Seeing cancer in a new light

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In this issue of the *Journal*, Okusanya and colleagues¹ present a study of a novel method used intraoperatively to visually differentiate adenocarcinoma from surrounding normal lung parenchyma. This technique leverages the significantly upregulated expression of a cell surface protein, folate receptor α (FR α), on the exposed surface of adenocarcinoma, with as many as 10^3 to 10^4 receptors per cell. A molecular conjugate, folate–fluorescein isothiocyanate, which binds to FR α , is then visualized with an intraoperative fluorescence imaging system. This work builds on the previous experience of Okusanya and colleagues¹ with novel optical imaging techniques for lung cancer.

Okusanya and colleagues¹ describe this as a pilot study, in which they investigated 50 patients undergoing thoracotomy for biopsy-proven adenocarcinomas. Disappointingly, only 7 of the 50 tumors were visible before resection. The visible tumors were all large and close to the pleural surface. On tumor bisection on the back table, however, all but 4 tumors fluoresced (92%). Not unexpectedly, the Achilles' heel of the technique is tumor depth beneath the pleural surface.

As we move toward the detection of smaller lesions through lung cancer screening, as well as toward the use of minimally invasive surgical techniques challenging direct palpation, more practical techniques for intraoperative localization are sorely needed. Knowledge of segmental anatomy is, of course, paramount. Beyond this, we are left with a cadre of techniques that are time-consuming, unreliable, or resource intensive. They include dye marking with either navigational bronchoscopy or computed tomographically guided percutaneous injection, preoperative localization with wires or microcoils, or intraoperative imaging with computed tomography or ultrasonography. All techniques have significant disadvantages. We need a reliable method to visualize subpleural tumors that can be performed safely, on the fly, and in the operating room.

There are 2 types of readers of this study. The reader drinking the half-empty glass of water will easily identify several weaknesses of both the technique and the study itself, many of which are acknowledged by Okusanya and colleagues.¹ The most important obstacle is the fact that tumors more than a centimeter below the pleural surface are not detectable until they have been removed and bisected. This is akin to the little light bulb remaining on behind a closed refrigerator door—no one is aware, and no one cares. Because this system is not endoscopic, all patients in the study underwent thoracotomy. It is not revealed why these patients were selected for thoracotomy rather than a video-assisted or robotically assisted approach. Furthermore, FR α is only expressed on adenocarcinomas, which comprised fewer than half the tumors discovered in the National Lung Screening Trial.² And of the 50 adenocarcinomas, 8% did not express FR α and therefore did not bind folate–fluorescein isothiocyanate. Because all these tumors were biopsy-proven cancers, we do not know how benign inflammatory nodules will behave and therefore do not truly understand the positive predictive value of fluorescence. Although Okusanya and colleagues¹ mention that there was no evidence of extrathoracic disease on positron emission tomographic scanning, we were not told whether ultimate tumor stage was a variable. This study would have been much more compelling had we learned of the optical characteristics of involved lymph nodes, either macroscopic or microscopic.

But let's say we reopen that refrigerator door and pour ourselves a half-full glass of water. Development of any new technology has to start somewhere, usually at proof-of-principle. What Okusanya and colleagues¹ have discovered is that they can make 92% of all adenocarcinomas glow to the naked eye, requiring no special training at all. Even the 3 ground-glass adenocarcinoma in situ and minimally invasive adenocarcinoma tumors with low standard uptake values emitted fluorescence. They believe that with some adjustments to the system they will eventually be able to visualize even the subpleural tumors with intraoperative spectroscopy, an imaging device with a longer exposure time, or a near-infrared tracer. We will patiently wait for this to be fitted to an endoscopic system so that it will have more practical utility for thoracic surgeons. We are already seeing the emergence of real-time optical technology to differentiate perfused from ischemic tissues in the open, video-assisted thoracoscopic surgery, and robotic surgery arenas.³⁻⁵ The in situ optical imaging took only

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8 minutes to perform—clearly more time efficient than our current localization options, with very little procedural risk. Imagine the possibility of having positive lymph nodes glow from beneath the mediastinal pleura, or glow during a mediastinoscopy. Sampling error might be greatly reduced, and full dissections or even random sampling might no longer be necessary. Involved lymph nodes within the hilar dissection of a video-assisted thoracoscopic surgical or robotic resection may be more easily visualized. These possibilities are certainly exciting.

Imagination is an essential component of any technologic progress. This study should be viewed as a launching pad, rather than be judged solely on practicality in its current form.

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