMA, INCLUDED A RELATIVELY YOUNG AGE AT DIAGNOSIS (MEDIAN AGE = 43 YEARS), PROLONGED OS (MEDIAN OS = 82 MONTHS), AND RELATIVE CHEMoresistance as reflected by the surrogmate marker of persistent tumor at the completion of primary treatment (48% OF patients) [12]. AFTER ADJUSTING FOR OTHER VARIABLES, PERSISTENT DISEASE AFTER PRIMARY CHEMOTHERAPY WAS ASSOCIATED WITH A SHORTER PFS TIME (HR = 2.64; P = 0.03). THE THEME OF RELATIVE CHEMoresistance, thought to be related to the indolent nature of low-grade serous carcinoma, was subsequently also observed in reports of patients treated with neoadjuvant chemotherapy and patients with primary peritoneal low-grade serous carcinoma [14, 35]. NEVERTHELESS, PLATINUM/TAXANE CHEMOTHERAPY GENERALLY REMAINS THE STANDARD THERAPY FOR WOMEN WITH LOW-GRADE SEROUS
carcinoma until such time that it is replaced by evidence-based alternative treatment. Despite the lack of evidence demonstrating superiority of therapeutic strategies other than platinum/taxane chemotherapy as primary systemic treatment, some have already begun to substitute hormonal therapy in this setting (see below).

The updated MD Anderson experience was recently reported and included 350 women with low-grade serous carcinoma of the ovary or peritoneum [36]. This study confirmed our previous observations of the major clinical features of low-grade serous carcinoma, including relative young age at diagnosis, prolonged OS, and relative chemoresistance. In addition, patients age ≤35 years had a significantly worse outcome than those age >35 years—an observation quite similar to that of young women with luminal breast cancer—and patients with primary peritoneal carcinomas had a significantly better outcome than those with primary ovarian carcinomas.

**treatment for recurrence**

Despite the relative good prognosis of low-grade serous carcinoma, over 80% of patients with this condition will experience relapse. For selected patients, depending on several clinical factors, secondary cytoreductive surgery may be recommended. Crane et al. [37] reported their experience with 41 women with recurrent low-grade serous carcinoma who underwent secondary cytoreductive surgery. It did appear that some patients derived benefit from such a procedure; the median PFS for patients who had no gross residual tumor at completion of the surgery was 60.3 months compared with only 10.7 months for those with gross residual tumor (P = 0.008).

Systemic therapy options for salvage therapy include cytotoxic chemotherapy, hormonal therapy, or targeted agents. In a report of 58 women who received 108 separate chemotherapy regimens (‘patient-regimens’) for recurrent low-grade serous carcinoma, the response rate was 3.7% (4.9% in patients with platinum-sensitive disease and 2.1% in those with platinum-resistant disease) [38]. However, stable disease was observed in over 60% of patients. Hormonal therapy may have somewhat better efficacy for low-grade serous carcinoma. Of 64 patients who received 89 separate hormonal patient-regimens with drugs such as aromatase inhibitors, tamoxifen, and leuprolide acetate, the objective response rate was 9%, the median time to progression was 7.4 months, and over 60% of women had stable disease [39]. In addition, ER/PR expression data were available in 50 patients in this study. Patients with ER+/PR− tumors had a shorter time to progression (HR = 1.8) than patients with ER+/PR+ tumors; however, this observation approached but did not reach statistical significance (P = 0.056). Thus, hormonal therapy remains a reasonable and potentially active treatment for women with metastatic low-grade serous carcinoma.

**targeted therapy**

Given the realization that cytotoxic chemotherapy has limited activity in low-grade serous carcinoma, a search for more effective systemic therapies is warranted. As with most cancer types, investigators have principally focused on the study of targeted therapies over the past few years. Coupled with these efforts is the continued study of the molecular biology of low-grade serous carcinoma through additional basic science and translational research studies.

Based on preclinical research findings, potential genes or pathways for targeting low-grade serous carcinoma include the MAPK pathway, IGFR-1, the angiogenesis pathway, and possibly the PI3K/AKT/mTOR pathway. The MAPK signaling pathway is one of the most activated and best characterized in cancer [40]. The MAPK cascade is triggered by the binding of a ligand that ultimately leads to phosphorylation of ERK [41, 42]. Thus, MEK is a good candidate for targeted therapy, and a number of MEK inhibitors (MEKi) have been developed in the past few years [43, 44]. Preclinical studies of ovarian cancer demonstrated significant growth inhibition in cell lines with KRAS or BRAF mutations compared with cell lines with wild-type cells [45, 46]. In view of the cumulative data indicating mutations within the MAPK pathway, as discussed above, exploration of MEKi in patients with low-grade serous carcinoma was a natural progression.

In a landmark GOG phase II trial (GOG 0239), Farley et al. [27] demonstrated promising results with a MEKi, selumetinib. Fifty-two women with recurrent low-grade serous carcinoma were enrolled in this trial and treated with the MEKi, selumetinib 50 mg twice daily. The overall response rate (ORR) was 15%, with one complete response (CR) and seven partial responses (PRs). Another 65% of patients in the trial had stable disease. The median PFS was 11.0 months. The most common toxicities were gastrointestinal (13), dermatologic (9), and metabolic (7). Three patients experienced grade 4 toxicities—one each cardiac, pain, and pulmonary. Mutational analysis was conducted on formalin-fixed, paraffin-embedded (FFPE) tumor samples from 34 patients in this trial. The primary tumor accounted for 82% of the cases. In these 34 cases, there were two (6%) BRAF mutations and 14 (41%) KRAS mutations. In this study, there was no correlation between mutations of BRAF or KRAS and objective response. Subsequently, the promising results of this trial in the context of the relatively low response rates of low-grade serous carcinoma to either chemotherapeutic or hormonal agents prompted further investigations. In addition, because most of the specimens were from primary surgery and not relapse, it could be that all recurrent tumor specimens would be more predictive of response. More importantly, it is likely that we do not yet fully understand the complex circuitry of the MAPK pathway. Mechanisms other than simple common mutations, such as KRAS or BRAF, may activate the pathway. For example, in analyzing the tumor tissue from an extraordinary responder from the GOG trial, Grisham et al. [47] identified a 15-nucleotide deletion in the negative regulatory helix of the MAP2K1 gene encoding for MEK1. Functional characterization demonstrated that this mutant induced extracellular signal-regulated kinase pathway activation, promoted anchorage-independent growth and tumor formation in mice, and retained sensitivity to selumetinib. Analysis of additional low-grade serous and serous borderline tumors identified aberrations predicted to induce extracellular signal-regulated kinase pathway activation in 82% of them. In addition, as yet unpublished data from GOG 0239 suggested that higher levels of pERK expression were associated with a greater frequency of serum CA 125 response to selumetinib.

Based on the findings of GOG 0239, three second-generation phase II or III clinical trials were activated. Each of these trials
includes a different MEKi. The MILO trial (NCT01849874) is an open-label phase III protocol that randomizes patients with recurrent low-grade serous carcinoma to either chemotherapy [physician’s choice of pegylated liposomal doxorubicin (PLD), paclitaxel, or topotecan] or MEK162. A second trial (NCT01936363) has randomized phase II design and includes the MEKi, pimasertib, with either placebo or SAR245409 (a PI3K/mTOR inhibitor). GOG 0281 is a randomized phase II/III trial (NCT02101788) that has been activated through NRG Oncology. This trial includes a randomization between standard of care (physician’s choice of letrozole, tamoxifen, PLD, weekly paclitaxel, or topotecan) and MEKi monotherapy, trametinib. This trial also includes a robust translational research component, with fresh and archival FFPE tissue for next-generation sequencing and proteomics as well as cell-free DNA and pharmacokinetic studies.

As noted above, although BRAF mutations are very common in serous tumors of low malignant potential and possibly early-stage low-grade serous carcinoma, in metastatic low-grade serous carcinomas, the frequency is quite low—5%. Nevertheless, Hyman et al. [48] reported a series of 122 patients with BRAF V600-mutation non-melanoma cancers treated with the BRAF inhibitor, vemurafenib. Among the responders was a patient with metastatic low-grade serous carcinoma whose PR persisted for over 12 months.

As noted above, the angiogenesis pathway may also be a target in patients with low-grade serous carcinoma. Bidus et al. [49] reported three patients with apparent recurrent low-grade serous carcinoma (one with primary peritoneal low-grade serous carcinoma, one with ovarian low-grade serous carcinoma, and another with a mixed low-grade serous-endometrioid carcinoma) treated with bevacizumab, a monoclonal antibody against the vascular endothelial growth factor A (VEGF-A). All three patients experienced a sustained response—two PRs and one CR. Subsequently, Grisham et al. [50] reported on 17 patients with low-grade serous carcinoma of the ovary or peritoneum who received bevacizumab. Two patients were treated with single-agent bevacizumab and the others with a combination of bevacizumab and chemotherapy. Fifteen patients were evaluable for response, and six (40%) had a PR. An additional five (33.3%) had SD lasting 3 months or longer.

To date, there have been no clinical trials exploring the role of IGF1-R-targeted therapy specifically in women with low-grade serous carcinoma. Likewise, although an agent targeting the PI3K/AKT/mTOR pathway in combination with an MEKi was administered to a proportion of women on one of the three trials above (NCT01936363), the results of this trial are pending, and no AKT inhibitor, PI3K inhibitor, or mTOR inhibitor monotherapy trials specifically for patients with low-grade serous carcinoma have been developed. However, there clearly is interest in further combination trials with MEKi+, an inhibitor of the PI3K/AKT/mTOR pathway.

conclusions

Low-grade serous carcinoma may occur de novo or following a diagnosis of serous tumor of low malignant potential. It is characterized by young age at diagnosis, relative chemoresistance, and prolonged survival compared with high-grade serous carcinoma. Initial surgical treatment may occur as a primary procedure or following neoadjuvant chemotherapy in selected patients. While platinum/taxane chemotherapy remains standard as first-line systemic therapy, there is a need for studying alternative strategies. For recurrent tumor, secondary cytoreduction may provide benefit in selected patients. Options for systemic therapy management include chemotherapy, hormonal therapy, or targeted agents. The latter is focus of several ongoing and future clinical trials.

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references


