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A Solution to the Dilution: The Role for Biomarkers in Advanced Ovarian Cancer

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Summary

Reliable approaches to predict residual disease prior to primary debulking surgery have been sought to further personalize surgical approaches. Reliance on molecular biomarkers alone in a complex clinical environment is challenging and algorithms that incorporate both molecular and clinical features may need to be considered.

In this issue of *Clinical Cancer Research*, Heitz and colleagues set out to validate gene expression signatures for residual disease after primary debulking surgery (1). Historically, the standard of care for ovarian cancer was primary debulking surgery (PDS) followed by chemotherapy. Residual disease at the conclusion of PDS is among the most important prognostic factors for patient survival. While phase III clinical trials have established non-inferiority of neoadjuvant chemotherapy (NACT) with interval cytoreduction compared to PDS in terms of progression-free and overall survival, some have raised concerns that lower overall complete gross resection rates in these studies could have contributed to these findings (2, 3). Nevertheless, the overall trends reflect increasing use of NACT internationally.

Most guidelines suggest PDS if there is a high probability of debulking to <1 cm and NACT if there is high surgical risk or a low probability of debulking to <1 cm. However, accurate means of calculating such probabilities have remained elusive. Various approaches (e.g., CA125, molecular markers, imaging, and laparoscopy) have been considered for assessment of tumor burden; but, most have not been deemed ready for implementation into standard of care practices. A validated laparoscopic predictive model has been used by many groups (4), but a clinical tool to predict residual disease prior to surgery has been sought to further personalize surgical approaches.

Riester et al. identified and validated a gene expression signature (GES) to predict gross residual disease >1 cm after PDS in patients with stage III/IV high grade serous ovarian cancer (HGSOC) (5). They demonstrated that this GES could accurately predict residual disease >1 cm in 77% of cases (area under the curve [AUC] 0.76 with qRT-PCR, compared to AUC 0.65 with microarray). Protein assessment of POSTN, CXCL14, and pSMAD2/3

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predicted residual disease >1 cm in 93% of cases (AUC 0.89) (5). Similarly, Liu et al. created and validated an 11 gene GES, which predicted suboptimal debulking (residual disease >1 cm) with an AUC of 0.754 in patients with stage III/IV serous ovarian cancer (6). Tucker et al. found that FABP4 mRNA levels in the top quartile predicted visible residual disease (>0 cm) in patients with HGSOC with a positive predictive value of 86% (7).

Heitz et al. tested these gene expression signatures in their own patient population, using the German dataset from ICON7, a phase 3 multi-institutional randomized trial comparing standard chemotherapy with and without the addition of bevacizumab in ovarian cancer. They were unable to validate these GES in their population. They tested a GES based on each of the aforementioned studies, as well as The Cancer Genome Atlas molecular, an “independent de novo gene signature,” and the “total gene expression data set” using microarray analysis, with none of these resulting in an AUC >0.65. Heitz et al. theorized that a “dilutional” effect was responsible for their inability to validate these GES, suggesting that many of the cases of residual disease could be related to factors that a GES would be unable to identify, such as patient age, frailty, and infiltrative metastatic disease (1).

The study by Heitz et al. highlights some of the many complexities in biomarker development for surgical decision making in ovarian cancer. Comparing across the four studies is complicated by the different methods of analysis utilized, including microarray, qRT-PCR, and IHC. In general, the genes/pathways identified in these studies point to pro-metastatic pathways. The rates of complete gross resection can vary from one center to another and may be rooted in either the beliefs of the gynecologic oncologists and/or the skill level in carrying out highly complex surgical procedures. Whether “ultra-aggressive” measures for achieving complete gross resection have clinical impact remains a matter of debate, but such variability could nevertheless create inconsistency in applying molecular assays to a broader population of ovarian cancer patients.

With regard to the proposed “dilutional” effect from patient factors such as age and frailty, it is possible that many of these could be tested and incorporated in clinical algorithms. While frailty does appear to be an important factor, reliable and validated scoring systems are needed that can be applied broadly. Moreover, it might be feasible to account for such factors in preoperative screening/surgical clearance along with a reproducible biomarker for residual disease. With improvements in imaging modalities and development of molecular imaging probes, it is possible that better resolution could offer greater level of detail in a non-invasive fashion to aid clinical decision making.

For molecular assays, there are other variables that may also contribute to variability of results. For example, it has become clear that most solid tumors, including ovarian cancer, have substantial heterogeneity depending on site of disease. Such heterogeneity can manifest as variability in gene or protein expression and even cellular content depending on location of disease. As a result, expression or extent of specific cellular presence may vary substantially depending on whether a sample was obtained from the primary site or a specific metastatic site. Careful consideration of such heterogeneity will be important for biomarker development.

Given the multitude of patient-specific and surgeon-specific variables, a molecular approach for accurate detection of disease burden may simply not be possible. The study by Heitz et al. is important in that it nicely highlights the challenges associated with application of molecular biomarkers in a highly complex clinical environment. Ultimately, the gynecologic oncologists may have to rely only on clinical variables such as age, performance status, nutritional status, and comorbidities; and imaging to gauge obviously unresectable disease such as bulky liver parenchymal metastases, large periportal lymph nodes, significant mesenteric distortion, and extraperitoneal spread. While laparoscopic evaluation may not be needed in all cases, it may be useful in assessment of disease status in patients with suspected advanced disease who do not have contraindications for surgery. The care of women with ovarian cancer continues to improve and reliable methods for personalized surgical and medical care for these women remains an aspirational goal.

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Abbreviations

PDS	Primary debulking surgery
NACT	Neoadjuvant chemotherapy
GES	Gene expression signature
HGSOC	High-grade serous ovarian cancer
AUC	Area under the curve

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