Author's response to reviews

Title: Clinical approaches to treating papillary squamous cell carcinoma of the uterine cervix

Authors:

Michikazu Nagura (mnagura@kuhp.kyoto-u.ac.jp)
Masafumi Koshiyama (koshiyamam@nifty.com)
Noriomi Matsumura (noriomi@kuhp.kyoto-u.ac.jp)
Aki Kido (akikido@kuhp.kyoto-u.ac.jp)
Tsukasa Baba (babatsu@kuhp.kyoto-u.ac.jp)
Kaoru Abiko (kaoruvc@kuhp.kyoto-u.ac.jp)
Junzo Hamanishi (jnkhmns@kuhp.kyoto-u.ac.jp)
Ken Yamaguchi (soulken@kuhp.kyoto-u.ac.jp)
Yoshiki Mikami (mika@kuhp.kyoto-u.ac.jp)
Ikuo Konishi (konishi@kuhp.kyoto-u.ac.jp)

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Author's response to reviews: see over
We answer the reviewer's question with underline sentences in this report. And we showed them with underline sentences in main manuscript.

1) Nagura et al report their approaches to treating papillary scc of the uterine cervix. The manuscript is long and the thought process and objectives are difficult to follow. The results section is very long and can be shortened by referring to the tables and figures.

Answer →

We change the constitution of the sentences to be easy to understand the contents of the manuscript. And we shorten “Results”. We are confused at Supplementary Tables and Figures. So, we delete Supplementary Tables and Figures. We rewrite Table 1-5 and Figure 1-6.

Result is long, so we delete the following sentences:
A) Twelve (43%) of the 28 PSCC cases diagnosed on the colposcopic selective biopsies were ambiguous with respect to the presence of stromal invasion.
B) Two of these three patients were ultimately found to exhibit no stromal invasion after surgery.
C) Ultimately, the surgical sections revealed that two (50%) of these patients exhibited no stromal invasion and that two (50%) exhibited stromal invasion.
D) (preinvasive or microinvasive carcinoma)

2) Line 86-94: This section should be in the methods and objectives for this study should be listed instead.

Answer → The following sentences in Background are deleted: “We then compared the tumor depth (particularly the degree of stromal invasion) on magnetic resonance imaging (MRI) with the microscopic tumor depth
observed during surgery. We also assessed treatment strategies for PSCC and evaluated the presence of lymph node metastases and the patients’ prognoses. Finally, we considered possible improvements in management strategies, especially with regard to selecting minimally invasive surgery in the patients desiring fertility with preinvasive and microinvasive disease.”

In addition, we distributively insert these sentences into Materials and Methods with underline. (new Line 106, Line 114.)

3) Line 88 and 110: Do you routinely perform MRI on all patients or is this for study purposes?

Answer → Yes! We think that MRI is very important method to inform the tumor depth, especially against papillary growing tumor. We perform MRI routinely when we find the uterine cervical cancer (see an algorithm Figure 6).

4) Line 110: What is the information used from MRI and how does this change surgical plans?

Answer→ In Japan, radical trachelectomy is carried out for the patients who hope fertility sparing-surgery and have 2cm or less uterine cervical cancers in the diameter. And the modified radical hysterectomy for patients with tumor diameter 2cm or less FIGO stage Ib1 uterine cervical cancer have been selected instead of radical hysterectomy. Furthermore, we can select a therapeutic conization against a small tumor with minimal invasion. So assessment of tumor size and depth before surgery is very important. The tumor size can change surgical plan.

5) Line 114: what does “best surgical procedure” mean and how determined?

Answer→ We delete the following sentences “Regarding treatment, we selected the best surgical procedure possible.”

6) Line 130: If the mean age of patients is 49-51, why is preop MRI important if fertility sparing is not an issue?
Answer→ In our PSCC study, we find 3 younger patients with 35, 30 and 32 years old. Two of three patients lost their uterus. We can select a fertility sparing-surgery (therapeutic conization or radical trachelectomy) for a younger patient with a PSCC, who hope to keep her uterus, using and these PSCC data and MRI findings in the future.

7) Line 152: Confusing what patients this refers to. In other areas line 151 and 204 no recurrence are mentioned.
Answer→ Twelve (75%) of the 16 false PSCC patients were alive and had no recurrence. But four (25%) patients of the 16 false PSCC patients developed recurrence! Line 204: all 12 patients with true PSCC exhibited no episodes of recurrence.
We then insert the following words: the 16 false PSCC patients (new Line 147)

8) Line 201: Why no ckc if possible micro invasion rather than MRI if not 100% accurate?
Answer→ If we find out carcinomatous lesions and papillary growth carcinomas in the uterine cervix, we can’t do ckc against all cases. If they are massive tumors, we perform only the selective biopsies and not ckc. If we encounter the PSCC, we can’t detect the tumor size and depth. Therefore, we need to do MRI and know the tumor size and depth. If the tumor depth is shallow (<3mm), we can do ckc to know the real tumor depth after MRI (see an algorithm Figure 6).

9) Line 201: Why radical hysterectomy and subjecting to increased morbidity?
Answer→ A radical hysterectomy can affect a woman’s ability to pass urine while the nerves in the tissue around the uterus are recovering from surgery. If a woman still cannot fully empty her bladder a few weeks after surgery, she may have long-term damage. To prevent urinary tract infections, she
may be taught to slip a small tube, called a catheter, through the urethra and into the bladder to drain out the remaining urine. This is called self-catheterizing. Furthermore, the patients suffer from lymph edemas. In brief, the QOL of the patient turns worse remarkably after a radical hysterectomy. Therefore, the gynecologic surgeons in the world tend to perform minimally invasive procedures recently.

10) Line 229 and 239: I am not sure where the authors found this recommendation. I do not believe this is part of NCCN guidelines and most 1a1-1b1/2a tumors are also treated with surgery in the US. Please provide a reference or delete this statement.

Answer→ Yes, we insert the 2 references. 7) “Radical hysterectomy versus radiation therapy for stage IB squamous cell cancer of the cervi. (1991, by Hopkins MP, Morley GW)” 8) “Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. (1997, Landoni F et al)

In following sentences, we insert (NCCN Guidelines, version 2.2013). In Europe and the USA, advanced cases of PSCC are diagnosed on the colposcopic selective biopsies and treated with radiation therapy and chemotherapy (NCCN Guidelines, version 2.2013) (new Line 240).

11) Conclusion: Why do the authors recommend MRI over ckc if a fair bit is micro invasive and would not require radical hysterectomy?

Answer→ We can select some treatments for uterine cervical cancer, for example, conization (stage Ia1), radical trachelectomy, simple hysterectomy, modified radical hysterectomy, radical hysterectomy or radiation therapy according to tumor depth and size. We can’t perform ckc against all cervical cancers. Firstly, we assess the tumor size macroscopically. But PSCCs are difficult for us to assess the tumor depth...
or size, so we recommend MRI analysis. If the MRI show a small tumor and minimal invasion (<3mm), we can secondly select ckc (see an algorithm Figure 6).

<Reviewer’s report 2>

We answer the reviewer’s question with underline sentences in this report. And we showed them with underline sentences in main manuscript.

Major Compulsory Revisions

Lines 183-188: The numbers in this paragraph don’t add up to me. Seven patients had no stromal invasion on MRI. How many of these actually had invasion? You don’t list this here. You then refer to six cases with stromal invasion on MRI. That adds up to 13 cases and you only have 12 total. This should be clarified. I would state how many patients had no invasion on MRI and then how many of these actually had invasion. I would then list how many patients with invasion on MRI had invasion on histologic analysis. Overall, this entire paragraph is difficult to read. It is a critical part of your manuscript and must be rewritten for clarity.

Answer → We are sorry. Total number is 12. No stromal invasion cases on MRI are 7 (58%) and stromal invasion cases are 5 (42%). So we exchange six (42%) for all of five (42%) cases. (new Line 171)

We add the following sentences: Three of seven cases exhibited actually
microscopic no stromal invasion. (new Line 168)

Lines 296-304: You have just described an algorithm for the management of PSCC. Why not go one step further and write out your algorithm in a flow diagram with decision points? This would be tremendously helpful and potentially raise the interest of this article to the level of seminal article on the topic.

Answer → We add the following sentences and Figure 6.

We show an algorithm for the management of PSCC (Figure 6). (new Line 308)

You have not addressed how the diagnosis of PSCC was changed in the 16 cases with an initial diagnosis of PSCC. What was it about these cases that led to the change? Is this an issue of not sampling enough of the tumor or are there other factors influencing the change in diagnosis? You could discuss in your results or just mention in your discussion but the issue must be addressed. Also, it will help your colleagues understand the importance of surgical staging. I think that this really highlights the differences in management of these tumors in Japan versus US/Europe as more extensive sampling or surgical management would be considered in these areas if more extensive sampling could confirm the more indolent nature of true PSCCs.

Answer → We add the following sentences in Discussion: We experienced 16 cases of false PSCC. We analyzed the surgical specimens microscopically, which involved the tumor heterogeneity. The surface components consisted of papillary growth and the major deep-components consisted of non-keratinizing SCC. Therefore, two or three colposcopic selective biopsies detected only superficial PSCC-like lesions. (new Line 231)

And we add the next sentence: In the cases of advanced PSCC treated with radiation therapy, the deep biopsies should be performed to obtain the exact diagnosis before its therapy. (new Line 247)
Minor Essential Revisions

Lines 66-68: This sentence is incomplete. It should be reworded after the comma to construct a complete sentence.

Answer→ We are sorry. We inserted the follow words: However, they may be

(new Line 67)

Lines 80-83: This is a great point. You have identified several unanswered questions in the literature. Could you please separate out the statements about lymph node metastasis and the role of minimally invasive surgery into two sentences? As written, this sentence is too long and needs to be separated to highlight the uniqueness of your report.

Answer→ We separate the long sentence: To our knowledge, there are no previous reports of lymph node metastases in patients with preinvasive and microinvasive disease. The clinical behavior of this entity is not well understood. In addition, there are no reports of the prognosis of minimally invasive surgery in these patients. Therefore, it is difficult to identify the best treatment strategy for PSCC. (new Line 80)

Lines 114-115: This statement is unnecessary as we would expect as much. I would consider replacing this with a comment that fertility preservation was considered in patients desiring fertility and when cervix confined disease was identified (or whatever criteria you used).

Answer→ We delete the following sentence:

Regarding treatment, we selected the best surgical procedure possible.

And we add the next sentence: We considered possible improvements in management strategies, especially with regard to selecting minimally invasive surgery in the patients desiring fertility with preinvasive and microinvasive disease. (new Line 116)
And we add the next sentence: In conclusion, the number of surgeries for fertility preservation therapy using minimally invasive procedures to treat PSCC can be increased. in Conclusion. (new Line 309)

Lines 165-167: This statement is awkward and a bit misleading. I believe that you are saying that several of the tumors were smaller or non-invasive on final pathology. I would consider separating these out according to how they were down-staged. For example, three were downstaged due to lack of stromal invasion, two due to tumor size, etc.

Answer→ We add the following sentence: Three were downstaged due to lack of stromal invasion, three due to tumor size. (new Line 188)

Line 276-278: This is an extremely helpful conclusion. You need to follow this up with a comment about the role of MRI in preoperative assessment. In my opinion, this suggests that MRI can be used to evaluate patients that may be excellent candidates for fertility preservation therapy. I see that you include this in your conclusion paragraph but it should also be stated here as it is an important point.

Answer→ Thank you very much for your advice. We add the next sentence: MRI can be used to evaluate patients that may be excellent candidates for fertility preservation therapy. (new Line 286)

Discretionary Revisions
Line 71: Perhaps you could use a more specific term than “surgical methods” here? Do you mean a diagnostic surgical procedure or definitive surgery? In other words, do you mean hysterectomy, excisional biopsy, or both?

Answer→“surgical methods” means definitive or radical hysterectomy. Therefore, we change “surgical methods” for radical hysterectomy. (new
Lines 161-162: I would rewrite as: “In four of these cases, no tumor was apparent on MRI.”

Answer→Yes, thank you very much. We change “These cases included no apparent tumors on MRI in four cases” for “In four of these cases, no tumor was apparent on MRI.” (new Line 182)

Line 179: You can eliminate the “with or without” as it is implied by the definition of accuracy.

Answer→Yes, we eliminate the “with or without”.

Line 210: This statement is unnecessary. Perhaps you mean to say that it has been rarely reported?

Answer→Yes, we eliminate “Papillary carcinoma of the uterine cervix has been documented.”