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Comment on 'External multicentre validation of a nomogram predicting the risk of relapse in patients with borderline ovarian tumours'

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Sir,

We read with interest the paper by Bendifallah *et al*, 2013 on the validation of our previous nomogram (Obermair *et al*, 2013) to estimate the risk of recurrence after surgery for Borderline Ovarian Tumours (BOT) and we congratulate the authors on their work.

A diagnosis of BOT is typically established only postoperatively and many women diagnosed with BOT are in their childbearing years. Although most BOT patients will expect excellent outcomes, a small proportion of women will recur. Prediction of relapse is critical. Patients with remotely low risk of relapse can be discharged from regular follow-up. By contrast, patients at high risk of relapse may benefit from extended surgery or regular, lifelong follow-up because recurrences may develop late after surgery (Silva *et al*, 2006).

Our nomogram was the first attempt to quantify a patient's individual risk of relapse and included covariates from readily available clinical, biological and pathological characteristics. We made every attempt to create a representative sample and therefore included all consecutive patients from six gynaecological cancer centres. Hence, almost 80% of patients in our group were classified stage 1.

The French group of clinicians abstracted information from 314 patients from two French institutions between 1980 and 2008. To validate our nomogram, they repeated our study using identical covariates. However, their patient sample was distinctly different to ours. Stage 2, 3 and 4 was almost five times as common in the French study than in ours. The pre-operative median serum CA125 was more than double as high in the French paper than in ours ($77.6\,U\,ml^{-1}$ *vs* $36\,U\,ml^{-1}$). Expectedly, relapses developed in 5.5% *vs* 29.9% (Bendifallah *et al*, 2013).

After discussions with the French authors, it became clear that pathologists at those two French institutions regularly review high-risk BOT cases referred from other institutions. It seems that those cases were included in the reporting of this series, thus resulting in a very significant over-representation of high-risk cases.

While the Australian series reported the outcomes of a representative sample of all BOT, the French cohort was not representative of all BOT cases but provided an over-representation of high-risk patients.

Although both samples overlap to a degree, the French cohort was not a comparable patient cohort and therefore was not suited to validate the Australian cohort. Both samples were profoundly different in regards to patients' characteristics and outcomes. A comparison of those two samples should have excluded samples from external review to level the field.

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Response to 'Comment on external multicentre validation of a nomogram predicting the risk of relapse in patients with borderline ovarian tumours'

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Sir,

We would like to thank Dr Obermair (Obermair, 2014) for the comments regarding our recent article (Bendifallah *et al*, 2013). Although the postoperative Obermair's nomogram (Obermair *et al*, 2013) was based on the common evidence-based high-risk factors and constitute a valuable contribution for improving health care for women with borderline ovarian tumours (BOT), we demonstrated that the tool showed limitations in its generalisability to a new and independent French population.

Theoretically, the published nomogram offers the advantage of condensing the high heterogeneity of the disease into a simple and easily interpretable format to guide the decision-making process towards the most adapted treatment options or follow-up strategies.

The comments of Dr Obermair suggest that the proper question to ask is how to study the generalisability, clinical utility and level of complexity of the published tool. As previously reported, we were unable to confirm the validity of the nomogram due to differences in the epidemiological and surgical characteristics and histological patterns between the French cohort and the Australian series. We highlighted that the relatively low incidence of patients with stage II–IV in the Obermair *et al* cohort is a potential cause of underestimating the relapse rate, and therefore reciprocally a potential cause of overestimating that rate into the French cohort (Bendifallah *et al*, 2013).

Secondarily, we also underlined that the low rate of BOT stage I in our cohort (45% *versus* 80%) in contrast to the prevalence of classical BOTs could be explained by the fact that the two institutions that participated in the study are reference centres (Bendifallah *et al*, 2013). In comparison, both samples were profoundly different with regard to patients' characteristics and outcomes.

Nevertheless, this fact does not represent a limitation to validate the published nomogram. The French cohort was representative of all BOT cases treated at the two reference centres, which represents an illustration of the real practice scenario.

The predictive accuracy studied with our external validation set represents the gold standard technique. Indeed that external validation aims to address the accuracy of a model in patients from a different but plausibly related population, which may be defined as a selected study population representing the underlying disease domain (Iasonos *et al*, 2008).

The French physicians should ensure that the model is applicable both in terms of clinical relevancy and statistical accuracy before using it as a guide in the decision-making process. To achieve this level of evidence, the model should predict accurately which patients will and will not reach the end point (discrimination), demonstrate maximal correlation between actual and predicted values (calibration), should be accurate consistently when applied to different data sets (validation), be easy to use (level of complexity) and applicable to heterogeneous novel populations with the same accuracy (generalisability) (Iasonos *et al*, 2008).

To conclude, our intention is to promote individualised predictive approach with evidence-based results of its relevancy.

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Comment on 'Existing prognostic models, but not neutrophil-to-lymphocyte ratio, are prognostic in malignant mesothelioma'

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Sir,

We feel compelled to comment on the article of Meniawy *et al* (2013) to provide perspective on the value of the neutrophil to lymphocyte ratio (NLR) as a prognostic indicator in patients with malignant pleural mesothelioma (MPM). The Western Australia-based authors of this article have concluded from their analysis that the NLR did not provide prognostic value, whereas the Cancer and Leukemia Group B (CALGB) and European Organisation for Research and Treatment of Cancer (EORTC) prognostic guides did.

However, there are some flaws in the data that have not been adequately acknowledged and that might have had a major impact on the conclusions. The principal flaw was that although intended to be an analysis of 369 consecutive patients presenting to a single treatment centre, this number was reduced by 95 (26%) based on failure to meet fairly arbitrarily defined inclusion criteria of: availability of a full blood count within 90 days of diagnosis; cytologically or histologically confirmed diagnosis of MPM; absence of concurrent haematological malignancy and duration of follow-up >90 days. A majority of patients (64) were excluded on the basis of missing laboratory data (unspecified as to which). There was no attempt to compare the characteristics of those excluded with those included to determine comparability of populations. In addition, of the remaining 274 patients, 169 (46% of initial) were treated with chemotherapy, whereas 105 (28%) received no systemic chemotherapy. In spite of 28% of patients receiving no treatment at all, the median survival for the entire group was 13.3 months with a median of 15.3 months for the chemotherapy group. These data appear to show unusually good overall survivals and are suggestive of selection bias, possibly caused by the exclusion of the 95 patients. In our original study in consecutive patients receiving systemic chemotherapy for MPM (Kao *et al*, 2010), the median survival was very similar to that reported by Vogelzang *et al* (2003) in their phase III study that compared pemetrexed and cisplatin with cisplatin alone.

The findings of Meniawy and colleagues are also contradictory to the findings of other investigators in regard to the prognostic significance of NLR in MPM and numerous investigators in other tumour types (Cedres *et al*, 2012, 2013; Pinato *et al*, 2012; Guthrie *et al*, 2013; Paramanathan *et al*, 2014); however, the contradictory nature of their own findings was not adequately highlighted or explanation attempted. We have recently presented the outcomes of prognostic factors in a large cohort of patients ($n=913$) based on the clinical and laboratory data extracted from the records of the Dust Diseases Board of New South Wales (NSW), where median survival of patients was 10 months (Linton *et al*, 2013). In this large population-based study including $>90\%$ of the NSW patients seeking compensation from 2002 to 2009, NLR>5 was again found to be an independent poor prognostic factor (HR$=1.21$; CI: 1.02–1.44; $P=0.03$) in multivariate analysis (624 patients in the model), along with non-epithelial histology, age >70 years, male gender, stage III/IV, platelet count $\geqslant 400$, haemoglobin $>1\,\mathrm{g\,dl^{-1}}$ decrease, negative calretinin staining in tumour specimen, not receiving pemetrexed chemotherapy and not receiving extrapleural pneumonectomy (EPP). Although the clinical factors were not in the final multivariate model, performance status was indirectly assessed in the model by including patients who received chemotherapy and EPP.

In addition, we felt that the interesting observation of the significant predictive value of normalisation of NLR after one cycle of chemotherapy was brushed over in the article. This confirmatory finding after our initial article (Kao *et al*, 2010), along with the recent study demonstrating normalisation of NLR (<5) predicting for a survival benefit of 7 months in a series of 118 patients participating in phase I trials (Pinato *et al*, 2014), suggests that prospective validation of NLR is warranted.

Finally, there appears to be a misconception that we were seeking a universal prognostic marker that could guide treatment outcomes for all. The series investigated by us confirm that determination of the NLR is a relatively simple way to assess prognosis in certain groups of patients with MPM; however, (ongoing) prospective validation will teach us how to properly use this parameter in clinical practice.

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