Author's response to reviews

Title: Intraoperative radiotherapy electron boost in advanced and recurrent epithelial ovarian carcinoma: a retrospective study

Authors:

Ying Gao (togaoying@163.com)
Zi Liu (liuzmail@163.com)
Xi Chen (2002chenxi@163.com)
Wei Luo (luoweimail@163.com)
Long Zhang (zhanglonglongmail@163.com)
Juan Wang (wangjuan3890@sina.com)

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Author's response to reviews: see over
Dear editor,

Thank you for the feedback. I am very grateful for your advices and the reviewers’ comments on our manuscript (Intraoperative radiotherapy electron boost in advanced and recurrent epithelial ovarian carcinoma: a retrospective study. MS: 8040348655164645).

Here are the point-to-point responses to the reviewers’ comments:

**Major compulsory revisions**

1. Define how patients were selected for IORT in the primary disease setting. In the rare case of isolated local relapse there is a rationale for including IORT along with EBRT. However, the majority of primary stage III patients have extensive intraperitoneal involvement and there is no rationale for considering IORT in these patients. Were all primary ovarian patients treated at the institution included or do the patients represent a subset. If a subset, please describe the characteristics that suggested local control might be a problem.

   **Revision:** Not all primary ovarian patients treated at our institution were included. The patients who were allowed to freely choose IOERT only represent a subset. The prognosis of epithelial ovarian carcinoma remains poor due to a high rate of recurrence. About 50-75% of women with ovarian cancer will develop persistent or recurrent disease. Thus innovative treatments to improve the local control of EOC are anticipated. IOERT was shown to be able to reduce the local recurrence rate with an impact on survival by numerous non-randomized series of the literature for several years, which is the reason that IOERT were selected in advanced epithelial ovarian carcinoma. This part has been added in the section of Background.

   The pelvis or abdomen is the initial recurrence site in around 85% of ovarian cancers. IOERT decreases the recurrence in pelvis by whole pelvic radiotherapy. The National Cancer Institute and GOG have issued a clinical announcement recommending that patients with stage III ovarian cancer should be considered for intraperitoneal chemotherapy after undergoing optimal surgical cytoreduction.
Since the majority of primary stage III patients have extensive intraperitoneal involvement, the outcome of IOERT plus IP chemotherapy was studied in our institution.

2. Define what is meant by whole pelvic radiotherapy. This is not a term used in the literature. What applicators were used? What area of the pelvis was treated? What normal tissues were in the field? What were the dimensions of the applicators? Where was the radiation dose specified? What equipment was used to deliver the intraoperative radiotherapy? Where was it delivered?

Revision: The target volume for intra-operative radiotherapy was determined by the surgeon and the radiotherapist. Please see the section of Methods for the technical details.

3. Revise the acute toxicity section to include potential acute toxicities based on the normal tissues irradiated. It does not make sense to report on radiation induced hepatitis and pneumonitis when the liver and lungs were not exposed to radiation. How was fatigue assessed in the postoperative setting? What is meant by acute rectum failure? Was there rectum irradiated?

Revision: The toxicity section has been revised accordingly. The rectum was not irradiated. By acute rectum failure we actually mean intestinal failure, which was due to surgery, sorry about the confusion. The part of the section on hepatitis and pneumonitis was deleted. All 45 patients with IOERT did not have fatigue.

4. If the presacrum or pelvic sidewall was irradiated there would essentially always be peripheral nerve in the radiation field. What is meant by the statement "if the peripheral nerve had been included" and "if the nerve had not been irradiated"? What nerve? How is it possible to irradiate the pelvis with 12 MeV electrons and not include peripheral nerves?

Revision: By “the nerve” we mean a part of obturator nerve in the pelvis. It can be shifted out of the radiation field partly. The manuscript was revised accordingly.
5. Define what is meant by late cystic injury. What is meant by crura edema and how was this related to late IORT injury?

Revision: One patient in our study developed urinary urgency and chronic urinary tract infection after surgery. The crura edema is associated with unsmooth blood and lymph circulation which related to surgery.

6. In the discussion section, should relate results (survival and local control) to what is reported with non-IORT approaches. What is the justification for calling this approach specially effective and associated with a survival benefit?

Revision: The discussion section was revised accordingly.

This study is a retrospective study regarding the IOERT effect on the outcome of ovarian carcinoma. It confirmed the feasibility of the technique. However, further demonstration of the IOERT effect for the treatment of ovarian carcinoma in the future is still necessary. Revisions can be made in the conclusion section accordingly.

Minor Essential Revisions

1. The manuscript would be improved by presenting patient characteristics and results data in tabular format.

Revision: The patient characteristics and results data in tabular format have been added.

All changes made when revising the manuscript have been highlighted with red coloured letters.

Yours sincerely,

Ying Gao