



Standard Chemoradiation Superior to Deintensification for HPV-Related Oropharyngeal Cancer

Lower radiation dose and substituting immunotherapy for chemotherapy did not match 98% success rate of standard treatment for mouth and throat cancer.

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Researchers looking to de-intensify radiation treatments for people with early-stage, HPV-associated oropharyngeal cancer to prevent long-term side effects halted a large, randomized Phase II/III trial after patients in the control arm reached a record high, two-year progression-free survival rate of 98%. De-intensified treatments involving a lower radiation dose and immunotherapy in place of chemotherapy did not perform as well as the more rigorous chemoradiation approach. Findings of the NRG Oncology HN005 trial [were] presented at the [American Society for Radiation Oncology \(ASTRO\) Annual Meeting](#).

“In cancer treatment, 98% progression-free survival at two years is a number you just don’t see,” said Sue S. Yom, MD, PhD, FASTRO, principal investigator of the trial and the Irwin Mark Jacobs and Joan Klein Jacobs Distinguished Professor in Head and Neck Cancer Radiation Oncology at the University of California, San Francisco. “It’s the highest that has ever been published in the literature for head and neck cancer, and in and of itself, it is strong evidence that modern chemoradiation therapy is highly effective for these patients.”

“Deintensification of chemoradiation treatments for HPV-associated oropharyngeal cancers is of very high interest to patients and researchers, but our study makes clear that these approaches should remain very experimental. Further work needs to be done to find ways that we can reduce side effects while maintaining these extremely high cure rates,” she said.

Oropharyngeal cancer is a type of head and neck cancer that affects the middle part of the throat. An estimated 70% or more of newly diagnosed cases of oropharyngeal cancer in the U.S. are caused by the human papillomavirus (HPV), and incidence rates of HPV-related disease are increasing rapidly in most developed nations, including the U.S. It is the most common HPV-related cancer for men, and the second most common for women, following cervical cancer.

People diagnosed with HPV-associated oropharyngeal cancers tend to be younger — the average age at diagnosis in the U.S. is 55 — and typically have much better outcomes than those with

throat cancer caused by tobacco or alcohol use. Radiation therapy is an especially effective treatment for tumors caused by HPV, which are more radiosensitive and therefore typically more responsive to treatment, and it can be used as a standalone treatment or combined with systemic therapy and/or surgery.

But many patients experience severe side effects during treatment, and a smaller number also experience long-term side effects from chronic inflammation and tissue damage that can arise up to two decades later, including difficulty swallowing or recurring infections of the soft tissue in the mouth and throat.

“Now that our chemoradiation treatments have improved to this point, we have a substantial number of patients surviving for longer durations, and we are starting to understand their experiences at very late follow-up,” Dr. Yom said. “The new challenge when treating these patients is how to keep them healthy and well for 25 or 35 years. We know that there is a minority of these patients who will have negative effects many years later.”

In this study, Dr. Yom and her team tested two lower-intensity treatment regimens against a control arm of more standard chemoradiation for people with HPV-associated, locoregionally advanced oropharyngeal squamous cell carcinomas. A total of 382 patients were randomly assigned to one of three treatment arms: (1) usual radiation dosing (70 Gy total mildly accelerated over six weeks) combined with cisplatin chemotherapy; (2) a reduced radiation dose (60 Gy total over six weeks) combined with cisplatin; and (3) a reduced radiation dose (60 Gy total mildly accelerated over five weeks) combined with an immunotherapy drug, nivolumab, in place of chemotherapy. All patients received intensity modulated radiation therapy, and most were male (90.6%), white (87.5%) and never-smokers (79.4%).

The Phase II trial was designed to trigger a futility analysis for each experimental arm after a predetermined number of patients experienced disease progression. These tests showed that neither de-intensified treatment approach met the threshold for non-inferiority compared to the standard treatment, however, and the trial was closed early.

“In very rigorous testing, those experimental arms did not produce equivalent results to the control arm,” said Dr. Yom. “The experimental arms were close to meeting their expected goals, but the patients treated on the control arm had such incredible results that we had an ethical responsibility to halt the study. I believe we have to take stock of this new benchmark and that new trial designs for this disease will need to account for this result.”

With a median follow-up of 2.2 years, the two-year PFS estimates were 98.1% following treatment on the control arm, 88.6% after reduced radiation with chemotherapy and 90.3% after reduced radiation with immunotherapy. The two-year overall survival estimates were 99%, 98% and 96.1%, respectively.

“I think this study is a good reminder that patients with this disease have really outstanding cure rates after we treat them with contemporary chemoradiation,” Dr. Yom said. “At this point, neither of the deintensification options we tested would be appropriate for standard of care use, because

you would actually be changing some patients' chance for a cure."

"This remains a work in progress, however. Most patients diagnosed with HPV-positive oropharyngeal cancer have a very long life trajectory ahead of them. As researchers, our focus now should be on identifying which patients can benefit from these newer paradigms, and then finding a more personalized therapy that works for each of these different groups of patients. The future goal would be that each patient gets what they need, but no more than what they need."

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