Reviewer’s report

Title: Adrenocortical cancer: mortality, hormone secretion, proliferation and urine steroids - Experience from a single centre spanning three decades

Version: 0 Date: 26 Jan 2016

Reviewer: Matthias Kroiss

Reviewer's report:

In this paper, the authors report on the outcome of 50 patients treated at their Institution for ACC.

The paper has the particular merit to include data on urinary Steroid profiling.

Overall, the paper is written in an acceptable style and the conclusions are well supported by the results. I strongly support that the authors clearly state the limitations, where applicable, of their work. It may be perceived as a disadvantage that the paper covers an overly long period of time rendering treatment regimens and Management difficult to compare.

I have a few comments to improve the paper:

- in the abstract, I would include the number of patients in each tumor stage and provide their prognosis to make this more meaningful

- p 3 l 10: weight loss at present is seldomly found in ACC patients, many patients in contrast present with pain or abdominal discomfort

- p 3 l 22: Mitotane has

- p 3 l 39 ff: Here citations are not completely correct. The lymph node dissection does not refer to repeat surgery but to the primary Intervention
- p 4 l 24ff: The citations provided here may be perceived as outdated but I admit that there has been published little re LC-MS in urine for ACC. Maybe rephrase.

- p 5 l 4: and other occurrences throughout the paper: etiocholanolone would be correct

- p 5 l 44: Proliferation index is the preferred term

- p 5 l 50ff: how was catecholamine excess defined?

- p 6 l 5: why was survival calculated from time of surgery? Should be from date of diagnosis. If unavailable, please comment.

- p 6 l 10: rephrase sentence "As well as . . ."

- p 6: disease specific death should be given as a term for the Primary end Point since the description of the methods suggests this and not all cause

- p 6: the paper has the shortcoming of not providing multivariate analyses. This may be linked to unavailability of suitable software (Graph Pad does not provide this function), however some obvious clinical parameters may be accounted for and lead to different results (e.g. Ki67 <-> stage; age might be reasonable to include as well; this is also true at other instances throughout the manuscript.

- p 7 l 7: it is very unusual to have two patients with NF1 in a series who both develop ACC. This should be commented on.

- p 7 l 51: the fact that two patients are reported to have pheochromocytoma at the same time with ACC is at least very surprising. Is it possible that these were either not pheos or that pheos were misdiagnosed as ACC?
- p 7 l 54: was it laboratory evidence of Primary aldosteronism? 15% is quite high for ACC.

- p 7 l 56: was the Patient with elevated testosterone male?? Should be provided. Low testosterone in my opinion does not contribute to the diagnosis of ACC. This is not helpful for the reader.

- p 8 l 10: the patients with missing values should be excluded before reporting abnormal/normal lab.

- p 8 l 51: doxorubicin would be corect

- p 9 l 19: Mortality -> Survival

In this entire paragraph, adjustment for above mentioned factors in a Cox proportional hazards model may much improve the results and strengthen the viewpoint of the authors that USP significantly adds to the Management of ACC

This logically then would have impact on the discussion which therefore I do not comment on in much Detail.

- p11 l 53: the steroid panel reported here has yet been proposed for diagnostic purposes. How do the authors imagine it could impact on prognosis? It may be a tool to discover recurrence . . .
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.

Yes

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

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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