New technology used in first fluorescence-guided ovarian cancer surgery

September 18 2011, by Elizabeth K. Gardner

A surgeon's view of ovarian cancer cells with and without the tumor-targeted fluorescent imaging agent. (Image courtesy of Philip Low)

The first fluorescence-guided surgery on an ovarian cancer patient was performed using a cancer cell "homing device" and imaging agent created by a Purdue University researcher.

The surgery was one of 10 performed as part of the first phase of a clinical trial to evaluate a new technology to aid surgeons in the removal of malignant tissue from ovarian cancer patients. The method illuminates cancer cells to help surgeons identify and remove smaller tumors that could otherwise be missed.

Philip Low, the Ralph C. Corely Distinguished Professor of Chemistry who invented the technology, said surgeons were able to see clusters of

cancer cells as small as one-tenth of a millimeter, as opposed to the earlier average minimal cluster size of 3 millimeters in diameter based on current methods of visual and tactile detection.

"Ovarian cancer is notoriously difficult to see, and this technique allowed surgeons to spot a tumor 30 times smaller than the smallest they could detect using standard techniques," Low said. "By dramatically improving the detection of the cancer - by literally lighting it up - cancer removal is dramatically improved."

The technique attaches a fluorescent imaging agent to a modified form of the vitamin folic acid, which acts as a "homing device" to seek out and attach to ovarian cancer cells. Patients are injected with the combination two hours prior to surgery and a special camera system, called a multispectral fluorescence camera, then illuminates the cancer cells and displays their location on a flat-screen monitor next to the patient during surgery.

The surgeons involved in this study reported finding an average of 34 tumor deposits using this technique, compared with an average of seven tumor deposits using visual and tactile observations alone. A paper detailing the study was published online Sunday (Sept. 18) in Nature Medicine.

Gooitzen van Dam, a professor and surgeon at the University of Groningen in The Netherlands where the surgeries took place, said the imaging system fits in well with current surgical practice.

"This system is very easy to use and fits seamlessly in the way surgeons do open and laparoscopic surgery, which is the direction most surgeries are headed in the future," said van Dam, who is a surgeon in the division of surgical oncology and Bio-Optical Imaging Center at the University of Groningen. "I think this technology will revolutionize surgical vision. I

foresee it becoming a new standard in cancer surgery in a very short time."

Research has shown that the less cancerous tissue that remains, the easier it is for chemotherapy or immunotherapy to work, Low said.

"With ovarian cancer it is clear that the more cancer you can remove, the better the prognosis for the patient," he said. "This is why we chose to begin with ovarian cancer. It seemed like the best place to start to make a difference in people's lives."

By focusing on removal of malignant tissue as opposed to evaluating patient outcome, Low dramatically reduced the amount of time the clinical trial would take to complete.

"What we are really after is a better outcome for patients, but if we had instead designed the clinical trial to evaluate the impact of fluorescence-guided surgery on life expectancy, we would have had to follow patients for years and years," he said. "By instead evaluating if we can identify and remove more malignant tissue with the aid of fluorescence imaging, we are able to quantify the impact of this novel approach within two hours after surgery. We hope this will allow the technology to be approved for general use in a much shorter time."

Low and his team are now making arrangements to work with the Mayo Clinic for the next phase of clinical trials.

The technology is based on Low's discovery that folic acid, or folate, can be used like a Trojan horse to sneak an imaging agent or drug into a cancer cell. Most ovarian cancer cells require large amounts of the vitamin to grow and divide, and special receptors on the cell's surface grab the vitamin - and whatever is linked to it - and pull it inside. Not all cancer cells express the folate receptor, and a simple test is necessary to

determine if a specific patient's cancer expresses the receptor in large enough quantities for the technique to work, he said.

Ovarian cancer has one of the highest rates of folate receptor expression at about 85 percent. Approximately 80 percent of endometrial, lung and kidney cancers, and 50 percent of breast and colon cancers also express the receptor, he said.

Low also is investigating targeting molecules that could be used to carry attached imaging agents or drugs to forms of cancer that do not have folate receptors.

He next plans to develop a red fluorescent imaging agent that can be seen through the skin and deep into the body. The current agent uses a green dye that had already been through the approval process to be used in patients, but cannot easily be seen when present deep in tissue. Green light uses a relatively short wavelength that limits its ability to pass through the body, whereas the longer wavelengths of a red fluorescent dye can easily be seen through tissue.

"We want to be able to see deeper into the tissue, beyond the surface," Low said. "Different cancers have tumors with different characteristics, and some branch and wind their way deeper into tissue. We will continue to evolve this technology and make improvements that help cancer patients."

In addition to Low and van Dam, the paper's authors include George Themelis, Athanasios Sarantopoulos and Vasilis Ntziachristos of the Institute for Biological and Medical Imaging at the Technical University of Munich in Germany; Lucia Crane, Niels Harlaar, Rick Pleijhuis, Wendy Kelder and Johannes de Jong of the division of surgical oncology of the BioOptical Imaging Center at the University of Groningen; Henriette Arts and Ate van der Zee of the division of gynaecological

oncology at the University of Groningen; and Joost Bart of the Department of Pathology and Molecular Biology of the University Medical Center of Groningen.

Low is the chief science officer for Endocyte Inc., a Purdue Research Park-based company that develops receptor-targeted therapeutics for the treatment of cancer and autoimmune diseases. Endocyte holds the license to the folate receptor-targeting technology and is spinning this technology off into a new company called OnTarget.

Ntziachristos led the team at the Technical University of Munich that developed the camera system. A startup company named SurgOptix BV is working to commercialize the camera system.

Provided by Purdue University