Dilution of Molecular–Pathologic Gene Signatures by Medically Associated Factors Might Prevent Prediction of Resection Status After Debunking Surgery in Patients With Advanced Ovarian Cancer

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ABSTRACT

Purpose: Predicting surgical outcome could improve individualizing treatment strategies for patients with advanced ovarian cancer. It has been suggested earlier that gene expression signatures (GES) might harbor the potential to predict surgical outcome.

Experimental Design: Data derived from high-grade serous tumor tissue of FIGO stage IIIC/IV patients of AGO-OVAR11 trial were used to generate a transcriptome profiling. Previously identified molecular signatures were tested. A theoretical model was implemented to evaluate the impact of medically associated factors for residual disease (RD) on the performance of GES that predicts RD status.

Results: A total of 266 patients met inclusion criteria, of those, 39.1% underwent complete resection. Previously reported GES did not predict RD in this cohort. Similarly, The Cancer Genome Atlas molecular subtypes, an independent de novo signature and the total gene expression dataset using all 21,000 genes were not able to predict RD status. Medical reasons for RD were identified as potential limiting factors that impact the ability to use GES to predict RD. In a center with high complete resection rates, a GES which would perfectly predict tumor biological RD would have a performance of only AUC 0.83, due to reasons other than tumor biology.

Conclusions: Previously identified GES cannot be generalized. Medically associated factors for RD may be the main obstacle to predict surgical outcome in an all-comer population of patients with advanced ovarian cancer. If biomarkers derived from tumor tissue are used to predict outcome of patients with cancer, selection bias should be focused on to prevent overestimation of the power of such a biomarker.

See related commentary by Handley and Sood, p. 9

Introduction

Ovarian cancer is the most lethal gynecologic malignancy, with an estimated 22,240 new cases and 13,980 deaths expected for 2019 (1). At current time, there is no effective screening strategy and thus most of these malignancies present with widespread intra-abdominal disease. Primary debulking surgery (PDS) followed by platinum- and taxane-based chemotherapy has been the standard treatment over the last decades (2). Although advances in treating primary advanced disease have improved long-term survival, complete resection to no gross residual disease (RD) at PDS remains one of the most important prognostic factors in advanced-stage ovarian carcinoma. In contrast to patients with macroscopically complete resection, patients left with 0.1–1 cm and >1 cm of RD have substantially lower overall survival rates (3). Large variation in success of obtaining optimal cytoreduction exists. By implementing quality insurance programs and surgical education, complete resection rates of up to 70% in advanced disease are reached in experienced centers, however, even there at least one third that do not achieve an optimal surgical outcome (4, 5), including...
more than 10% of patients who experience either large RD exceeding 1 cm or died postoperatively of complications or did not start chemotherapy for any other reason (6). At least the latter subgroup of patients is candidate for alternative treatment strategies as neoadjuvant chemotherapy (7, 8). Many models have attempted to preoperatively define this subgroup prospectively. Alletti and colleagues and Thrall and colleagues focused mainly on patient-associated factors as age, performance status, and comorbidities (9, 10) to identify patients who might not benefit from standard strategies with PDS. Others tried to predict RD by using clinical variables as preoperative CA-125 levels, radiological imaging, laparoscopic assessment, and physical examinations, none of them being reliably enough to be incorporated into general practice so far (9). Another approach is evaluating the predictive power of intrinsic tumor biology. Subsequently, numerous studies have investigated molecular markers from tumor tissue to predict postoperative RD. First, Riester and colleagues (11) developed a gene signature made up of 11 genes that was associated with or without bevacizumab. All patients underwent primary debulking surgery. Of the 533 patients enrolled in this trial, 266 were noted to have stage III or IV high-grade serous ovarian cancer with appropriate gene expression array data. Specialized central pathologic review had been undertaken and reported previously (15). Residual disease was determined by the treating surgeon at the end of surgery (16). Patients were then stratified into following categories: (i) those with no macroscopic residual disease after cytoreductive surgery (RD0), and those with any macroscopic residual disease (RD > 0); (ii) those with macroscopic disease ≤1 cm (RD ≤ 1), and those with residual disease >1 cm (RD > 1).

Methods and data on whole-genome cDNA-mediated annealing, selection, extension, and ligation (DASL) microarray analysis were published previously (17). For the purposes of this article, in silico analyses were undertaken. For transcriptome profiling, the Illumina Whole-Genome DASL HT Assay with the HumanRef-8 Bead Chip (catalog no. DA-905-1096) corresponding to 29K gene transcripts or 21K unique genes was used. Criteria for exclusion were median stress >1 (0 samples were excluded) and median dfbeta >1 (35 samples were excluded). Determination of molecular classification was blinded to demographic and clinical information. Briefly, each given sample was assigned to a subtype according to similarity between observed expression and per-subtype expression centroids learned from The Cancer Genome Atlas. In both TCGA and our own de novo clustering studies, consensus clustering approach was used to ensure that only stable clustering solutions were kept after multiple reruns.

Molecular gene expression signature selection and previously identified gene signatures

Our set of predictors included a molecular subtype developed on this dataset and three previously published gene expression debulking signatures of meta-analyses by Riester and colleagues (11), Liu and colleagues (12), and Tucker and colleagues (13). Supplementary Table S1 summarizes the most important information on patient selection and methods used in all resource data of the, respective, meta-analyses and a comparison to the data used from AGO-OVAR 11/ICON7. The Riester and colleagues study included seven genes (POSTN, CXCL14, FAP, NUAK1, PITCH1, TGFBR2, and TNAIP6). The Liu and colleagues study included 11 genes (POSTN, FAP, TIMP3, COL11A1, EDNRA, CT5K, COL5A2, TNAIP6, TMEM158, MMP11, and CXCL14), and the Tucker and colleagues study included two genes (FABP4 and ADH1B). The genes identified as molecular signatures in these studies were taken and were mapped to probes in our gene expression data. We also considered previously reported four molecular subtypes obtained from unsupervised learning method Non-negative Matrix Factorization (17, 18), as potential predictors for debulking. The four molecular subtypes consortium are encoded as three binary variables, indicating the molecular subtype membership for each tissue sample.

De novo gene signature discovery

To derive de novo gene signatures from the data, we applied the generalized local learning (GLL) algorithm to discover potential molecular signatures for debulking status (19–21). Markov Boundary induction algorithm has the property of identifying parsimonious set of variables that are predictively optimal under broad assumptions. Its application on datasets collected from various domains, including gene expression datasets, has resulted in highly accurate predictive models. We embed GLL in a cross-validation framework (see section below) to ensure unbiased variable selection. In addition, we also tested the
Predictive modeling

The above five gene sets were used to construct predictive models with RD as the target of interest. We tested two ways of defining residue disease: (i) RD0 versus RD > 0 and (ii) RD ≤ 1 versus RD > 1. To construct the predictive models, we employed the following three classification methods: logistic regression, support vector machine with polynomial kernel, and random forest. We chose logistic regression because it was applied in the articles of Riester and colleagues and Liu and colleagues, and we chose support vector machine and random forest because these two methods have the capacity to capture complex relationships and have internal safeguard against overfitting in high-dimensional small-sample size situation like this dataset. Furthermore, these methods have shown success in similar tasks, such as prognosis of various types of cancer using gene expression data. We embed all modeling procedure in a 10-fold cross-validation to ensure unbiased performance estimation. The 10-fold cross-validation was repeated 5-times with different random splitting to account for splitting variation. We used ROC AUC as the metric for predictive performance. AUC ranges from 0 to 1. An AUC of 1 indicate perfect predictivity and AUC of 0.5 indicate the prediction is no better than random.

Theoretical model for the inability to validate debulking signatures

We developed a theoretical model explaining the inability to predict RD using a molecular debulking signature. The model was built of the fact that there might be tumor–biologic reasons and medically associated reasons for RD. Tumor localization inform the distinction between tumor–biologic and medically associated reason. Data of ICON7 (AGO-OVAR 11) could not be used for this purpose due to surgical heterogeneity, low complete resection rates, missing information about tumor localization of RD, and missing presurgical medical data. Instead, clinical data from a recently published article of the ESGO Center of Excellence for Ovarian Cancer Surgery (https://www.esgo.org/explore/esgo-credited itio) and tertiary gyneco-oncologic clinic “Kliniken Essen-Mitte” (“KEM”) were used (6). The team of KEM has repeatedly documented its experience in surgery for advanced ovarian cancer (23, 24), with increasing complete resection rates due to specialization and implementation of a quality insurance program (25). All KEM patients gave written consent, that their data might be used for scientific analyses. Figure 1 displays the definition of medically associated and tumor–biologic reasons for RD to characterize the proportion of tumor–biologic versus medically associated. Supplementary 1 describes the detailed methodologic approach to quantify the effect of medically associated reason on the performance of predictive models for RD outcome.

Results

Outcomes

Patient characteristics for 266 eligible patients with high-grade serous ovarian cancer and available molecular expression array data are presented in Table 1. For the first set of analyses, patients were divided on the basis of size of residual disease (RD). A total of 104 (39.1%) patients were found to have microscopic RD (RD0), and 162 (60.9%) patients had macroscopic RD (RD > 0). For the second analysis, 188 patients (70.7%) were classified as having RD ≤ 1 and 78 (29.3%) patients were classified as having had suboptimal debulking (RD > 1).

Gene signatures

The genes identified as molecular signatures in previous studies were taken and were mapped to probes in our gene expression data. Liu and colleagues reported a 11 gene signature, which mapped to 16 probes in our gene expression data. Riester and colleagues reported a seven gene signature, which mapped to 12 probes in our gene expression data. Finally, Tucker and colleagues reported a two gene signature, which mapped to two probes in our gene expression data. GLL discovered 126 ± 10 probes as potentially predictive of debulking status for RD0 versus RD > 0, and 117 ± 10 probes as potentially predictive of debulking status for RD ≤ 1 versus RD > 1 over five repeated 10-fold cross-validation.

Predictive performance

The predictive performance of using the six molecular signature and three classification algorithms for RD0 versus RD > 0 prediction is shown in Supplementary Table S2. The predictive performance averaged across five repeated 10-fold cross-validation runs for all combinations of molecular signature and classification algorithms shows poor performance. No combinations resulted in AUC > 0.60. Predictive performances using the six molecular signature and three classification algorithms for RD ≤ 1 versus RD > 1 prediction is shown in Supplementary Table S3. The predictive performance averaged across five repeated 10-fold cross-validation runs for all combinations of molecular signature and classification algorithms show poor performance. No combinations resulted in AUC > 0.65.

Theoretical model for the inability to validate debulking signatures

To explain the negative validation of previously described debulking signatures and the inability to find any new signature, the impact of probable medically associated reasons influencing the performance of hypothetical biomarkers predicting tumor–biologic features was undertaken. Figure 1 displays the definition of medically associated and tumor–biologic factors. A total of 19.9% of patients with incomplete resection (6.6% of all patients) were defined to have medically associated and 82.7% (27.3% of all patients) were defined to have tumor–biologic reasons for RD.

In Fig. 2, a hypothetical molecular signature with perfect ability (100%) to distinguish between patients with RD0 and RD > 0 and RD ≤ 1 and RD > 1, respectively, due to tumor–biologic reasons, was assumed. Number of tumor–biologic and medically associated cases was derived from the KEM data. As shown in Fig. 1, tumor–biologic factors responsible for RD are present in a maximum of 27.3% of all patients undergoing primary debulking surgery. Hence, the power of a perfect biomarker for tumor biology RD > 0 and tumor–biologic suboptimal debulking RD > 1 is reduced to a maximum of AUC = 0.83 and AUC = 0.71, respectively. Assuming the same ratio of tumor–biologic versus medically associated reasons, even if the previously published biomarker by Riester and colleagues, Liu and colleagues, and Tucker and colleagues would have had a predictive power of 100% to distinguish between RD0 and RD > 0 or RD ≤ 1 and RD > 1 for the tumor–biologic cases, the predictive performances for these signatures would be reduced to an AUC of smaller than 0.65.
Discussion

Our study tried to answer a question of urgent clinical need, namely developing a reproducible biology-driven model for identification of patients who might not benefit from upfront surgery of advanced ovarian cancer and subsequently should be scheduled for alternative treatment strategies. Previously published gene expression signatures for predicting residual disease (RD) in patients with advanced ovarian cancer undergoing primary debulking surgery (PDS) were analyzed (11–13). In addition, de novo gene signatures were developed using state-of-the-art feature selection methods in a data-driven manner. Using these different sets of gene signatures, we were unable to predict resection status, whether this was classified by zero RD or RD < 1 cm. There was not one combination of model or signature that approached a clinically adequate level, and in most cases, the predictive value was close to 0.5, which is essentially chance. This contrasts with above mentioned studies that had logistic regression values of around 0.7. A value of >0.7 suggests predictive capabilities of the respective gene signatures, however, even at 0.7, the clinical utility has been questioned (26).

It is thought, that patients undergoing complete resection have a favorable prognosis compared with patients with RD (3, 27), but subgroup analyses of the EORTC trial emphasize that the prognosis for patients with complete resection after PDS is better than for patients undergoing interval debulking surgery (IDS) (8). Hence, the preferred approach for the vast majority of patients with advanced ovarian cancer is PDS (28, 29). Nevertheless, patients in which there is RD left after PDS might have had an added benefit from upfront chemotherapy and IDS. At this point, there is not enough evidence in literature to
support the role of any presurgical diagnostic tool to predict surgical outcome in advanced ovarian cancer. Therefore, a tumor molecular selection process via direct tumor analysis would be of great value. In that process, a minimally invasive biopsy would be analyzed with respect to the gene signature that could potentially predict postoperative debulking status. Patients in whom complete resection would be deemed feasible would undergo PDS and patients in whom the signature would predict postsurgical RD would undergo neoadjuvant chemotherapy and IDS.

Reasons why complete resection is not feasible to obtain in all patients are diverse. Miliary carcinomatosis on the small bowel is the most frequent reason for RD in the KEM series and in up to 90% of patients with RD in surveys among gynecologic oncologists in Australia/New Zealand and the United States (30, 31). Large overlapping might indicate a common tumor–biologic reason for miliary carcinomatosis on the small bowel and recent data showed that miliary carcinomatosis was more frequently associated with the mesenchymal subtype in high-grade serous ovarian cancer (32). However, the pattern of RD between centers with large experience in debulking surgery and less experienced centers is tremendous, for example, diaphragmatic metastases and bulky para-aortic lymph nodes were no reasons for RD in the KEM series (6). In comparison, metastatic disease at the diaphragm was the reason for RD in 74% and 51% and bulky para-aortic lymph node metastases in 12% and 23% of cases in the above-mentioned surveys (30, 31). These data indicate that there is a certain relativity of the surgical limitations, which barley indicate a biological background for the cause of RD and might be described as medically associated reasons for RD. In addition to these surgical discrepancies, further medically associated reasons might lead to RD. If surgery must be prematurely ceased because of complications during surgery, RD must be left not due to tumor–biologic, but due to medically associated reasons. Moreover, there might be residual tumors which have grown at sites, which rather not display a different tumor biology, but are localized at structures, where the disease had more time to grow ("lead-time biologic factors"). For example, tumor nesting up against/infiltrating the pancreas, the stomach, or lymph nodes at the truncus coeliacus. These tumors are potentially resectable, however due to large anticipated risks for severe postsurgical complications, these tumors cannot be removed.

A main issue with the evaluation of molecular debulking signatures in an all-comer cohort of patients undergoing PDS might be the dilution of tumor–biologic reasons for RD with medically associated reasons. In KEM patients, a molecular signature with a 100% power to distinguish between patients with and without postoperative RD, the AUC would decrease to a maximum of 0.83 due to medically associated reasons. Moreover, it was shown that the power of a molecular signature further decreased as the frequency of RD due to medically associated factors increased. If the complete resection rate was lower (hence the frequency of medically associated reasons increased), as published by Riester and colleagues, Liu and colleagues, and Tucker and colleagues, and the herein described AGO-OVAR 11, the AUC of this perfect signature would further decrease to an AUC ranging between 0.5 and 0.6.

### Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>RDO</th>
<th>RD &gt; 0</th>
<th>RD &lt; 1</th>
<th>RD &gt; 1</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>(n = 104; %)</td>
<td>(n = 162; %)</td>
<td>(n = 188; %)</td>
<td>(n = 78; %)</td>
<td>(N = 266; %)</td>
</tr>
<tr>
<td>ECOG</td>
<td>56.7 (11.3); 38–72</td>
<td>60.8 (10.4); 45–73</td>
<td>58 (11.1); 39–73</td>
<td>63 (9.6); 48–75</td>
<td>59 (10.9); 39–73</td>
</tr>
<tr>
<td>FIGO</td>
<td>0</td>
<td>46 (44.2)</td>
<td>70 (43.2)</td>
<td>81 (43.1)</td>
<td>35 (44.9)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>46 (44.2)</td>
<td>80 (49.4)</td>
<td>87 (46.3)</td>
<td>39 (50.0)</td>
</tr>
<tr>
<td></td>
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<td>12 (7.4)</td>
<td>20 (10.6)</td>
<td>4 (5.1)</td>
</tr>
<tr>
<td>IIC</td>
<td>85 (81.7)</td>
<td>123 (75.9)</td>
<td>153 (81.4)</td>
<td>55 (70.5)</td>
<td>208 (78.2)</td>
</tr>
<tr>
<td>IV</td>
<td>19 (18.3)</td>
<td>39 (24.1)</td>
<td>35 (18.6)</td>
<td>23 (29.5)</td>
<td>58 (21.8)</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG: Eastern Cooperative Oncology Group performance Status; FIGO: Fédération Internationale de Gynécologie et d’ Obstétrique.

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![Figure 2](https://example.com/figure2.png)

**Theoretical model describing the predictive power (AUC) of a perfect debulking signature, which would be able to predict RD (RD > 0; blue lines) and suboptimal debulking (RD > 1, black lines) 100% correctly for tumor–biologic cases, based on KEM data. n−, the number of cases with RD > 0 or RD < 1 due to tumor–biologic; n+, the number of cases with RD0 or RD < 1 due to tumor–biologic. Δ is the number of medically associated cases. As the ratio of Δ/n− increases, the ability to discover debulking signature decreases when n−/n+ ratio is fixed. The solid line represents n−/n+ ratio derived from KEM. The dashed curves represent when n−/n+ is doubled and the dotted curves represent when n−/n+ is halved; worst case AUC were derived according to published resection rates of the respective articles and data of this analysis (Liu and colleagues, 817 patients included and 294 patients RD > 1, Tucker and colleagues, 491 patients included and 378 patients RD > 1; and Riester and colleagues, included 1,273 patients and 672 patients RD > 1).**
On the basis of the inability to replicate earlier published data (11–13) and the possible explanation of this failure (medically associated reasons), we are not confident at this point in the ability of these gene signatures to accurately predict which patients should forgo primary cytoreduction. To overcome the above-mentioned shortcomings, direct molecular–biologic analyses of tumors with RD due to tumor–biologic factors compared with tumors without RD should be undertaken.

Resection status of patients included to the AGO-OVAR 11 trial was determined by the surgeon at the end of debulking surgery, which might be prone to bias and thus might be a limitation of this study. We have shown recently that 22% of patients without RD determined by the surgeon at the end of a debulking surgery had evaluable disease at a baseline CT scan. However, analyses could not prove the hypothesis that the reason for these discrepant findings was due to surgical misclassification, but rather a question of timing of the baseline CT scan after debulking surgery (33). The comparison of results from different molecular–genetic platforms and biostatistical models might lead to different results displaying a limitation of this study. A comparison of materials and methods of the resource studies of the included meta-analyses of Riester and colleagues, Liu and colleagues, and Tucker and colleagues and AGO-OVAR 11 ICON 7 are shown in Supplementary Table S1. Moreover, the hypothetical statistical model is an explanation on how medically associated variables may substantially reduce the predictability of RD. However, if different sites of residual disease (e.g., military carcinosis on the bowel and bulky nonresectable lymph nodes) are associated with different molecular features, as emphasized in this paper, it is not sufficiently studied until now. Further studies are needed to verify this with real measurements. These studies need to measure both tumor–biologic variables (e.g., gene expressions), and medically associated variables (e.g., tumor localization or surgical complications). Nevertheless, the article has several strengths. Data and samples were retrieved from a pivotal trial and tumors underwent histopathologic review. Biostatistical analyses were undertaken with very recent methods and to our knowledge all previously published data on this topic were included for validation.

In summary, we were not able to find a tumor expression–based marker to predict postsurgical resection status in a well-characterized cohort of patients with advanced high-grade serous ovarian cancer. Moreover, results of previously published articles describing tumor expression–based marker to predict resection in advanced ovarian cancer could not be validated. However, we showed that dilution of potentially detectable tumor–biologic factors by medically associated factors might be of importance when looking after molecular-based predictors in an all-comer cohort of patients.

Disclosure of Potential Conflicts of Interest

F. Heitz reports receiving speakers bureau honoraria from AstraZeneca and Clovis; is an unpaid consultant/advisory board member for Roche and Tesaro; and reports receiving other remuneration from AstraZeneca, Roche, Tesaro, Clovis, and PharmaMar. U. Canzler reports receiving speakers bureau honoraria from Roche, AstraZeneca, and Lilly, and is an unpaid consultant/advisory board member for Roche and AstraZeneca. B. Ataseven reports receiving speakers bureau honoraria from Roche, Tesaro, Clovis, AstraZeneca, and Celgene, and is an unpaid consultant/advisory board member for Roche and Amgen. R. Kimmig reports receiving speakers bureau honoraria from Medtronic, Riester, Roche, Prostrakan, Intuitive Surgical, Teva, and CMB. C. Kruzeder is an unpaid consultant/advisory board member for Roche, AstraZeneca, PharmaMar, and Tesaro, and reports receiving other remuneration from Astra. E.I. Braicu is an unpaid consultant/advisory board member for Roche Pharma, AstraZeneca, MSD, Clovis, Tesaro, and Incyte. P. Harter is an employee/paid consultant for Roche. No potential conflicts of interest were disclosed by the other authors.

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): F. Heitz, S. Kommoss, A. Grandelis, A. du Bois

Study supervision: F. Hilpert, A. du Bois

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References


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