

Jia-Ping Yan

Science Editor,

Editorial Office,

World Journal of Clinical Cases,

January 20, 2019

Dear Dr Yan,

Re: Manuscript reference No. 45026

Please find attached a revised version of our manuscript "PDT as salvage therapy for residual-microscopic cancer after ULAR: A case report", which we would like to resubmit for publication as a Case Report in World Journal of Clinical Cases.

Your comments and those of the reviewers were highly insightful and enabled us to greatly improve the quality of our manuscript. In the following pages are our point-by-point responses to each of the comments of the reviewers as well as your own comments.

Revisions in the text are shown using yellow and pink highlight for additions, and deletions are marked to the right of the text. For example - Delete: This case provides a new approach for patients with positive microscopic resection margins. According to the requirements of editors, (1) We change the overlapping statements, and have finished the language modification again. (2) we increase the running title, CARE Checklist (2016) the statement, the final diagnosis, treatment and outcome and follow-up and conclusion, but the part of the discussion, we think don't need to add subtitle. (3) We provide new figures, audio core tip and grant application forms ect. In addition, I would like to thank the two reviewers for their comments and their recognition of the manuscript. In accordance with the reviewer's (number:00504708) third

opinion, we added some structuring complications of PDT in the discussion section of the manuscript. In the following pages are our point-by-point responses to each of the comments of the reviewers. We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in World Journal of Clinical Cases.

We shall look forward to hearing from you at your earliest convenience.

Yours sincerely,

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Responses to the comments of Reviewer #1

I found this case report interesting as PDT is not usually considered for rectal cancer as it for esophageal malignancies. Theoretically, there are similarities between the two anatomic areas.

Response: *First of all, I am very honored you think my manuscript is interesting. Photodynamic appeared in more than 100 years ago, was mainly used for skin diseases at the beginning, but as the tireless efforts of scholars in recent years, application scope expands unceasingly, not only have you mentioned the esophageal malignancies - Photodynamic therapy (PDT) was first introduced to treat esophageal*

cancer in the early 1980 s, but also colorectal cancer-mainly used for palliative and salvage treatment^[1]. However, with the continuous improvement of photosensitizer and PDT combined with other treatments, it is believed that photodynamic therapy will be more widely used.

2. Nonetheless, I do not understand why the patient did not receive directed radiation therapy-possibly via CyberKnife. This would work well with the already administered chemotherapy.

Response: (1) First of all, I think this is a very good question. There are indeed similarities between the two therapies, but there are also differences: CyberKnife is an image-guided stereotactical dose delivery system designed for both focal irradiation and radiation therapy (SRT). Focal irradiation refers to the use of many small beams. To deliver highly focus dose to a small target region in a few fractions^[2]. As mentioned in my manuscript, PDT is composed of photosensitizer, light and reactive oxygen species (ROS). The photosensitizer accumulates in cancer cells, and then induces ROS formation in cancer cells through the stimulation of light irradiation, the ROS affect all intracellular components, including proteins and DNA, resulting in necrosis or apoptosis. Thus, only cells with intracellular photosensitizer are selectively on, and the surrounding tissue is spared^[3]. In this case report, the patient with low rectal cancer, after radical surgery, have been founded a microscopic-residual cancer- cancer cells observed only by the microscope, but it's not recognizable to the naked eye. As a result, we felt that photodynamic therapy might be more accurate and less damaging to the surrounding normal tissue than cyberknife. (2) As far as I know, there are only four cyberknife instruments in China, and the application of photodynamic therapy is more mature than cyberknife therapy in our hospital, so we adopted photodynamic therapy in this case report.

3. The paper should have mentioned more of the potential complications-especially structuring.

Response: *Thank you very much for your valuable advice, I have added some structuring complications of PDT in the discussion section of the manuscript.*

4. Overall, this was a good case report but its applicability to general practice is suspect

Response: *I am delighted for your positive comments on my manuscript, and I also understand your doubts about the applicability of the treatment. After all, this is a case report, which has not been rigorously proved by statistics. However, recent studies have indicated a beneficial role for PDT in salvage treatment for locoregional failures after definitive chemoradiotherapy (CRT) for esophageal cancer^[1]. As you said, there are similarities between the two anatomic areas. Therefore, from this successful case report, it may be possible to further study whether photodynamic therapy is also a positive effect for the salvage treatment of rectal cancer. Compared with esophageal cancer, the reoperation of rectal cancer is closely related to the preservation of anal sphincter, so its salvage treatment may be more valuable.*

5. Moreover, PDT is extremely expensive to maintain with need for laser, catheters and drugs.

Response: *The relatively high cost of photodynamic therapy is a real problem. Because the research of photosensitizers and instruments, PDT is relatively expensive. However, if photodynamic therapy is widely used more, the cost should be reduced. At the same time, the total cost of multiple cycles of chemoradiotherapy, and the cost of cyberknife with the cooperation of robots, may be also not cheap.*

Responses to the comments of Reviewer #2

The paper is well written and conclusions are adequate to the scientific presentation

Response: *I am very honored and thank you for giving me such a high evaluation of the manuscript, which is a great encouragement to me.*

参考文献

- [1] Lee H H, Choi M, Hasan T. Application of photodynamic therapy in gastrointestinal disorders: an outdated or re-emerging technique?[J]. The Korean Journal of Internal Medicine, 2017,32(1):1-10.DOI:10.3904/kjim.2016.200.
- [2] Ding C, Saw C B, Timmerman R D. Cyberknife stereotactic radiosurgery and radiation therapy treatment planning system[J]. Medical Dosimetry, 2018,43(2):129-140.DOI:10.1016/j.meddos.2018.02.006.
- [3] Rkein A M, Ozog D M. Photodynamic Therapy[J]. Dermatologic Clinics, 2014,32(3):415-425.DOI:10.1016/j.det.2014.03.009.