Author's response to reviews

Title: Preoperative workup in the assessment of adrenal incidentalomas. Outcome from 506 consecutive laparoscopic adrenalectomies.

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Author's response to reviews: see over
Dear Ms. Costoy, as requested by referees, a thorough revision of the paper was done. Here you have the comments for both of them.

Yours Sincerely

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Title: Preoperative workup in the assessment of adrenal incidentalomas. Outcome from 506 consecutive laparoscopic adrenalectomies. Version: 3 Date: 29 July 2013
Reviewer: Michael Brauckhoff

Reviewer’s report:
This is a retrospective multi-institutional study on patients who underwent laparoscopic adrenal surgery due to “adrenal incidentaloma” (n=282 procedures) and symptomatic adrenal tumors (n=224 procedures). Main aim of this study was to examine the impact of existing guidelines for diagnostic work-up in incidentally discovered adrenal tumors on surgical quality. To answer this question, the authors compared patients with incidentaloma who were preoperatively examined according to those guidelines (n=230 procedures, group A) to patients who did not undergo these examinations before surgery (n=52 procedures, group B). As main result of this study, the authors concluded that the guidelines were effective in detection of serious lesions (endocrine active tumors, cancer) as well as in avoiding unnecessary surgery.

In its present form the paper cannot be recommended for publication. It is of low scientific quality and does not fulfill the requirements of a scientific paper at all. It will need a complete and thorough revision in terms of scientific structure, language as well as editing at all. The paper is almost not to understand and the conclusions are not covered by the results. The paper mixes many aspects but did not answer one of them completely.

Dear Prof. Brauckhoff, we would like to thank you for the time you spent with our paper. Most of the points you raised have been modified according to your criticism.

Major concerns
(1) The authors need to define clearly what’s their definition of surgical indication in incidentalomas.
   We considered a valid surgical indication the indications suggested in guidelines\(^1,2\). Only patients studied and treated according to those protocols were considered suitable for group A, as extensively reported (methods section, page 5, rows 25-30 and page 6 rows 1-4)

(2) Performing biochemical tests followed by surgery is not necessarily “following guidelines” if the tests did not reveal any pathological results. What definition did the authors use for “subclinical Cushing” or “subclinical aldosterone secretion”? What cut offs did they use in pheochromocytoma?
   Good point. Now the cut off values for cortisol, aldosterone or metanephrine secretion are reported. Patients with pathologic values were treated as suggested\(^1,2\) (methods section, page 5, rows 5-14)

(3) A stringent definition what type of imaging was required allowing the definition of “sufficient” work up is needed. When the authors would need more than a CT scan?
   In 38/230 cases MRI was used alternatively to CT scan. In 28/230 PET/CT was used in addition in uncertain cases to enhance imaging power. This is now reported (methods section, page 5, rows 17-19)

(4) The authors need to describe more in detail how the data were acquired. They used a questionnaire – but what parameters were included and how were these parameters recorded? Who filled out the questionnaire?
   An extensive re-editing of all the methods section was done. We hope the timing, the
setting and the design, of this prospectively collected database, performed on a retrospective series, are clearer now.

(5) Is it possible to re-identify all included patients? Yes it is for all patients surgically treated.

(6) Did they perform a quality control of the collected data (a study dealing with quality control of medical treatment should at least control the quality of the registered data)? Yes we did. It was done at the time all data charts were introduced in the database. (Methods section, page 4, row 31)

(7) Who decided eventually if a preoperative work up was sufficient or not? Starting from 2001, all surgical units began to collaborate with the endocrinology unit of the "Federico II" University. The biochemical assessment and the radiographic features of the lesions, although performed elsewhere, were discussed among surgeons and endocrinologists to reach consensus about the adequacy of preoperative workup. Surgical indication was therefore given, in group A, at that time (Methods section, page 4, rows 12-14).

(8) The patients in group B need to be described more in detail. What made that they were classified as "insufficient" preoperative work up patients. This group might include patients who underwent all recommended examinations apart a dexamethasone suppression test (which might be disputable in a healthy young patient with a BMI of 19 and a 4.5 cm large adrenal tumor without any clinical signs of cortisol secretion) but also those patients with metabolic syndrome and bilateral adrenal tumors with a diameter between 2.5 and 3 cm who did not receive biochemical testing at all. In other words, this group might be very heterogeneous in terms of quality of preoperative examination/work up. This group includes patients presenting without any clinical manifestation of endocrine activity in presence of an incidental adrenal lesion detected at CT scan that was not biochemically tested. They, according to the authors of the questionnaire, did not fulfill the preoperative study criteria requested to belong to group A and were therefore classified as group B. This is now reported (Methods section, page 6, rows 5-11).

(9) What was the reason to accept patients without complete work up to surgery? In my country the surgeon is responsible and patients without complete work up would never be accepted to surgery. Is this different in Italy? Thank you for your observation. This is probably the clue of the entire review and allows us to explain our point of view. Well, of course in Italy it is not different. Patients presenting with an incidentally discovered adrenal lesion must be studied according to protocols to evaluate if surgery is needed or not. In the case surgery is needed, an adequate workup providing information about the functional status of the lesion as complete as possible must be followed. Nevertheless, if we consider the period ranging from the early 1990’s until the publication of NIH guidelines, it is undeniable that the spread of operative laparoscopy, led, not only in Italy, to perform an unjustified number of laparoscopic adrenalectomies. Small (< 4cm) incidentalomas have probably represented the ideal step for all endocrine and general surgeons to improve their laparoscopic skills. The results we detected in those patients, later classified as group B in our study, seem to confirm this hypothesis. The lack of clear guidelines, togheter with an emerging
surgical technique requiring a certain learning curve, and with the improvement in imaging quality which allowed the identification of smaller and smaller non-functioning lesions, explain the existence of patients classified as group B in the present study. Many surgeons, although officially very respectful of guidelines, have probably experienced that period. In this light we tried to see if any unexpected result, in terms of final histology (cancer, functioning lesions) came out from this group of patients which, for our current understanding, are considered understudied. (Discussion section, page 10, rows 2-7)

(10) (a) Table 1 and 2 are not necessary (patients with symptomatic tumors should be excluded; all other information can be given in the text). Tables 1 and 2 have been deleted. Table number 3 (modified) is now number 1.
(b) Table 4 is interesting but has nothing to do with the aim of the study. Table number 4 has been deleted.
(c) Table 5 and 6 should be combined resulting in a clear presentation of both groups. The information regarding the correlation of diameter and histological diagnosis has nothing to do with the aim of the study. It would be much more interesting to could compare both groups in terms of tumor diameter and biochemical activity. Tables 5 and 6 appear now as tables 2 and 3. By considering that the first aim of the study was to define in both groups in which rate preoperative workup has matched final diagnosis when an incidentaloma was detected, especially for suspected pheochromocytoma and primary ACC, we considered interesting to provide final histological diagnosis.

(11) Remarkably, in group B the number of patients with tumors <4 cm was not significant higher when compared to patients with “sufficient” work up (58% vs. 49%) – and even lower for those patients with non-functioning adrenal tumors (48% vs. 56%). So, what was the indication to surgery in patients without hormone secretion and tumors < 4 cm in group A? What was the indication to surgery in myelolipoma?
The number of tumors smaller than 4 cm was not significantly higher in group B but it was indeed higher. The indication to surgery in patients without hormone secretion and tumors < 4 cm in group A was in all cases the increasing dimension². (Methods section page 5, rows 25-30 and page 6 rows 1-4). Finally, your observation about a wait and see policy for small myelolipomas is undisputable, but it must be remarked that in our series those lesions presented as undefined growing adrenal incidentalomas, myelolipoma was just final histology. Radiologists were not in the position, in those 8 cases, to formulate a certain preoperative diagnosis.

(12) Table 3: “other adrenalectomies” can be removed. It was removed. Table 3 (modified), now table 1, refers only to incidentalomas.

(13) Is this correct: conversion in 7.6% in group B but only 1.7% in group A? The differences in surgical morbidity between group A and B are difficult to understand. Group B had smaller tumors (as expected) giving as potential disadvantage of “insufficient” preoperative work up only possibly undetected biochemical activity with potential consequences for the intraoperative (pheo) or the postoperative (Cushing) course. This has obviously not been examined at all.
Yes it is correct. It is evident that intraoperative spleen or liver injuries, that occurred in group B patients, were in any case unrelated to a correct preoperative biochemical evaluation. However in the definition “understudied patients” are included those who
did not have an appropriate preoperative imaging often suggested for small non functioning lesions < than 4 cm\(^6\). We should in fact consider that laparoscopic adrenalectomy has a morbidity rate reaching 11%\(^7\) that we cannot predict before any intervention. A correct preoperative study would have therefore probably prevented useless surgery with its postoperative complications in most cases. Table 1 shows morbidity in relation to final histology for patients in both groups.

(14) Were there differences between the participating hospitals?
There were no significant differences.

(15) Patients with suspected ACC need complete staging (including CT thorax). Was this standard in group A? What ACC stage (N and M status) had the patients in both groups?
Yes it was. We had 1 stage1 (T1,N0, M0) 9 stage2 (T2,N0,M0) and 1 stage3 (T3,N0,M0) cancers in group A. In group B we found 2 stage1 cancers. (Methods section page 8, rows 4-5).

(16) The title is misleading. There were 506 procedures but only 282 due to incidentaloma.
The title has been changed.

(17) How many patients with incidentaloma were seen in these institutions at all? Did the authors have follow up information regarding patients who were not operated? Are there patients who were primarily not classified as surgical patients but later – due to increasing tumors or biochemical activity?
It is just a surgical series. Unfortunately no data was obtained about non operated patients. The electronic form for some patients reported in the indication to surgery “operated due to lesion increasing dimensions during the last year”. This happened in 74/230 patients (32.1%) belonging to group A. 1/230 (0.4%) patients in the same group was reported as “operated due to initial hormonal activity”.

**Level of interest:** An article of insufficient interest to warrant publication in a scientific/medical journal
We hope our corrections may modify your opinion.

**Quality of written English:** Not suitable for publication unless extensively edited
A new language revision has been performed.

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
No interests.
References


Best regards

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Reviewer's report Title: Preoperative workup in the assessment of adrenal incidentalomas. Outcome from 506 consecutive laparoscopic adrenalectomies. Version: 3
Date: 10 August 2013 Reviewer: Ernst von Dobschuetz

Reviewer's report:
The authors provide an interesting clinical topic on the preoperative workup of laparoscopic adrenalectomies. They conclude that operation of patients with criteria other than NIH an AAES guidelines or not respecting these guidelines in each case do not lead to a higher detection rate of Adrenocortical Cancer.
It is a multicentric work with its limitations on variability of preoperative workup and a time frame of 19 years.

Dear Prof. von Dobschuetz, we would like to thank you for the time you spent with our paper. Most of the points you raised have been modified according to your criticism.

Major Compulsory Revisions:
Unfortunately the authors give no clear methodologic insight how they have evaluated the data only citing the guidelines in the text (citation 4 and 5).

An extensive re-editing of all the methods section was done. We hope the timing, the setting and the design, of this prospectively collected database, performed on a retrospective series, are clearer now.

Of course it is difficult in this multicentric setup but they should state more clearly at what cutoff levels in the biochemical evaluation one patient was divided to subgroup A or B.

Good point. Now the cut off for cortisol, aldosterone or metanephrine secretion is reported. (Methods section, page 5, rows 5-14)

Since guidelines can always be interpreted differently a clear statement is missing about at which point the guideline 4 or 5 was considered to be fulfilled in the methodological section.

This has been now better defined. All issues about the preoperative functional status and indications to surgery for all lesions are now reported. Again, a thorough revision of all the methods section was done. (See all methods section)

Level of interest: An article of importance in its field.
Thank you for your flattering comment.

Quality of written English: Acceptable.
A new language revision has been however performed.

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests
Best regards
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