

Doctoral Thesis - Opponent's report

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Title of thesis: THE CLINICAL RELEVANCE OF BIOMARKERS FOR AGGRESSION ASSESSMENT AND PROGNOSIS IN NON-SMALL CELL LUNG

This study is focused on a current illness, frequent and deadly: Non-Small cell lung cancer that is one of the most important issues in Oncology nowadays. Low survival in lung cancer is due to a late diagnosis and explains the needs in parameters that can help in the early diagnosis, diagnosis, prognosis and therapy monitoring. Tumor markers may be useful in these purposes but there are not any tumor marker totally accepted in this malignancy. To evaluate an important panel of tumor marker and their comparative clinical performance is an open issue in lung cancer. The author include the most used tumor markers in this malignancy as CEA, CYFRA or SCC and compare the results with other similar tumor markers available as other cytokeratins (TPA or TPS) or other non usual tumor markers but that may introduce new information about the tumor behaviour as metaloproteases, VEGF or cytokines. In summary the author follow the recommendations of the European Group on Tumor markers that new tumor markers may be compared with the usual tumor markers to know the benefits of their introduction in clinical routine.

Characteristics of the work and documentation

Aims of the study

They are clearly expressed in several areas, including the most important questions in patients with operable NSCLC and also were answered in the thesis

Introduction

The introduction is brief but clearly shows the current status of lung cancer.

Theoretical part:

It is an exhaustive review about the most important aspects of lung cancer, from the incidence of this disease to clinical and therapeutic aspects. It is also updated, including recent ideas and publications about lung cancer screening that may be important to increase survival in the future.

Tumor marker are widely evaluated indicating their possible clinical applications and clearly indicating the problems to use them in clinical practice, and the discrepancies according to the author consulted. The problems in the use of conventional tumor markers as well as the lack of a clear panel of tumor markers clearly suggest that are necessities studies to clarify the use, justifying this recent study.

Patients and Methods

Methodologies and patients characteristics, including inclusion criteria are clearly explained. Patients object of this study are convenient for the objectives previously expressed and the diagnostic criteria, clinical data and follow-up are adequate. My only concern is the low number of patients included in the control group. This group is

important to decide cut-offs, and this cut-offs will be used to decide sensitivity and specificity, the possible relationship to clinical factors (tumor stage, tumor size, etc) or their prognostic value. It would be important to increase the number of patients in the control group, as well as to include the most frequent diseases in which the differential diagnosis with lung cancer is important. However, results obtained, and expressed in the study, are similar to other publications about the use of tumor markers and justify the conclusions.

The Author evaluates a high number of tumor markers and parameters related to the presence of a malignancy. Techniques and methodologies are well reported and are reproducible. Statistical analysis is adequate to response the questions indicated in the aims of this study.

Results

This chapter is subdivided in different sections according to the different objectives or clinical situations in lung cancer. To evaluate 22 parameters according to the most important factors related to this malignancy is difficult, and explain the high number of tables used in this study. However the author describes the results in detail and they are easily followed in the different tables and figures. These results are in agreement in relation to the tumor markers more used. However are some discrepancies, difficult to understand as for example with CEA, one of the tumor marker most used. Author does not find utility in diagnosis or relation to tumor stage, in contradiction with other publications. By contrast other results as for example the relationship between CEA and histological type or SCC mainly in squamous are totally logical. Author suggests in the discussion that this lack of sensitivity may be related to the early stages of the majority of patients.

Discussion

Discussion is exhaustive and complete, comparing the experimental data with other publications and explaining the correlations or discrepancies according their experience. The 22 evaluated parameters and the correlation between them explain the great effort in this part. The only negative comment is that with the wide experience, the author could indicate more clearly what are the most useful tumor markers and what are the advantages with respect to each other, especially when compared several markers of similar characteristics, for example cytokeratins. The evaluation of 4 cytokeratins is expensive and this study show the evaluation of all them in the same patients, and with this information, it will be interesting to know what is the author's opinion about them: use only one? Which one is the best?

Conclusions

The evaluation of a high number of parameters in different clinical situations, explain that the number of conclusions is high. However the most important findings generated for this study are clearly and satisfactory summarized. Relevant data is the improvement of the knowledge of the most important clinical applications of the classical tumor markers and their possible relationship to the most important clinical prognostic factors, to explain these utilities.

Likewise author shows the possible clinical applications in diagnosis and prognosis of some biomarkers not frequently studied in serum as for example, metalloproteases or VCAM-1 and PAI-1.

Comments and questions

This is an outstanding work, being one of the most extensive tumor marker panel evaluation in non-small cell lung cancer. The study was well designed, with correct objectives, well performed and analyzed and the discussion is clear and extensive. In summary this is an excellent study.

Minor comments:

- 1) All information provided by this study indicate that the author is an expert in all these tumor markers in non-small cell lung cancer, and I would like to know what are the markers that suggests to use in routine practice and why? Which is the best combination?
- 2) ROC curves are an interesting tool to compare different tumor markers in the same population, as the author did. However my personal opinion is that ROC curves have also limitations. The use of ROC curves to decide cut-points had the problem that this information is mainly useful in the studied population, but may be not the same in other population (different benign diseases, false positive results, etc), for this reason it is very important the control group. For example in your work, you found different cut-offs for different tumor markers (CEA, SCC, TPA, TPS...) in different clinical situations (tables 33, 39). In summary I know that the majority of researchers suggest the use of ROC curve for evaluating cut-offs, sensitivity and specificity, but often different cut-off in different populations are observed and it is difficult to compare results from different groups or obtain clinical information. What is the author opinion about the use of ROC curve? What is the best system to decide the cut-off for tumor markers?

Conclusion

Marketa Prazakova, MD did an excellent work, extensive, well done, that answer all questions indicated in the objectives and with clear information about the use of tumor markers in lung cancer. For this reason my opinion is that Marketa Prazakova, MD has fulfilled all requirements for a doctoral thesis. I recommend that it be awarded after the successful defence of the academic title Doctor – PhD.

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