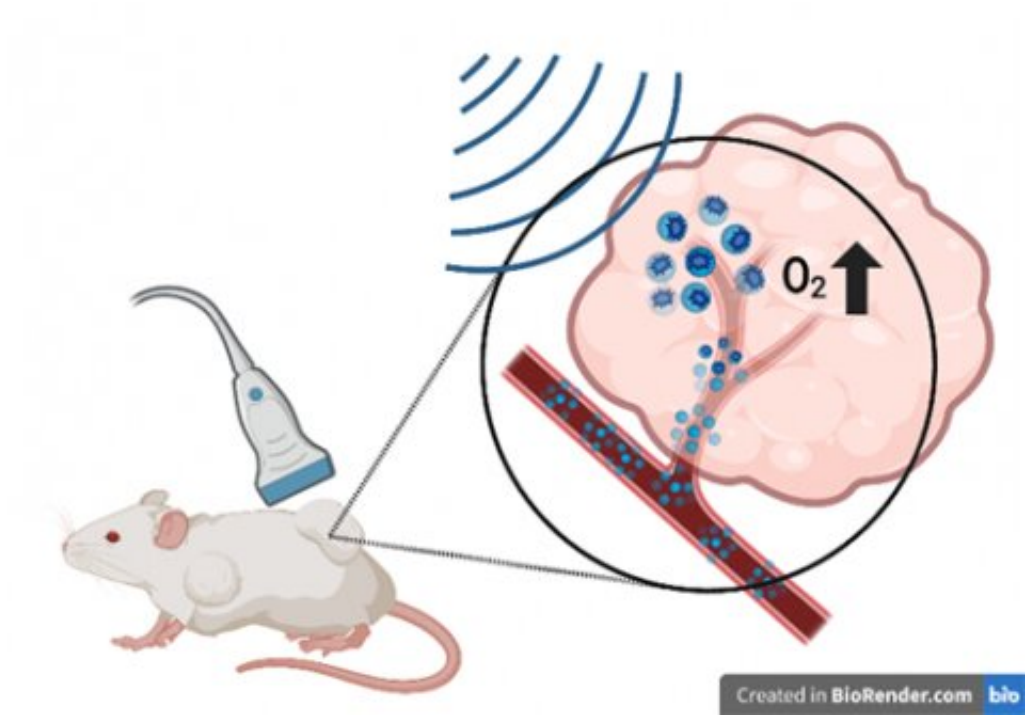
Delivering oxygen to tumors may be key in overcoming radiation therapy resistance

July 10 2023



Oxygen in tumors is necessary for radiotherapy to effectively treat cancer, but when tumors are hypoxic, this method can fail. A new strategy for raising tumor oxygen levels entails injecting oxygen-filled bubbles into the body and using ultrasound to burst them just at the tumor site. Credit: NIH, Created with BioRender.com

For most of our tissues and cells, a lack of oxygen, or hypoxia, is bad news. Cancer cells, on the other hand, can thrive in these hypoxic conditions, which render tumors less susceptible to anti-cancer

treatments, including radiation. Now, new research may offer a way to break through cancer's hypoxia-induced defenses.

A team led by researchers at Thomas Jefferson University and Drexel University has devised a strategy that combines ultrasound with microbubbles to deliver oxygen and cancer drugs to tumors. The results of their study, published in *Pharmaceutics*, indicate that the method—tested in mice—primed tumors to be more vulnerable to radiation therapy, resulting in slowed tumor growth and increased survival. The study authors suggest that with further development, their approach could be used to enhance the effectiveness of radiation therapy in the clinic for a variety of cancers.

"At the moment there's very little we can do on the clinical side to overcome hypoxia for radiation therapy, despite it being a well-known and documented limitation," said study author John Eisenbrey, Ph.D., an associate professor of radiology at Thomas Jefferson University. "The hope is that a more localized, more aggressive targeting of hypoxia, like what we've done here, will overcome some of that."

A long-standing staple of cancer management, radiation therapy, also called radiotherapy, is used to treat more than half of all patients with cancer. With this method, clinicians use high doses of radiation to kill cancer cells.

But many tumors are resistant to radiotherapy, and hypoxia is one of the major reasons why, Eisenbrey said.

"Whenever I say we're delivering oxygen to tumors, a lot of people say, 'Well, that's crazy. You're going to encourage them to grow,'" said study co-author Margaret Wheatley, Ph.D., a professor of biomedical engineering at Drexel University. But radiation therapy, which prevents cancer cells from replicating, requires an ample supply of oxygen close

by to be effective, she explained.

Seeking to beat radiotherapy resistance, Wheatley, Eisenbrey, and their colleagues designed a method that sensitizes tumors to radiotherapy using tiny, delicate bubbles (called microbubbles) that are about the size of red blood cells.

To increase oxygen levels in tumors, they packaged oxygen molecules into the microbubbles. And to prevent cancer cells from consuming the oxygen for their own benefit, they also added the drug lonidamine, which interrupts cancer cell metabolism.

After assembly, the microbubbles are injected and circulate throughout the body, only releasing their payload at the intended target, sparing healthy tissues. The trick to the targeted release is ultrasound. By specifically casting ultrasound waves at a tumor, the researchers can cause the microbubbles that have traveled there to pop and release their contents.

In a previous study, the researchers used the method to treat mice with tumors derived from breast cancer cells, producing favorable results. They upped the ante in the new work, instead working against head and neck cancer cell-derived tumors.

"They are notoriously more hypoxic than other solid tumors and also relatively resistant to radiation therapy," Eisenbrey said.

The study authors injected mice with microbubbles containing oxygen and lonidamine, bursting them at the tumor site with ultrasound, while also administering a drug called metformin—known to slow cancer growth—orally. Other groups of mice were given less than the full treatment, not receiving one or many of the elements of the strategy prior to radiotherapy.

After exposing the animals to radiation, the researchers tracked the size of the tumors over the following three months.

All groups that received some degree of treatment saw varying levels of slowed tumor growth. Mice treated with fully loaded bubbles and metformin prior to radiotherapy lived the longest, their tumor growth slowing drastically. The authors suggest the reason why is that the increase in oxygen within the tumors made them more vulnerable to radiation treatment.

Gaining ground on head and neck cancer is a very encouraging result, even in mice, Eisenbrey said. However, the team intends to continue fine-tuning the method by optimizing radiation and drug doses for better results and streamlining microbubble fabrication, ultimately bringing their solution closer to reality for patients with cancer.

"The authors are using ultrasound and microbubbles in an innovative way, delivering oxygen and drugs to tackle a very serious clinical dilemma. They obtained some promising results, so I'm curious to see how this approach fares with additional development," said Randy King, Ph.D., director of the ultrasound program in the Division of Applied Science and Technology at the National Institute of Biomedical Imaging and Bioengineering (NIBIB).

More information: Quezia Lacerda et al, Improved Tumor Control Following Radiosensitization with Ultrasound-Sensitive Oxygen Microbubbles and Tumor Mitochondrial Respiration Inhibitors in a Preclinical Model of Head and Neck Cancer, *Pharmaceutics* (2023). DOI: 10.3390/pharmaceutics15041302

Provided by National Institute of Biomedical Imaging and

Medical Xpress

Bioengineering