

April 18, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ESPS Manuscript NO 8348-edited.doc).

Title: Scientific and clinical impact of human papillomavirus (HPV) on head and neck cancer

Author: Jeffrey M. Friedman, Mark J. Stavas, Anthony J. Cmelak

Name of Journal: *World Journal of Clinical Oncology*

ESPS Manuscript NO: 8348

The manuscript has been improved according to the suggestions of reviewers:

1. reviewer #1 had no suggestions

2. from reviewer #2

- 1) The references have been reformatted
- 2) A table was added to illustrate the change in the incidence of HPV+ HNSCC
- 3) A table was added summarizing select references examining HPV+ HNSCC and prognosis
- 4) We stated the differences between our review and existing reviews
- 5) The reviewer wrote "The summaries of the various headings of the article has not been mentioned clearly and it has failed to deliver concrete conclusive points to the readers and is likely not be reading friendly." We feel we have included appropriate sections for the review including Introduction, Epidemiologic changes, Clinical changes, Molecular Differences, and Future Directions. These are clearly outlined at the top of each section. We have added 2 Tables that will synthesize the data into a cohesive format for Epidemiology and Clinical Findings sections, and improve the flow of the manuscript.

3. from Reviewer #3

- 1) We changed the title of the review, we described the goal of the manuscript, and we suggested other reviews for extensive discussions of therapeutic approaches
- 2) We clearly stated that induction chemotherapy, alternative systemic regimens to cisplatin and other approaches have been investigated prior to the era of HPV-positive disease
- 3) We clarified the meaning of the 5th most common cancer in the abstract
- 4) The language and grammar was reviewed
- 5) We mention the unusual patterns of distant spread that appeared in some reports
- 6) We feel that the molecular changes are the current drivers of the future directions in diagnosis and treatment and therefore, the flow would be disrupted if we inserted that section before the clinical section
- 7) We state that there is current debate regarding the OS for metastatic HPV positive and negative disease and list the appropriate references that suggest both equivalent and superior OS.

Thank you again for publishing our manuscript in the *World Journal of Clinical Oncology*.

Sincerely yours,

Jeffrey M. Friedman