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

A Obermair\*,1

<sup>1</sup>Research Gynaecological Oncology, Queensland Centre for Gynaecological Cancer, Royal Brisbane & Women's Hospital, 6th Floor Ned Hanlon Building, Brisbane, Queensland 4029, Australia

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).

\*Correspondence: Professor A Obermair; Email: Obermair@powerup.com.au Published online 21 January 2014

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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.

### REFERENCES

Bendifallah S, Uzan C, Fauvet R, Morice P, Darai E (2013) External multicentre validation of a nomogram predicting the risk of relapse in patients with borderline ovarian tumours. *Br J Cancer* **109**: 2774–2777.

Obermair A, Tang A, Kondalsamy-Chennakesavan S, Ngan H, Zusterzeel P, Quinn M, Carter J, Leung Y, Janda M (2013) Nomogram to predict the probability of relapse in patients diagnosed with borderline ovarian tumors. *Int J Gynecol Cancer* 23: 264–267.

Silva EG, Gershenson DM, Malpica A, Deavers M (2006) The recurrence and the overall survival rates of ovarian serous borderline neoplasms with noninvasive implants is time dependent. Am J Surg Pathol 30: 1367, 1371

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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'

S Bendifallah\*,1,2 and E Darai<sup>1,3</sup>

<sup>1</sup>Department of Obstetrics and Gynaecology, Hôpital Tenon, Assistance Publique des Hôpitaux de Paris, Université Pierre et Marie Curie, Paris 6, Institut Universitaire de Cancérologie, Paris, France; <sup>2</sup>INSERM UMR\_S 707, 'Epidemiology, Information Systems, Modeling', University Pierre and Marie Curie, Paris, France and <sup>3</sup>INSERM UMR S 938, Université Pierre et Marie Curie, Paris, France

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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#### REFERENCES

Bendifallah S, Uzan C, Fauvet R, Morice P, Darai E (2013) External multicentre validation of a nomogram predicting the risk of relapse in patients with borderline ovarian tumours. *Br J Cancer* 109: 2774–2777.

Iasonos A, Schrag D, Raj GV, Panageas KS (2008) How to build and interpret a nomogram for cancer prognosis. *J Clin Oncol* 26: 1364–1370.

\*Correspondence: Dr S Bendifallah; E-mail: sofiane.bendifallah@yahoo.fr Published online 22 April 2014

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Obermair A (2014) Comment on 'External multicentre validation of a nomogram predicting the risk of relapse in patients with borderline ovarian tumours'. *Br J Cancer* 111: 2375.

Obermair A, Tang A, Kondalsamy-Chennakesavan S, Ngan H, Zusterzeel P, Quinn M, Carter J, Leung Y, Janda M (2013) Nomogram to predict the probability of relapse in patients diagnosed with borderline ovarian tumors. *Int J Gynecol Cancer* 23: 264–267.



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

S C-H Kao\*,1,2, N van Zandwijk<sup>1,3</sup> and S Clarke<sup>3,4</sup>

<sup>1</sup>Asbestos Diseases Research Institute, Sydney, New South Wales, Australia; <sup>2</sup>Department of Medical Oncology, Chris O'Brien Lifehouse, Sydney, New South Wales, Australia; <sup>3</sup>Faculty of Medicine, University of Sydney, Sydney, New South Wales, Australia and <sup>4</sup>Department of Medical Oncology, Royal North Shore Hospital, Sydney, New South Wales, Australia

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 ≥400, haemoglobin >1 g dl<sup>-1</sup> 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.

\*Correspondence: Dr SC-H Kao; E-mail: steven.kao@lh.org.au Published online 8 April 2014

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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.

### REFERENCES

Cedres S, Montero M, Martinez P, Martinez A, Rodriguez-Freixinos V, Torrejon D, Gabaldon A, Salcedo M, Ramon Y, Cajal S, Felip E (2012) Exploratory analysis of activation of PTEN-PI3K pathway and downstream proteins in malignant pleural mesothelioma (MPM). Lung Cancer 77: 192–198.

Cedres S, Montero M, Zamora E, Martinez A, Martinez P, Farinas L, Navarro A, Torrejon D, Gabaldon A, Ramon Y, Cajal S, Felip E (2013) Expression of Wilms' tumor gene (WT1) is associated with survival in malignant pleural mesothelioma. *Clin Transl Oncol*; e-pub ahead of print 10 December 2013; doi:10.1007/s12094-013-1146-6.

Guthrie G, Charles K, Roxburgh C, Horgan P, McMillan D, Clarke S (2013) The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. *CritRev Oncol Hematol* 88: 219–230.

Kao S, Pavlakis N, Harvie R, Vardy J, Boyer M, van Zandwijk N, Clarke S (2010) High blood neutrophil-to-lymphocyte ratio is an indicator of poor prognosis in malignant mesothelioma patients undergoing systemic therapy. Clin Cancer Res 16: 5805–5813.

Linton A, Pavlakis N, Kao S, Clarke S, Vardy J, van Zandwijk N (2013) Disease an patient characteristics related to survival in a large population-based cohort of patients with malignant pleural mesothelioma (MPM). J Thorac Oncol 8(S2): S311–S312.

Meniawy T, Creaney J, Lake R, Nowak A (2013) Existing models, but not neutrophil-to-lymphocyte ratio, are prognostic in malignant mesothelioma. Br J Cancer 109: 1813–1820.

Paramanathan A, Saxena A, Morris D (2014) A systematic review and meta-analysis on the impact of pre-operative neutrophil lymphocyte ratio on long term outcomes after curative intent resection of solid tumours. Surg Oncol 23(1): 31–39.

Pinato D, Mauri F, Ramakrishnan R, Wahab L, Lloyd T, Sharma R (2012) Inflammation-based prognostic indices in malignant pleural mesothelioma. *J Thorac Oncol* 7: 587–594.

Pinato D, Stavraka C, Flynn M, Forster M, O'Cathail S, Seckl M, Kristeleit R, Olmos D, Turnbull S, Blagden S (2014) An inflammation based score can optimize the selection of patients with advanced cancer considered for early phase clinical trials. PLoS One 9(1): e83279.

Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, Gatzemeier U, Boyer M, Emri S, Manegold C, Niyikiza C, Paoletti P (2003) Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 21: 2636–2644.



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