By Mike Martin

Martin Fuss, M.D., remembers the old days when radiologists treated a large area to get at a small tumor. Back then, the bone-encased male prostate seemed like an immovable object, recalled Fuss, who directs the image-guided radiation therapy department at the Oregon Health Sciences University in Portland. But advanced imaging technology now makes it possible to spot the slightest movement, he said. “We’ve found that even the prostate can move.”

These slight movements are critical to radiation therapists who can now take precise aim at tumors, sparing surrounding tissues. “Because we are now able to zero in very tightly on a tumor,” Fuss said, “motion is so much more important.”

And nowhere more important than in the lung, where every breath can move a tumor.

In radiation therapy, tracking lung tumor motion has become a hot area of research. Implanted devices are one way to track motion, but they require surgery and have been associated with a 20%–50% greater risk of pneumothorax, or air in the pleural cavity, which can collapse or lead to infection of an already embattled lung. A better way, according to some experts, is to use anatomic surrogates—organs or structures, usually near the tumor, whose movements closely track tumor motion.

Tracking tumor motion during radiation therapy is “one of the most important things we do,” said Stephen Feigenberg, M.D., a radiation oncologist at Fox Chase Cancer Center in Philadelphia. “Everyone is trying to figure out how to do it without implanted tracking devices. It would be wonderful to come up with a noninvasive approach, and that’s the appeal of anatomic surrogates.”

Recently, two groups proposed different anatomic surrogates for lung tumor motion—the diaphragm and the carina, a cartilaginous ridge that divides the trachea into the primary bronchi. Their latest studies have ignited debate over which surrogate works best.

In June, Steve Jiang, Ph.D., Laura Servino, Ph.D., and fellow researchers from the Center for Advanced Radiotherapy Technologies at the University of California, San Diego, published the results of a 2-year study that favors the diaphragm as a lung tumor motion surrogate. Their findings appeared in the journal Physics in Medicine and Biology.

In July 2008, radiation oncologists Suresh Senan, Ph.D., and Lineke van der Weide, heading a seven-person team from Amsterdam’s VU University Medical Center, published a study supporting the carina as anatomic surrogate in the International Journal of Radiation Oncology and Biological Physics. They confirmed and extended those findings in the same journal this June and presented their findings, with some new caveats, at a meeting in early September.

Case for the Diaphragm

Jiang and colleagues studied 10 patients with stage I–IV lung cancers, examining 513 images across 32 fluoroscopic sequences, or 16,416 images per patient. Jiang said his team deliberately took multiple images to overcome difficulties they saw in an earlier diaphragm-as-surrogate study that used only 10 images per patient.

“If there is some error when marking tumor or diaphragm position in some images, those errors will smooth out because we have so many images per respiratory cycle,” he said.

Tumor and diaphragm positions varied widely across the study cohort. Mean tumor motion ranged from 12 to 24 mm. Mean distance between the tumor and diaphragm ranged from 2 to 46 mm. With these data, Jiang’s team created two mathematical models to express a simple correlation: If the diaphragm is here, then the tumor, which may not be visible, must be there. Because first the diaphragm moves, and then the tumor moves, a brief delay between the two motions, called a phase shift, occurs. To compensate for the phase shift, the Jiang team’s second model also considered the diaphragm’s previous positions, making it slightly more precise than the first model.

The straightforward math behind the models gives the position of the tumor as a function of the diaphragm’s position at any time:

\[ T = a + bd, \]

where \( T \) is the tumor position, \( a \) and \( b \) are constants derived from analyzing the images, and \( d \) is the diaphragm’s position.

Calling a perfect correlation between the tumor and diaphragm positions 1.0, Jiang and his team reported a mean correlation of 0.94 in the first model; 0.98 in the second, more precise version; and one much poorer 0.76 correlation, which they labeled an outlier. Jiang attributed the outlier to “inconsistent motion” inside the patient’s lungs, illustrating that “correlations should be examined on a patient-by-patient basis.”

That’s good advice, said Harvard Medical School radiation oncologist Ross Berbeco, Ph.D., a frequent Jiang coauthor who views all surrogates as “clinically useful” but “equally suspect.” The diaphragm “may be OK for some cases but should not be used universally,” he said.

Carina Conclusions and Caveats

Senan and colleagues conclude that the carina is the best surrogate for tracking lung tumors but with a caveat: The diaphragm works better than the carina for some tumor locations, and vice versa. They presented this finding in early September at the 2009 meeting of the European Society for Therapeutic Radiology and Oncology, in Maastricht, The Netherlands.
For the July 2008 report, Senan—a professor of clinical experimental radiotherapy at the VU University Medical Center—along with radiation oncologists Ben Slotman, M.D., and Frank Lagerwaard, M.D., examined 30, 4-dimensional computed tomography (4D CT) scans (a series of scans showing movement) from each of 14 patients with locally advanced stage III lung tumors. They monitored the carina’s position in patients whose breathing was both free and coached.

Audio coaching, which can be as simple as a recorded voice saying “in” and “out,” can improve 4D CT image quality by improving breathing regularity, Senan said. Studies have also shown that without coaching, surrogates are almost useless. “Without coaching, predictive errors were found to be unacceptable,” said Kalamazoo, Michigan–based radiation oncologist William Dunn, M.D.

Comparing carina to diaphragm motion in three different directions, the VU team found that craniocaudal (head-to-toe orientation) carina motion correlated better with tumor motion than did diaphragmatic motion. Audio coaching increased this correlation while also increasing carina mobility twofold in every direction.

Senan’s team reaffirmed these results in a longer June 2009 study with VU radiation oncologist Femke Spoelstra, M.D., correlating the 3D tumor position in 59 artifact-free 4D CT scans, acquired during uncoached breathing, in each of 23 patients. “This second analysis again revealed the carina to be a better surrogate of 3-D tumor position than the diaphragm,” Senan said.

But they looked more closely at tumor location after considering a possible weakness in their earlier research. “Our work with Spoelstra studied only four lower-lobe tumors, which could have been less favorable to the assessment of the diaphragm as surrogate versus the carina,” Senan said. For a more extensive analysis, they repeated the study in 40 patients, with 17 that had lower-lobe tumors.

Although they confirmed that the carina is generally a better surrogate than the diaphragm for verifying the position of both upper- and lower-lobe tumors, they also found that the correlation works best between 4 and 13 cm from the diaphragm. “For tumors located less than 4 cm from the diaphragm, the diaphragm is a superior surrogate,” Senan said. “For tumors more than 13 cm from the diaphragm, both surrogates had a similar association with tumor position.”

Basing surrogate choice on a range of positions makes sense to clinician Dunn. “I would choose the surrogate closest to the tumor as the reference,” he explained. “For instance, if the tumor were in the middle of the lung, I’d defer to the carina.”

Debate Not Over

Despite the carina study’s caveat, Jiang and his UC–San Diego team still disagree with its conclusions. In their June 2009 report, Jiang and colleagues argue that the VU team did not take into account the phase shift between the motion of diaphragm and lung tumor, thereby underestimating the correlation between their two positions.

“Delays between diaphragm motion and tumor motion may be different from that between carina motion and tumor motion,” Jiang team member Laura Cervino said. “Because the VU model did not account for these delays, the diaphragm may only look like a worse surrogate than the carina. In our study, we accounted not only for these delays but also for differences in motion patterns.”

Jiang’s team also questions using 4D CT imagery to study real-time motion. A CT scan is one image at one point in time, rather than a series of images through several points in time, Jiang argues. “Scans of the diaphragm and scans of the tumor position correspond to different breathing cycles, which might have different breathing amplitudes,” he writes. “Therefore, diaphragm position . . . might not correspond to tumor position in a CT scan.”

Naturally, Senan and his team see it differently. “Jiang’s group used fluoroscopy, a 2-dimensional technique that is not suitable for 3D analysis of tumor motion,” Senan said. “We have previously shown that 4D CT is superior.”

But Jiang remains unmoved. “Since we used much more informative data and much better models for our study, our conclusion is on much more solid ground,” he said.

Plethora of Choices

Despite this debate, the choice of best lung tumor surrogate is not restricted to the diaphragm and carina. Reflective markers tracked by a 3-D camera make skin a “useful surrogate,” noted Washington University’s Bradley. And tumors themselves can be surrogates for their own motion. “A tumor on a chest x-ray can be used to guide fluoroscopic imaging just prior to turning the beam on to treat the patient,” Bradley said.

Worried that softer tissues such as the diaphragm make for surrogate-tracking results that are hard to reproduce, Fox Chase’s Feigenberg said he prefers bone. “I usually use vertebral bodies to follow lung tumors, which don’t move that much on breathing.”

Given a choice between the diaphragm and carina, Ohio State University Medical School cancer research chair Arnab Chakravarti, M.D., said he uses both. But surrogates also have limits, doing little, for instance, to overcome the “intrinsic radiore sistance of these tumors.” For that reason, surrogate research “isn’t that much of a big leap forward” in lung cancer treatment, said Chakravarti, who also directs the department of radiation oncology at the Arthur James Comprehensive Cancer Center in Columbus.

And despite concerns about pneumothorax, experts such as radiation oncologist Percy Lee, M.D., of the University of California, Los Angeles, David Geffen School of Medicine, still prefer implanted fiducial, or reference, markers. Implanting tiny strands of radiation-opaque gold into the tumor “isn’t much different from performing a needle biopsy,” he said. “I rarely use surrogates and I’ve rarely seen a case of pneumothorax. If you have the technical expertise, implanted markers are safe and work well.”

Similar to fiducial markers, wireless transponders are an up-and-coming option. A company called Calypso Medical is developing a transponder that acts like a radio frequency identification chip, Bradley said, giving off a signal that can be triangulated by an antenna array to precisely show tumor locations. But the transponder must be implanted surgically, with “significant risk of pneumothorax,” he added.

All the interest in anatomic surrogates aside, Fuss predicts that they’ll be obsolete in a few years, replaced by direct, noninvasive systems that can track moving tumors.
in real time. Although it’s expensive and not yet widely available, the robotic Accuray Cyberknife, Fuss said, is one example of where the direct-tracking state of the art ultimately resides.

“Direct tracking is highly preferable to the use of anatomic surrogates,” agreed Harvard’s Berbeco. “Jiang and I and others have been working on methods for tracking lung tumors directly and are of the same mindset on this issue. We collaborate and compete in this field, but we also build on each other’s work toward a common goal.”