Prognostic factors in ovarian cancer: how close are we to a complete picture?

Ovarian cancer is the fourth most common cause of cancer-related death in women, but is the most lethal of the gynaecological malignancies with 30–40% overall survival at 5 years [1]. This is in part because the majority of patients with ovarian cancer present with advanced disease, and treatment options at presentation are confined to a combination of debulking surgery and platinum-based chemotherapy, which are only partially effective [2]. Consequently, almost all patients with advanced disease ultimately relapse and die of their disease. Advances in the management of these patients are therefore urgently required.

Prognostic factors are defined as phenotypes which correlate with overall survival. In general prognostic factors reflect the intrinsic biology of a tumour (e.g. histological subtype, grade), disease extent (e.g. stage) and/or the capacity of a patient to cope with the morbidity associated with the tumour and treatment (e.g. performance status). As well as these pretreatment factors, others which may impact on outcome include the treatment received by a patient (e.g. optimal surgical cytoreduction, platinum-based chemotherapy), and the effect of treatment on the tumour (e.g. complete response) or the patient (e.g. myelosuppression).

As clinical tools, prognostic factors can potentially help in individualising treatment for patients. In properly staged early disease (stage Ia/b), patients have a better prognosis and the benefits of adjuvant chemotherapy may be confined to those with adverse features (e.g. histological subtype or grade) [3]. In this context a prognostic factor with a good positive or negative predictive value for individual patients, would be useful in deciding which patients should receive chemotherapy and those for whom the toxicity was not justified. In contrast, in advanced disease, the majority of patients benefit from paclitaxel–carboplatin chemotherapy and debulking surgery. As there are no established alternatives for patients with either good or poor prognosis, pretreatment prognostic stratification has little influence on clinical management [2]. Instead, pretreatment markers predictive of response or resistance to individual cytotoxic drugs would be more useful in this context for treatment selection.

As research tools, prognostic factors can help identify subgroups of patients with especially poor prognosis and alert us to the need to develop alternative treatment strategies for these patients, while in clinical trials prognostic factors are used to balance patients between treatment arms to minimise the risk of confounding.

Prognostic factor studies can also provide useful insights into tumour biology. One example is breast cancer, in which identification of tumour-derived molecular markers associated with a good or poor outcome, such as estrogen receptor and Her2 status in breast cancer, has had an impact in clinical management [4]. In the case of Her2 this information has led to the development of effective anti-Her2 targeted therapies such as Herceptin [5]. In ovarian cancer pretreatment prognostic factors have proved harder to identify. EGFR is frequently over-expressed and a prognostic factor in some studies; this has led to clinical trials of EGFR inhibitors in ovarian cancer [6].

Established prognostic factors in ovarian cancer are age, stage, histology, grade, volume of ascites, performance status, extent of residual disease following debulking surgery and findings at second-look laparotomy [7,8]. In view of the simplicity of assessing most of the currently established prognostic factors, the utility of new prognostic markers in clinical practice lies in the additional information they provide once existing prognostic factors have been considered.

CA125 was first identified in 1981, and is one of the most extensively studied and useful molecular markers in ovarian cancer [9]. CA125 is expressed by over 80% of ovarian cancers, and levels at presentation correlate with the risk of malignancy, stage of disease and histology [10]. In addition changes in CA125 levels can be used to predict response to chemotherapy, while changes during follow-up CA125 can predict relapse with a lead time of approximately 60 days [10].

It is therefore not surprising that several different CA125 indices have also been extensively evaluated for their prognostic ability. These include CA125 levels at presentation, following initial debulking surgery, prior to the second or third cycle of chemotherapy, half-life during chemotherapy, at the end of chemotherapy prior to second look laparotomy, and at relapse [10]. However, none has found a role as yet in clinical practice. The main reasons for this are: the small and retrospective nature of the majority of these studies, the lack of prospective confirmatory studies, and most importantly the inability of the results of these indices to be applied to individual patients with sufficient predictive value to justify changes in management [11,12].

The study by Crawford and Peace reported in this journal describes the apparent prognostic value of nadir CA125 within the normal range, at the end of first-line chemotherapy [13]. This information if reliable could certainly be useful in stratifying patients in clinical trials of maintenance or relapse therapy, and the authors should be congratulated on bringing this to our attention.

The ability of CA125 at the end of first-line chemotherapy to convey useful clinical information in ovarian cancer was
first reported by Gallion et al. in 1992 [14]. They observed a higher rate (92%) of residual disease in patients with a CA125 of 20–35 U/ml at second-look laparotomy compared to only 49% in patients with a CA125 less than 20 U/ml. These findings were subsequently confirmed by three other studies [15–17]. Together these studies suggest that CA125 even in the normal range is able to reflect tumour burden.

However, all of these studies are relatively small, retrospective, and included patients heterogeneous with respect to baseline prognostic factors and/or treatment received. More importantly, the inclusion of information on known prognostic factors in the generation of the final prognostic model is variable. In the current report the only variables reported to have been considered in model development were nadir CA125, CA125 at the time of the third cycle of chemotherapy and whether the patient received a taxane or not. The lack of information on known prognostic variables and their relationship to the nadir CA125 in this study makes it very difficult to assess the true importance of the findings reported here. This is highlighted by the fact that six of 38 patients in group A had CA125 values less than 10 U/ml at the start of treatment suggesting that this group may have included a high proportion of stage I patients who have a better prognosis relative to the other groups. Furthermore response to chemotherapy is another important prognostic factor in ovarian cancer. The rising CA125 levels in one patient in group B and 2 patients in group C suggests progressive disease and highlights the fact that the groups were unbalanced with respect to response to chemotherapy.

Nevertheless, the fundamental premise being proposed by the authors is a reasonable one, and it should be the subject of further investigation and confirmation in an appropriately powered prospective study.

Over the last 5 years at least 234 papers have been published on prognostic factors in ovarian cancer, yet no new prognostic factor (including p53, Her2, EGFR and MDR) has so far fulfilled all the criteria for acceptance into clinical or research practice in ovarian cancer [18]. This is partly because a number of studies, while demonstrating independent prognostic value for the factor under study, do not adequately account for the effect of known prognostic factors in the statistical analysis [19]. A second reason is the limited clinical utility of the information provided by the prognostic factor [11, 12]. A third reason is that measurements of single markers may be unable to capture sufficient prognostic information to be clinically useful, and instead multiple factors may need to be measured simultaneously to predict prognosis in ovarian cancer [18].

One solution to this problem is offered by recent developments in proteomics and microarray-based expression profiling technologies, which enables thousands of molecular markers to be measured simultaneously. In a recent study using oligonucleotide arrays, the authors identified a 115 gene expression signature with independent prognostic value while controlling for other prognostic factors such as age, stage and grade, and debulking status in 68 patients with ovarian cancer [20]. While small and in need of validation, this study provides a glimpse of the potential of these techniques.

In order to harness the opportunity offered by these new technologies, we need to adopt a more critical and systematic approach to the evaluation of prognostic factors in ovarian cancer, emphasising the need for statistical validity of the analyses performed, the reproducibility of the results in independent datasets, and most importantly the identification of prognostic factors that are likely to have practical utility in clinical practice and/or research.

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References


