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In Reply to Smith et al

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trials are expected to find no difference between their study arms and cannot claim to be "negative" but are more properly termed inconclusive. The Cook et al study lacked the statistical power to provide substantive evidence against mild to moderate effects of gabapentin; however, it does represent some level of evidence against large effects, which it would have been more adequately powered to detect. Further studies of greater size are needed to confirm or refute the findings of our initial study of gabapentin's effectiveness in the head and neck cancer population.

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In Reply to Smith et al.

To the editor: We would like to sincerely thank Drs Smith and Murphy for their careful and critical evaluation[1] of our recently published double-masked, randomized, placebo-controlled trial regarding the role of prophylactic gabapentin in alleviating mucositis-related pain in patients receiving radiation therapy for oropharyngeal cancers.[2]

They have conducted a detailed statistical analysis to conclude that approximately 190 patients, randomized between 2 treatment arms, would be required to prove or disprove the role of gabapentin. As per their evaluation, the 60 patients in our study are inadequate to conclude that this is a "negative" trial. We completely agree with this statement and, in fact, acknowledged this limitation in the Discussion section of our published manuscript.

Disclosures: none.

We would again like to highlight some of the unique strengths of our study. It is the only existing study which was double-masked and placebo-controlled. All patients had a diagnosis of oropharyngeal cancer and received radiation to a dose of 70 Gy in 35 fractions with intermediate- and low-risk areas receiving 63 Gy and 56 Gy, respectively. We used a simultaneous integrated boost technique delivered using volumetric modulated arc therapy. T- and N-stages were well balanced between the arms. All patients received platinum-based radiosensitizing chemotherapy concurrent with radiation. Analysis of oral cavity and pharyngeal constrictor mean dose showed no difference between the 2 arms (Table 1 of the manuscript). This group of patients was specifically chosen as treating oropharyngeal cancers results in the inclusion of a significant portion of the oral mucosa. Analyzing patients with laryngeal/ hypopharyngeal cancers or those receiving adjuvant radiation therapy for oral cavity cancers would have resulted in highly variable doses of radiation therapy to the oral cavity. We wanted to minimize heterogeneity in the patient population enrolled in our trial. Our strategy contrasts with the Smith et al study,[3] which was not placebo-controlled and included patients with different head and neck subsites, radiation doses, use of induction chemotherapy and different chemotherapy or targeted agents which are also known to impact oral mucositis. Between 20% to 25% of the patients received postoperative radiation therapy. The inclusion of such a heterogenous group of patients can introduce variability and serve as confounding factors. Again, we view our homogenous inclusion criteria as a strength.

Understandably, one of the downsides to having narrow inclusion criteria is that it takes a long time to accrue subjects and complete a trial. Ours was a single institution, single enrolling site trial, that took 3 1/2 years (June 2017-December 2020) to enroll 60 patients with oropharyngeal cancer. During this period, several new and exciting treatment de-escalation trials were also opened at our institution and patients were preferentially offered enrollment on these cooperative group trials. A successful trial with the number of patients recommended by Drs Smith and Murphy, to be appropriately powered, would have likely taken us a decade or longer to accomplish using our inclusion criteria.

An additional surprising finding in our trial was the significantly higher number of patients who required placement of a feeding (Dobhoff nasogastric) tube in the gabapentin arm. As this was a masked trial, investigators had no way of knowing which patients were requiring feeding tubes while the trial was ongoing. At our institution, we do not place prophylactic percutaneous endoscopic gastrostomy tubes. We have a reactive feeding tube policy where all patients receiving radiation therapy are evaluated on a weekly basis by speech-language pathologists and cancer dietitians. When the need for a feeding tube is deemed necessary, based on multidisciplinary evaluation, a Dobhoff tube is placed in the Radiation Oncology clinic by the treating head

and neck radiation oncologist (F.S.) or the head and neck team nurse practitioner.

The number of patients who required a feeding tube placement were 18 of 29 in the gabapentin arm and 6 of 29 in the control arm. As mentioned in our manuscript, 23 of these (96%) were Dobhoff tubes and only 1 patient received a percutaneous endoscopic gastrostomy tube. Thus, although we were unaware of this during the trial, in retrospect, it appears that patients receiving gabapentin require feeding tubes at a much higher rate. The exact cause of this is not clear to us.

These findings, along with a lack of clear and unequivocal benefit in minimizing neuropathic pain resulting from oral mucositis, has resulted in the discontinuation of prophylactic gabapentin for patients receiving head and neck RT in our institution.

We definitely agree with the sentiment that further large scale, adequately statistically powered double-masked placebo-controlled trials should be conducted to answer this question.

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