

What clinical trials can teach us

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For decades, researchers at the University of Michigan Rogel Cancer Center have been searching for ways to fundamentally change the approach to treating laryngeal cancer and underlying assumptions to improve clinical care for patients. Laryngeal cancer can severely alter patients' ability to talk and breathe. Treatment is limited, relying on aggressive surgery and insufficient therapeutics, which leaves patients

with few options.

A clinical trial from Rogel researchers used novel cytotoxic therapies and [chemotherapy](#), to try to improve outcomes for patients. Although the trial did not show that the approach was beneficial, the knowledge gained to a long history of evolving and re-evaluating standard of care.

Up until the 1990s, treatment for head and [neck cancer](#) was always surgery to remove the voice box. But Paul Swiecicki, M.D., clinical associate professor in [medical oncology](#), says that Michigan Medicine was instrumental in changing this therapeutic course. "The University of Michigan Head and Neck Oncology Group at the [cancer](#) center revolutionized the therapy by using chemoradiation first to try and avoid surgery with the end goal of saving the voice box and improve patients' quality of life." Although chemoradiation very effective, some patients still required a difficult surgery. Furthermore, this paradigm did not improve survival compared to previous treatment approaches.

Since then, the Rogel Cancer Center has a been a pioneer of discovering new ways to treat head and neck cancer, including the use of targeted agents. A decade ago, the Head and Neck Oncology Program began using an approach called bio-selection, borne from research showing that chemotherapy was able to predict if chemoradiation would be effective in eradicating head and neck cancers.

With bio-selection, patients are given one dose of chemotherapy as a predictor of response. If the tumor shrinks, they go on to receive chemoradiation. If the tumor does not shrink, patients receive surgery upfront.

"This approach was the first treatment that actually improved long term survival for patients with [laryngeal cancer](#)," Swiecicki explained. His group built on this advancement to try to further improve patient survival

and increase the rate of laryngeal preservation.

In the lab, researchers had identified a potential target: the protein BCL2, which is altered significantly in people with head and neck cancer. Moreover, it is highly expressed in those forms of head and neck cancer for which treatments are largely ineffective and is hypothesized to be the mechanism that causes these poor outcomes. Targeted inhibitors including one called AT-101 were developed in Rogel labs to try to reverse the effects of the protein BCL2.

The use of targeted inhibitors like AT-101 plus chemotherapy helped to kill head and neck cancer cells much more effectively. This finding was confirmed in many [preclinical studies](#), so it was moved forward into the clinical trial to test this approach's potential to translate into improving patient outcomes.

In a trial, Swiecicki and colleagues combined chemotherapy with AT-101 to try to improve efficacy.

Given that additional chemotherapy drugs often mean more tumor shrinkage, Swiecicki's team incorporated two cycles of chemotherapy, to the AT-101 compound, and evaluated if it would improve the rate of laryngeal preservation.

Unfortunately, this trial, published in *Head & Neck*, did not show improvement in laryngeal preservation. "Although we developed a great study and hypothesis," Swiecicki said, "it just didn't give us the information we'd hoped."

Still, Swiecicki is clear that this is an important part of the research process and, while unsuccessful in the short term, ultimately continues to create questions for researchers to explore and unearth avenues that lead to other paradigm shifts.

Swiecicki and his team remain encouraged. He believes the method of bioselection—versus the traditional approach of just chemoradiation and surgery—is still a promising approach to improve patient survival. But his goals have changed. "This study shows that adding more chemotherapy doesn't always equate to more success. The compound, although built on great preclinical data, didn't translate to improved patient outcomes. Instead, we need to focus on different treatment modalities."

With this knowledge, he and his team are looking to explore the role of immunotherapy combined with chemotherapy in future trial iterations.

"A lot of times in oncology, we think more is better. And this trial presumed that if we give more chemotherapy, patients will have better outcomes. Yet, that is not what our trial demonstrated. Although negative, this trial could potentially save people from unnecessary or excessive treatment in the future," Swiecicki said.

These findings also shed light on the importance and potential engrained in interdisciplinary research. Swiecicki is co-director of the [cancer center](#)'s Phase 1 Clinical Trials Program and says that the Head and Neck Oncology Program is one of Rogel's most multidisciplinary groups, with researchers in otolaryngology, hematology/oncology, radiation oncology, dentistry, pharmacology, and more. "It really draws on many disciplines to help direct patient care. The entire team uses innovation and basic science to improve quality of life outcomes."

More information: Paul L. Swiecicki et al, Randomized trial of laryngeal organ preservation evaluating two cycles of induction chemotherapy with platinum, docetaxel, and a novel Bcl-xL inhibitor, *Head & Neck* (2022). [DOI: 10.1002/hed.27043](https://doi.org/10.1002/hed.27043)

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