Penn team makes cancer glow to improve surgical outcomes

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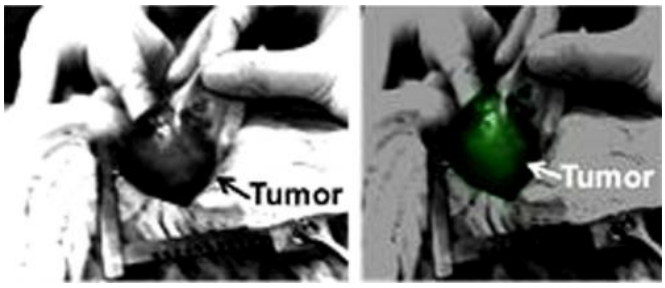

Viewed under infrared light, a tumor in a dog's lung glows green. The targeted dye ICG concentrates in cancerous tissues, allowing surgeons to tell normal tissue from tumor. The result may be a better surgical outcome. Credit: University of Pennsylvania

The best way to cure most cases of cancer is to surgically remove the tumor. The Achilles heel of this approach, however, is that the surgeon may fail to extract the entire tumor, leading to a local recurrence.

With a new technique, researchers at the University of Pennsylvania have established a new strategy to help surgeons see the entire tumor in the patient, increasing the likelihood of a positive outcome. This approach relies on an injectable dye that accumulates in cancerous tissues much more so than normal tissues. When the surgeon shines an infrared light on the cancer, it glows, allowing the surgeon to remove the entire malignancy.

"Surgeons have had two things that tell where a cancer is during surgery: their eyes and their hands," said David Holt, first author on the study and professor of surgery in Penn's School of Veterinary Medicine. "This technique is offering surgeons another tool, to light tumors up during surgery."

Holt collaborated with a team from Penn's Perelman School of Medicine led by Sunil Singhal, an assistant professor of surgery. Their paper appears in the journal *PLOS ONE*.

Between 20 and 50 percent of cancer patients who undergo surgery end up experiencing a local recurrence of their cancer, indicating that the surgeon failed to extract all of the diseased tissue from the site. Identifying the margins of a tumor can be difficult to do during a procedure, and typically surgeons have had to do this by simply looking at the tumor and feeling for differences with their fingers.

Seeking an alternative, Holt, Singhal and colleagues turned to near-infrared, or NIR, imaging. They chose to test the only Food and Drug Administration-approved contrast agent for NIR, a dye called indocyanine green, or ICG, that fluoresces a bright green under NIR light. ICG concentrates in tumor tissue more than normal tissue because the blood vessels of tumors have so-called "leaky" walls from growing quickly.

"Since 1958 when ICG was initially FDA approved, it has been used to examine tissue perfusion and clearance studies," Singhal said. "However, our group has been experimenting with new strategies to use ICG to solve a classic problem in surgical oncology: preventing local recurrences. Our work uses an old dye in a new way."

To see if visualizing ICG under NIR could help them define cancerous from non-cancerous tissues, the Penn-led team first tested the approach in mice. They administered ICG to mice with a type of lung cancer and found that they could use NIR to distinguish tumors from normal lung tissue as early as 15 days after the mice acquired cancer. These tumors were visible to the human eye by 24 days.

Next the researchers evaluated the technique in eight client-owned dogs, of various breeds and sizes, that had naturally occurring lung cancer and

were brought to Penn Vet for surgery. They received ICG intravenously a day before surgery, then surgeons used NIR during the procedure to try to visualize the tumor and distinguish it from normal tissue.

"It worked," Holt said, the tumors fluorescing clearly enough to permit the surgeon to rapidly distinguish the cancer during surgery. "And because it worked in a spontaneous large animal model, we were able to get approval to start trying it in people."

A human clinical trial was the final step. Five patients with cancer in their lungs or chest participated in the pilot study at the Hospital of the University of Pennsylvania. Each received an injection of ICG prior to surgery. During the procedure, surgeons removed the tumors, which were then inspected using NIR imaging and biopsied.

All of the tumors strongly fluoresced under the NIR light, confirming that the technique worked in human cancers.

In four of the patients, the surgeon could easily tell tumor from non-tumor by sight and by feel. In a fifth patient, however, though a CT and PET scan indicated that the tumor was a solitary mass, NIR imaging revealed glowing areas in what were thought to be healthy parts of the lung.

"It turns out he had diffuse microscopic cancer in multiple areas of the lung," Holt said. "We might have otherwise called this Stage I, local disease, and the cancer would have progressed. But because of the imaging and subsequent biospy, he underwent chemotherapy and survived."

Some other research teams have begun investigating NIR for other applications in cancer surgery, but this is the first time a group has taken the approach from a mouse model to a large animal model of spontaneous disease and all the way to human clinical trials.

One drawback of the technique is that ICG also absorbs into inflamed tissue. So in some patients that had inflamed tissues around their tumors, it was difficult or impossible to tell apart cancer from inflamed tissue. The Penn researchers are working to identify an alternative targeted contrast agent that is specific to a tumor cell marker to avoid this problem, Holt said.

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