What are the Characteristics of the Nodules that are Biopsied but Mistakenly Called Benign?

We know that there is a big difference between a lung (or pulmonary) nodule and having cancer. Formal screening studies or just random CT scans done for other reasons will often show nodules that are of questionable significance, leading us to recommend either follow-up imaging or an immediate biopsy, depending on the level of suspicion. Often, the biopsy gives us an explanation for the nodule: perhaps cancer, but otherwise, perhaps just inflammatory or scar tissue, or else infection. That answer is usually the right answer, but not always. There is a chance that a result that comes back as “not cancer” is actually a false negative result: this happens there is actually cancer, but the correct answer wasn’t detected. What are the features that suggest a greater probability that we can’t necessarily be as confident of a biopsy result that comes back as something other than cancer?

We can get some insight about this question from the published experience from the radiology groups at Cornell University and Mt. Sinai Medical Centers in New York City, who just published on their results of the clinical and imaging features of their false negative CT-guided biopsy results over a three-year period from the beginning of 2002 to the end of 2004 (Dr. Yankelevitz, who has great experience as an expert in CT screening and biopsies and who did a terrific webinar for us on detecting and evaluating lung nodules last year, is the senior author of this paper). To do this, they reviewed the results from 170 patients in that interval who had an initial biopsy that was reported as negative initially who were then either found to:

- have a lung cancer later diagnosed
- have a subsequent procedure (such as a surgery) that confirmed a benign cause, or
- showed resolution of the questionable nodule, or
- showed stable findings over at least two years of follow-up that would be considered very consistent with a benign nodule

From this group of 170 patients, further follow-up confirmed a benign cause for 152 of the cases (confirming that there are plenty of benign nodules out there, and these were only the ones suspicious enough to merit an initial biopsy), while 18 were later shown to be false negatives and had a cancer confirmed later (some lung, some other cancers). An independent radiologist who was not involved with any of the initial biopsy attempts reviewed the films from all of these procedures to assess the technical aspects of each case. What the group found when they compared the two groups was that the people with false nodules were more likely to have the following features (all differences statistically significant):

- larger nodules (mean size 27 mm vs. 17 mm)
- fewer imaging adjustments per attempted biopsy (4.5 vs. 6.4)
- higher proportion with the tip of the needle not documented to be within the target lesion (24% vs. 5%)
- more likely to experience a collapsed lung (called a pneumothorax) from the biopsy attempt (50% vs. 22%) — note that many of these were small enough to require hospitalization, a chest tube, or significant interventions
Because some of the features of the case are inter-related (harder cases to biopsy tend to require more imaging adjustments and have a greater chance of not having the needle tip confirmed to be in the lesion, for instance), the investigators also did a multivariate analysis where they removed the effects of certain overlapping features. When that occurred, they showed that the development of a pneumothorax, the presence of a solitary nodule, and the particular radiologist doing the biopsy procedure were significant factors.

Some of these results may make intuitive sense, but others less so. Certainly, learning that the less experienced radiologist was less accurate isn’t surprising, though this operator-dependency is worth noting as yet another clear example of where experience and specialization matter. It’s also very obvious that in cases where the needle tip wasn’t demonstrated to get into the target, the reliability of your biopsy is far more questionable. And it’s easy to imagine that when lung collapse was observed, this led to earlier termination of the biopsy and fewer attempts. And in the world of lung nodules, seeing a solitary one is generally more suspicious for cancer than seeing several, which is a pattern more suspicious for inflammatory or infectious changes.

You might think that it would be easier to biopsy a larger mass, and while that’s true, it’s easier to miss the cancer if the larger lesion is actually comprised of a combination of cancer and infection or collapsed lung. Larger lesions can also have areas of necrosis (cell death) within the center of the tumor, because the cancer can outgrow its blood supply, leading to a sampling from within the area of cancer that fails to demonstrate evidence of a viable cancer.

Similarly, because imaging adjustments tend to be more needed for difficult cases (smaller, inaccessible lesions), it’s counter-intuitive that the ones requiring fewer adjustments were more accurate. In this case, it may also be related to larger lesions being accessible but perhaps not sampled in the wrong place.

As CT screening for lung cancer is likely to become more prevalent, we’re likely to be seeing and biopsying a lot more lung nodules. Overall, it’s important to remember that the results of this work indicated that a biopsy will often yield a clear and collect answer, but not always. Suspicious findings still merit follow-up to ensure that findings remain stable or resolve with appropriate treatment. But it’s also a situation in which it’s helpful to have someone with experience doing the procedure to maximize the probability of coming away with the right answer.