Editorial

Can molecular subtyping be used to triage women with advanced ovarian cancer to Primary Debulking Surgery or Neoadjuvant Chemotherapy?

Standard treatment for newly diagnosed stage III-IV high-grade serous ovarian carcinoma (HGSOC) includes both debulking surgery and platinum-based combination chemotherapy. However, deciding between surgical or chemical debulking as the initial approach is steeped in clinical nuance and often hotly debated. Primary debulking surgery (PDS) can be associated with significant morbidity and even mortality due to the extent and complexity of the procedures that may be required to achieve optimal debulking status (R0). Furthermore, postoperative complications can necessitate complex and/or prolonged postoperative care. In cases where optimal debulking cannot be achieved, the patient is unlikely to benefit from surgery and may actually be harmed due to delays in initiating systemic chemotherapy. Neoadjuvant chemotherapy (NACT) with interval debulking surgery (IDS) is an alternative approach for patients with advanced stage ovarian cancer and has been shown to have equivalent outcomes in randomized controlled clinical trials [1,2]. While there is less post-operative morbidity with this approach, long term survival may be negatively impacted by the sheer number of tumor clones present at the start of treatment, which increases the likelihood of chemoresistance in the future. Patient selection, tumor biology and surgical skill are often called into question when evaluating PDS and NACT approaches side by side. At this time, there are no definitive laboratory or imaging tests or guidelines to assist physicians and patients in making the decision between PDS or NACT. A preoperative objective predictor would have great clinical importance. So, can determining molecular characteristics and tumor subtype from a needle or core biopsy aid in selecting the best first approach to tumor cytoreduction for women with advanced ovarian cancer?

In this issue, Torres et al. present data demonstrating that the molecular subtype of the cancer may have utility in objectively predicting the surgical risks associated with PDS in patients with advanced HGSOC [3]. Specifically, they investigated the mesenchymal molecular subtype as a contributor to the risk of postoperative morbidity in 329 patients with stage III-IV HGSOC. Among the 4 molecular subtypes (immunoreactive, mesenchymal, differentiated, and proliferative) originally identified by gene expression clustering analysis in the TCGA project [4], the mesenchymal subtype has been consistently associated with poorer clinical outcomes, including suboptimal debulking and worse overall survival [5–11]. The current study shows that patients with the mesenchymal subtype (which made up 28% of the HGSOC cohort) were more than twice as likely to have a severe postoperative complication (defined as 30-day morbidity or mortality) when compared to the non-mesenchymal subtype [31.5% vs 14.8%, OR 2.66, 95% CI 1.51-4.69]. This association remained significant in a multivariable model that included ASA score, preoperative albumin and surgical complexity. Previous

reports by this group demonstrated that patients with the mesenchymal subtype are also more likely to require complex surgery due to upper abdominal and bulky disease [9,12]. Notably, the current study shows that the mesenchymal subtype independently predicts postoperative morbidity even when adjusted for surgical complexity.

Expression profile subtyping is now widely accepted as a useful technology for disease stratification. However, its clinical utility and cost effectiveness remain debatable. Should multidisciplinary tumor boards consisting of oncologists, surgeons, pathologists and radiologists also include "omics" experts to better guide diagnosis, staging, prognosis, and the management of patient's disease? If a patient is fit for surgery and her imaging indicates potentially resectable disease but her percutaneous omental biopsy demonstrates tumor of the mesenchymal subtype, is NACT/IDS the better therapeutic approach to achieve remission, avoid unnecessary morbidity and increase quality of life? Before we can begin answering this question, it is necessary to better understand the underlying biology of the mesenchymal subtype.

Parsing out the biology of the mesenchymal subtype is the focus of a second study by the same research group published in this issue [13]. The study builds on previous pathology findings demonstrating that mesenchymal subtype HGSOC exhibit extensive desmoplastic reaction, matrix remodeling, and infiltration with cancer-associated fibroblasts [11]. Previous transcriptomic findings consistently indicated that many of the most highly expressed genes specific for the mesenchymal subtype were expressed by stromal cells rather than the epithelial cancer cells [14–18]. In the current study, primary and metastatic HGSOC of mesenchymal subtype were isolated from 15 patients undergoing PDS, and the expression patterns of 8 stromal proteins (ACTA2, COL5A1, COL11A1, FAP, POSTN, VCAN, ZEB1, and phosphorylated SMAD) were determined by immunohistochemistry (IHC). Overall, the results showed that these 8 proteins were primarily, if not exclusively, expressed by stromal cells and that the expression patterns for most proteins were similar between matched primary tumors and metastases.

This second study provides us with a clinically applicable platform where expression of these 8 stromal proteins could be quantified. IHC is a standard technique that can be automated to quantify protein expression intensity and patterns for clinical use. Could these 8 proteins be used for molecular subtyping based on preoperative biopsy and identify patients with mesenchymal subtype HGSOC to help us triage patients for PDT or NACT? Unfortunately, the study did not include samples of matched tumors from proliferative, differentiated or immunoreactive molecular subtypes and was not sufficiently powered to correlate protein expression with surgical outcomes. A potential impact of

sampling error based on a core biopsy would also need to be evaluated. Further study is needed to determine the specificity of this 8-protein overexpression pattern to distinguish primary tumors of the mesenchymal subtype from the other molecular subtypes. This study also showed that mesenchymal characteristics do not change significantly between primary and metastatic tumors, but we cannot assume that metastases from primary tumors of the immunoreactive, differentiated, and proliferative subtypes retain their subtype classification at all sites. A recent report by another group of investigators demonstrated that metastatic sites were typically of the mesenchymal subtype irrespective of the subtype of the primary tumor [19]. The distinction between primary and metastatic tumors will be important in deciding what biopsy site is best for determining the molecular subtype for patient stratification and prediction of surgical outcomes and risk. The samples used by Zhang et al. for the protein expression analysis were from an ovarian tumor mass resected at PDS. But if preoperative determination of molecular subtype is going to be clinically applicable to direct triage between PDS and NACT, prospective testing of biopsy samples from different sites, validation, and further development of this multiplex IHC testing is needed.

These studies raise another important question: what is the biological mechanism by which mesenchymal-type stroma in ovarian cancer leads to postoperative morbidity? Torres and colleagues suggest that patient frailty may play a role but we believe there may be an alternative explanation, at least in some cases. While host factors are very important in determining outcomes, we'd suggest that the tumor-recruited stromal component may be driving the invasiveness and aggressive tumor biology observed. The mesenchymal subtype is primarily determined by characteristics of tumor stroma, and it is possible that primary HGSOC of the mesenchymal subtype recruits cancer-associated stroma from metastatic sites. Omental stroma, in particular, has been shown to increase the "fitness" of metastatic tumors [20,21]. Omental stroma recruited by the primary ovarian tumor could directly increase the tumor's aggressiveness and destructive effects on the host, resulting in multiple adverse effects such as suboptimal debulking, postoperative morbidity, and poor overall survival, all of which have been associated with mesenchymal subtype HGSOC [5–11,18]. It is also possible that primary tumors of the mesenchymal subtype are actually metastases from primary peritoneal carcinoma sites or represent clones of metastatic tumors that have re-seeded the ovary along with stroma that has been acquired at metastatic sites in the peritoneal cavity. This hypothesis is supported by an earlier study from this group, which demonstrated that primary HGSOC of the mesenchymal subtype are almost always associated with upper abdominal metastases and miliary disease [9,12].

These novel lines of investigation contribute to our understanding of ovarian cancer biology and the role of cancer stroma as a significant contributor to tumor progression. They also point to new therapeutic targets and biomarkers for patient stratification. Practically, these studies have the potential to lead to a much needed objective preoperative predictor of debulking status.

Conflict of Interest

The authors have nothing to disclose related to this article.

Author Contributions

Both authors contributed to the writing and final approval of the manuscript.

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Sandra Orsulic*
Department of Obstetrics and Gynecology and Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Department of Obstetrics and Gynecology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA
Corresponding author at: Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA, 90048, USA.
E-mail address: sandra.orsulic@cshs.org

Beth Y. Karlan
Department of Obstetrics and Gynecology and Jonsson Comprehensive Cancer Center, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA