Reviewer’s report

Title: A predictive model of thyroid malignancy using clinical, biochemical and sonographic parameters for patients in a multi-center setting

Version: 0 Date: 25 May 2017

Reviewer: Nigel Glynn

Reviewer's report:

I was pleased to review this clinical research paper in which the authors report the results of a retrospective study assessing the performance of a clinical risk score for the prediction of malignancy in thyroid nodules. The data in clearly presented and the results are discussed in a balanced fashion.

General points:

Fine needle aspiration is, internationally, the diagnostic tool of choice for evaluating the malignant potential of thyroid nodules. While FNA is not perfect or fool-proof, a benign-appearing cytology has a very high negative predictive power for malignancy - well exceeding 90%. In this context, FNA will avoid the need for surgery in a large number of patients. In this study, across four tertiary referral centres, it seems that FNA was not performed. The authors state that this was due to patient compliance and lack of operator expertise. This seems unlikely if the study centres are truly tertiary. If there was a planned protocol for evaluation of nodules that did not involve FNA then the manuscript should be amended to explain this approach.

The predictive tool devised by the authors will be compared to FNA and while it offers advantages (e.g. non-invasive) its sensitivity is clearly lower than FNA. Can the authors predict how many patients would have avoided an unnecessary surgery if they had prospectively applied their model? Also, can they describe the cohort of patients who would have had a false negative result for malignancy using the prediction algorithm?

Specific Points:

Assay details, particularly for anti-thyroglobulin antibodies, should be described in more detail. There may be considerable assay variation across different platforms. Also, is the degree of elevation of the anti-body titre predictive of malignant potential? Could it be considered as a continuous variable rather than a categorical one?
Was the diameter of the nodule taken from US readings or the pathology specimen? The latter measurement is usually slightly smaller.

What was the range for nodule size? Does the study include microcarcinoma? If so, these should be presented and considered separately.

More details about the patient cohort would augment the paper. Did they all present with a clinically apparent nodule or were they incidentally detected? What was the duration of symptoms? Any pre-existing risk factor for thyroid cancer?

The authors suggest that thyroid inflammation may be the link between the elevation of anti-Tg antibodies in the serum and malignancy risk. Was this apparent on the histology specimen? What was the concordance between anti-Tg positivity and lymphocytic thyroiditis on histology?

More details on the stage of thyroid cancer among those with a malignant nodule would be useful.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

No

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

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