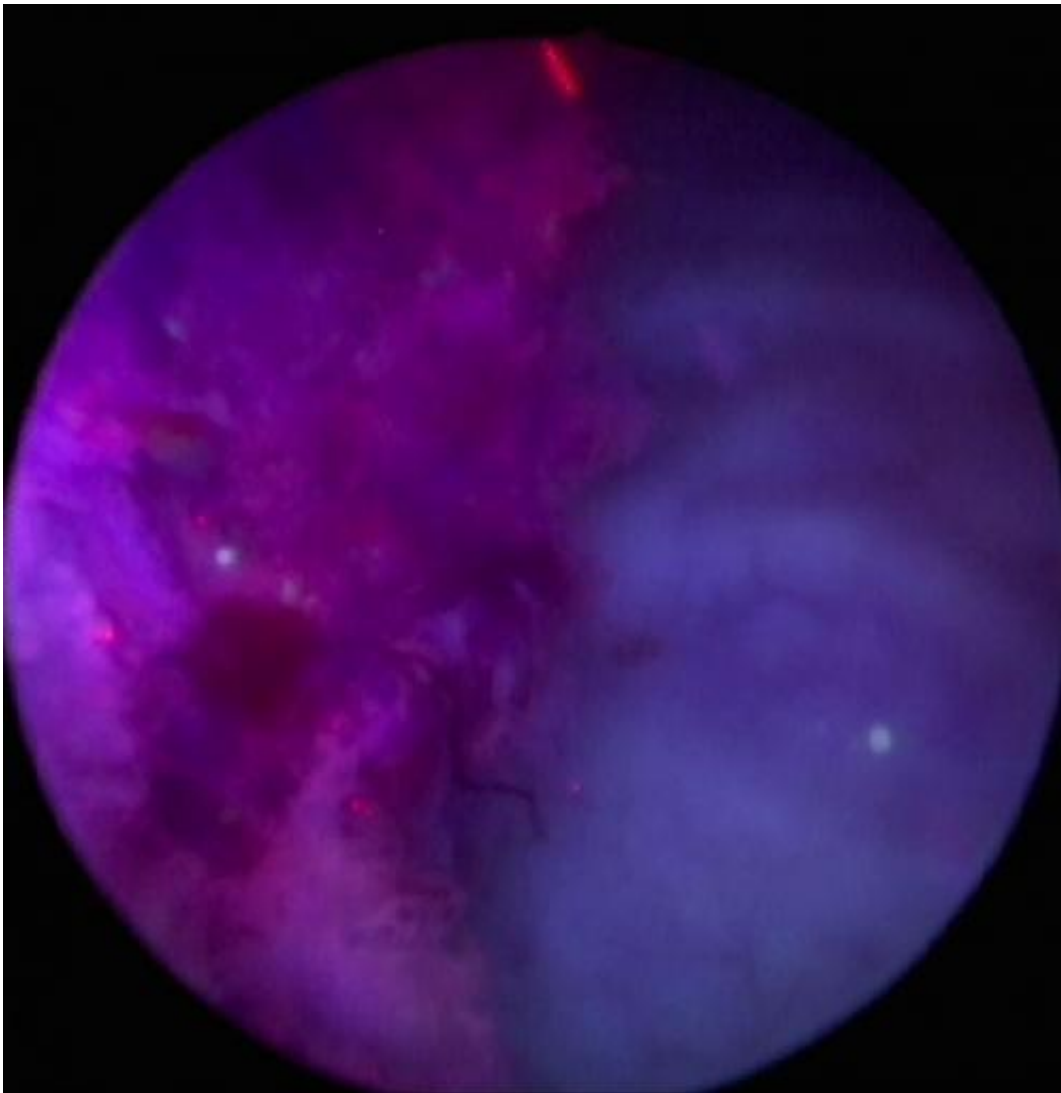


New molecular imaging technology could improve bladder cancer detection

October 29 2014



Endoscopic fluorescence imaging of a large papillary bladder cancer using anti-CD47. Credit: Ying Pan and Joseph Liao

Researchers at the Stanford University School of Medicine have developed a new strategy that they say could detect bladder cancer with more accuracy and sensitivity than standard endoscopy methods. Endoscopy refers to a procedure in which surgeons use an instrument equipped with a lens to see inside the patient.

The researchers identified a protein known as CD47 as a molecular imaging target to distinguish bladder [cancer](#) from benign tissues. In the future, this technique could improve bladder cancer detection, guide more precise cancer surgery and reduce unnecessary biopsies, therefore increasing cancer patients' quality of life.

The work is described in a paper that will be published Oct. 29 in *Science Translational Medicine*.

Bladder cancer, the fifth most common cancer in the United States, is generally identified in the clinic by a procedure called cystoscopy, an endoscopy in the bladder. Then in the operating room, surgeons remove the cancerous tissue for biopsy.

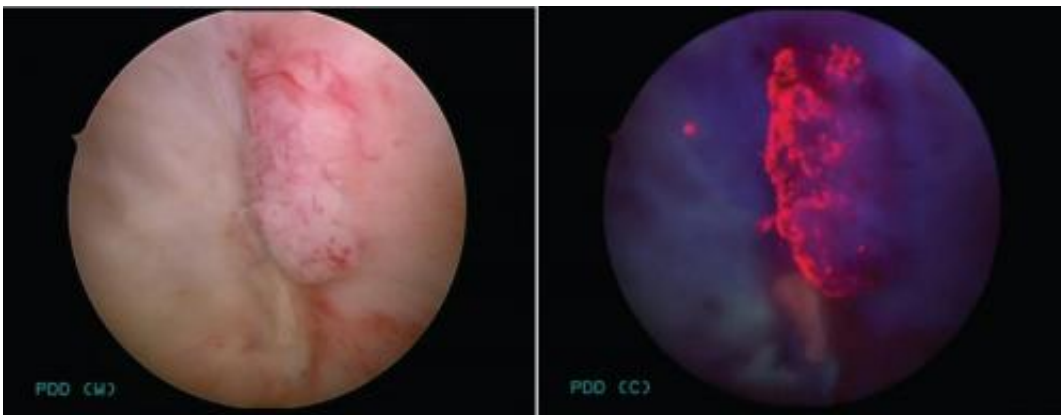
Need for close monitoring

Bladder cancer must be monitored closely because it has one of the highest recurrence rates of all cancers. It is important that cystoscopy imaging be both highly sensitive (able to detect subtle cancer) and specific (able to distinguish between benign and cancerous tumors) so surgeons can remove [cancerous tissue](#) at an early stage to prevent invasion into the underlying muscle, which may require complete removal of the bladder. However, standard cystoscopy has insufficient sensitivity and specificity, particularly for flat-appearing cancers that blend in with the bladder and may be confused with inflammation.

"Our motivation is to improve optical diagnosis of bladder cancer that

can better differentiate cancer from noncancer, which is exceedingly challenging at times. Molecular imaging offers the possibility of real-time cancer detection at the molecular level during diagnostic cystoscopy and tumor resection," said co-senior author Joseph Liao, MD, an associate professor of urology and the chief of urology at the Veterans Affairs Palo Alto Health Care System. The lead author is Ying Pan, PhD, a research associate in Liao's lab.

Some bladder cancer treatments irritate the bladder and cause inflammation. Although this may help kill the cancer, it makes detecting recurring tumors difficult because cancerous lesions and inflammation look very similar. The surgeon must perform a biopsy to know for sure. Often the biopsied tissue is free of cancer, but the procedure can cause unnecessary stress for the patient.



Endoscopic molecular imaging of a flat bladder cancer (carcinoma in situ) using anti-CD47 under white light (left) and blue fluorescence (right). Credit: Ying Pan and Joseph Liao

"What you'd really like to do is decide how dangerous the tumor is in the office," said Eila Skinner, MD, professor and chair of urology and a co-

author of the paper. "Doing a biopsy is not a really difficult thing to do, but it's really hard on the patient."

Useful imaging target

To improve the specificity of the imaging, the researchers needed something that would distinguish [cancer cells](#) from benign cells. They needed a target, which they found in CD47, a protein on a cell's surface that signals the immune system not to attack the cell. Most cells produce it, but cancer makes a lot more CD47 than normal cells. In previous work, Irving Weissman, MD, professor of pathology and of developmental biology and co-senior author of the paper, discovered that blocking the "don't eat me" signal from CD47 in cancerous cells allowed the immune system to resume its attack against many different types of cancer, including bladder cancer. He and his team developed an anti-CD47 antibody that binds to the cancer cell's surface and blocks the signal.

"We hypothesized if it's a good therapeutic target and it's also expressed on the surface of the cancer cells, it may be a good imaging target," Liao said.

To test their hypothesis, the researchers added a fluorescent molecule to an antibody that binds to CD47. The modified antibodies were then introduced into intact bladders, which had been surgically removed from patients with invasive [bladder cancer](#). Because the bladders were kept in good condition, the study's imaging methods mirrored the process a urologist might use with a real patient.

After 30 minutes, they rinsed the bladder, so only the antibodies that bound to the CD47 protein remained. When the tumor was exposed to fluorescent light, the cancer cells "lit up" whereas normal or inflamed cells did not.

Liao and his team successfully tested two fluorescent tags and imaging technology combinations. Researchers attached the molecule fluorescein isothiocyanate, which glows in the presence of white light, to the anti-CD47 antibody and introduced it into the bladder. Then, they used confocal endomicroscopy, an instrument that shines white light and takes high-resolution images of the bladder. They also attached a fluorescent molecule quantum dot to the anti-CD47 antibody that glows in the presence of blue light. Then they used blue light cystoscopy to make an image of the bladder.

Avoiding unnecessary biopsies

"This will add to the existing technology and may help avoid unnecessary biopsies," said Badrinath Konety, MD, professor and chair of urology at the University of Minnesota, who was not involved in the study.

"Everyone is going to be excited about this."

The researchers performed biopsies of 119 tissue samples from 26 bladders. They removed 35 tissue regions that glowed pink (cancerous) and 84 tissue regions that did not (noncancerous). They sent the samples to co-author Robert Rouse, MD, professor of pathology and chief of the pathology service at VA-Palo Alto, who analyzed all the tissues samples and was blinded to the imaging diagnoses. Overall, they found the sensitivity of cancer detection to be 82.9 percent and the specificity to be 90.5 percent.

Some major hurdles to getting this technology to patients have been cleared: A candidate anti-CD47 antibody for therapeutic use in human cancers is currently being tested in a small clinical trial; clinical-grade imaging technologies are already available; and the whole-organ imaging approach closely mimics how a surgeon could use the method in patients. But before putting the technique into practice, the anti-CD47 antibody/fluorescent molecule would need to be approved for this

purpose by the U.S. Food and Drug Administration.

"Our goal through better imaging is to deliver a higher-quality cancer surgery and better cancer outcomes," Liao said. "I am very excited about the potential to translate our findings to the clinics in the near future."

More information: "Endoscopic molecular imaging of human bladder cancer using a CD47 antibody," by Y. Pan et al. *Science Translational Medicine*, 2014. [stm.sciencemag.org/lookup/doi/ ... scitranslmed.3009457](https://stm.sciencemag.org/lookup/doi/10.1126/scitranslmed.3009457)

Provided by Stanford University Medical Center

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