

Peer Review File

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Answer to reviewers' comments

We would like to express our sincerest gratitude to Reviewers for taking time and effort to provide detailed and constructive comments.

* Reviewer A (Remarks to the Author):

REQUESTED REVISIONS:

1. Is adrenal biopsy necessary if surgery is planned or if hormonal testing confirms ACC? The use of adrenal biopsy has been demonstrated to worsen prognosis in patients with ACC (J Surg Oncol. 2021 Dec;124(8):1261-1271. doi: 10.1002/jso.26639. Epub 2021 Aug 23.) . Could this have contributed to the outcomes?

→ Thank you for your valuable comments. We believe that adrenal biopsy for patients requiring surgical treatment in suspicion of adrenocortical carcinoma (ACC) is unnecessary. In this study, image data such as CT or MRI were used to differentiate ACC. However, seventeen patients suspected of having multiple metastatic lesions, biopsy was performed to diagnose the origin of carcinoma. We have made changes to the related sentence in the Methods section (page 6, lines 103-106) as 'Seventy-one patients were diagnosed of ACC through surgery while 17 patients having multiple metastatic lesions underwent percutaneous adrenal biopsy to diagnose the origin of carcinoma. And, 6 patients were diagnosed through image studies only.'

2. What type of surgery was performed? Open? Laparoscopic? We know that surgical approach does impact recurrences.
(Transl Androl Urol. 2021 May; 10(5): 2246–2263. doi: 10.21037/tau.2020.01.11)

→ Of the 71 patients who underwent surgery, open surgery was performed on 62 patients, and minimally invasive surgery including laparoscopic or robotic surgery was performed on 9 patients. This information was added on the Methods section, page 6, line 110-112. Minimally invasive surgery was performed only in stages 1 and 2, and the number of cases was too small to compare the prognosis according to the surgical method. Therefore, in this study, the difference in prognosis according to the surgical method was not analyzed separately. We have described this information in the Discussion section on page 13, line 259 and added the related reference as you recommended.

3. How was the decision to use mitotane made? Ki67?

What do the authors think the reason for the change in the prescribing practices was over time?

→ To date, there are no clear indications for the use of mitotane in ACC patients. The decision to use mitotane was made at the discretion of the multidisciplinary team decision including oncologist for each patient. The reason why prescription practices continue to

change to this day is thought to be because the treatment of ACC is so difficult and there is no clear treatment method other than surgery. Although mitotane is the only approved treatment for ACC so far, mitotane alone has limited therapeutic effects, so combinations with various other chemotherapy were tried.

4. What is multidisciplinary therapy? Is it radiation plus mitotane? Radiation and chemo? Chemo and mitotane? What was the role of radiation in this study?

→ In this study, the term ‘multidisciplinary therapy’ included any combination of treatment including surgery, mitotane, chemotherapy and/or radiation therapy. The treatment combination was decided by the departments of internal medicine, surgery, oncology, radiology, and nuclear medicine. The combination of multidisciplinary therapy used in this study are listed in the Tables, within the variable of Treatment.

*** Reviewer B (Remarks to the Author):**

REQUESTED REVISIONS:

1. The main issue is that an R0 resection is not defined as complete resection by surgical technique but is a microscopically negative margin on pathology. An R1 resection is defined as a macroscopically negative but microscopically positive margin on pathology. An R2 resection is defined as gross disease left behind. Given this incorrect definition of an R0 resection, all of the results regarding recurrence/disease-free survival are not reliable.

→ As you mentioned, the definition of R0 resection is based on pathologic negative margin. In this study, the definition was as you described. However, we were not clear enough to present accurate description of R0 in the previous version. We have made changes to the sentence in the Methods section, page 6 line 109-110 as ‘In this study, R0 resection was defined as complete surgical resection with pathologic negative margin’.

2. Some of the data does not seem consistent/appropriately calculated. For example, it is stated that 49% of patients underwent surgery and adjuvant chemotherapy, whereas 16% underwent surgery alone. This adds up to 65% of patients in total, whereas the authors report that a total of 75.5% of patients underwent surgery.

→ As shown in Table 1, 71 out of 94 patients (75.5%) underwent surgery. Looking down at the treatment classification, 15 patients (16.0%) had surgery only, 46 patients (49.0%) had surgery and adjuvant chemotherapy with mitotane, and 10 patients (10.6%) had surgery and adjuvant chemotherapy without mitotane. The sum of these three groups corresponds to the number of patients who underwent surgery.

3. The results overall are difficult to evaluate, with no graphical reports of trend data and lack of clarity regarding which trends/differences are statistically significant. For example, it is not known whether the significant p-value for treatment in Table 2 is related to differences in therapies or the trend over time.

→ Thank you for your valuable comments. As you said, we tried to express the trend using several graphs, but the presented figures were not better than tables. In order to make it clear

what the p-value values of Tables are about, the following explanation has been added along with the footnote.

Table 1, ‡ P-value means a statistically significant difference between stages.

Table 2, † P-value means a statistically significant difference between trends over time.

4. It is one of the main discussion points that mitotane use increased over time, however disease-free interval decreased over time. It is necessary to understand which patients, undergoing which treatments (and not just which disease stage), actually recurred.

→ With this study population, the recurrence pattern according to each patients and each treatments were too broad to present with order. Therefore, we grouped the recurrence by staging.

5. Data regarding hormone activity of ACC is of critical importance when evaluating the reason for operating, especially in patients with advanced disease.

→ Hormone activity is important in ACC patients. However, before year 2010, hormonal study was not uniformly performed and was not able to include the data in this study. We will try to analyze it in future study.

6. The introduction contains a significant discussion of mitotane without a similar discussion of other chemotherapeutic options, the relevance of which is unclear.

→ Mitotane is currently the only drug approved for ACC treatment. Therefore, we focused on mitotane usage in this study.

7. There is inconsistent grammar throughout the paper.

→ This paper has been proofread by an accredited English editing company. We have submitted the Editing Certificate. Nevertheless, we will do the official editing once more.