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The Science of Making Tumors Glow: Innovations from the Center for Precision Surgery

Narrator:
Welcome to Medical Breakthroughs from Penn Medicine: Advancing Medicine Through Precision Diagnostics and Novel Therapies.

Dr. Johnson:

This is ReachMD and I am your host, Dr. Shira Johnson, and with me today is Dr. Sunil Singhal, Director of Center for Precision Surgery and Assistant Professor of Surgery at the University of Pennsylvania. Today we're going to be discussing surgery for glowing tumors. Dr. Singhal, welcome to the program.

Dr. Singhal:

Hi, thanks for having me.

Dr. Johnson:
So to start out with can you explain to us what are glowing tumors and how do you make tumors fluoresce or glow?

Dr. Singhal:
The basic idea behind the technology is that before the operation, whether any cancer operation, the patient comes in and they get an injection of a dye into their intravenous line. It's a special dye. They're contrast agents, but they're fluorescent in the sense that when they arrive at their location they start glowing. So, the dyes are specially engineered. Some of them are based on a global **macros* 1:06** molecules that go to differences in pH's in tumors and also differences in vascularity. Some of the other dyes are actually targeted. We have a dye, for example, that targets tumors that express folate receptor and tumors are very highly metabolic so they tend to eat up a lot of folate. And once the patient gets the injection, the dye accumulates over time in the tumors, and when the patient goes to surgery the tumors start fluorescing. And that's the basic principle how we get the tumors to glow.

Dr. Johnson:

So what is the benefit to the patient in the tumors that you just discussed with us? How do they benefit from better localization, increased vascularity that you can visualize, what's the benefit for the patient?

Dr. Singhal:

It depends on the cancer type. So, for example, one benefit would be margins, especially, for example, in breast cancer. If you want to make sure that the entire nodule has been removed out of the woman's breast, it's nice to have the edges of the tumor glowing and it really can help pinpoint and complete a negative resection operation. And this is becoming more and more pertinent in all sorts of area of surgery where people are trying to make smaller and smaller incisions and more directed operations. Another big area would be localization. CAT sans are picking up nodules on people when they're smaller and smaller. I'm a thoracic surgeon. We have this problem all the time. People are picking up 5, 6, 7 mm nodules. When you get into surgery it's very hard to find them. So, when the tumors are glowing, it gives us the ability to localize easier. This is very important in situations where we're doing minimally invasive surgery where we're using endoscopy or thoracoscopy or laparoscopy and we don't have the benefit of being able to put our fingers or hands into the body cavity to feel the nodule. And the third area is lymph nodes, identifying which lymph nodes are cancerous, which lymph nodes are not cancerous would be very beneficial. For example, melanoma where you don't want to take out any more lymph nodes than you have to because you might cause lymphedema in the peripheral extremities. Or in situations, for example, the thoracic surgeon, mediastinoscopy where we're trying to identify which lymph nodes in the mediastinum should be harvested. So, the

implications of making tumors glow are pretty far reaching.

Dr. Johnson:

So, you mentioned breast, you mentioned lung, and you mentioned melanoma. Are those the main types of cancer patients that will benefit from having their tumor visualized with glowing?

Dr. Singhal:

Breast for surgery. Melanoma, the verdict is out. Sarcoma, this is an area that we've really had some benefit. Lung cancer, yes. We're also looking very closely at brain tumors. So, brain tumors seem to…there's a lot of value in knowing the exact margins in brain tumors and trying to avoid any normal **lung*3:54** parenchyma that could cause any downstream neurological deficits. We're looking also at cranial-based surgery where there's, again, a lot of sensitive structures nearby. We've been looking at ovarian cancer and mesothelioma, cancers where it's a debulking operation; you want to try to get as much of the tumor out as possible. The other area that we've been looking at is prostate cancer. Oh, and I should also mention, nephron-sparing renal cancer operations. So, we've really taken a broad sweep of many different types of cancer.

Dr. Johnson:

Dr. Singhal, can you tell us a little bit about what the Center for Precision Surgery is about?

Dr. Singhal:

The Center for Precision Surgery is the first of its kind in the United States and the whole center is focused on trying to bring this technology to the cancer patient. It's a collaboration between 8 surgeons, several more scientists, in the street trying to speed up the process of bringing new contrast agents that are fluorescent to the clinic. The center was started last year and we've had some remarkable successes. We've actually already enrolled 54 patients in clinical trials and we're pretty excited about the progress we're having at the University of Pennsylvania on this.

Dr. Johnson:

If you're just tuning in, you're listening to Medical Breakthroughs from Penn Medicine on ReachMD. I am your host, Dr. Shira Johnson, and I am speaking with Dr. Sunil Singhal, Assistant Professor of Surgery at the University of Pennsylvania.

How many fluorescent contrast dyes are available and do you find that they work differently?

Dr. Singhal:

Right now we have been using 3 types of dyes in patients. We have 2 more in the pipeline and then there are several other groups that are developing other dyes. So, I think that in the next 3 to 5 years you're going to see a large number of dyes coming quickly onto the scene. The dyes do work differently. Some work by global properties of a tumor. For example, differences in pH or the differences in permeability. For example, the lymphatics are very different than tumors. The endothelial cell that creates the barriers from the tumorsand the vascularity are different. So, that allows, these generic molecules to accumulate. Other properties include metabolism. For example, there are molecules called ALA which get broken down into fluorescent byproducts. So, it would only occur in tumors. And then, the third way is, again, by targeting, for example, the folate receptor as I mentioned. We have dyes using different techniques. Right now, like I said, we have 3 in people and we're hoping to bring more online soon.

Dr. Johnson:

So this is really pretty exciting news especially in the area of cancer surgery where you don't want to damage the surrounding tissue. How else do you see the future of cancer surgery changing as a result of the work that you're doing now?

Dr. Singhal:

Well, if successful, there are many ways that this could begin to affect surgeons. For example, if you have patients who have poor pulmonary function and a lot of times we end up radiating these patients because we cannot take a chance taking out their entire pulmonary lobe and their lymph nodes. On the other hand, if now we can get into a situation where we can confirm negative margins, and we can identify which lymph nodes we need to remove, we can do more directed operations. So you potentially have patients who wouldn't be surgical candidates becoming surgical candidates, especially high-risk patients. I think also you can begin to see how this would apply in situations where you don't have a diagnosis. So, one study that we recently completed was 50 patients who didn't have a diagnosis on a lung nodule and we took them to the OR and we were able to put an endoscope in and if the tumor was glowing then we knew it was going to be a cancer and we would proceed with the operation. And this was very effective, especially in situations

where it was hard to get a frozen section, or it was hard to reach the tumor, or it would have been quite invasive to get a wedge excision of these nodules. So, beyond just the margins and the lymph nodes and the localization, some of these other issues, we call them optical biopsies, potentially could affect medicine as well.

Dr. Johnson:

And I'm sure the patients you treat are very grateful for the work that you're doing and begin able to minimize the invasiveness of the surgery that they're having.

Dr. Singhal, thank you for being with us today and sharing your insights regarding surgery for glowing tumors.

Dr. Singhal:

Thank you.

Dr. Johnson:

I'm your host, Dr. Shira Johnson, and thank you for listening.

Narrator:

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