Micrometastases: What They Are and Why We Might Care

The notorious and always welcomed words after surgery are, “we got it all”, providing great relief to the patients and families who hear the phrase. We know that surgeons can take out all identifiable disease that they see when they do surgery, and that there is no evidence of visible disease on CT scans or on newer imaging techniques like PET scans. But why do we see that approximately 30% of patients with stage I NSCLC or about 50% of patients with stage II NSCLC recur? How do so many patients with SCLC achieve a complete response, with no evidence of visible disease on scans, but then have recurrence months later? These recurrences occur because of **micrometastases**, too small to be visible to the eye at surgery or on any scans, but travelling through the bloodstream or lymphatic system, destined to grow into visible recurrent cancer in the future. So we’re actually mistakenly staging patients as early stage lung cancer, when they actually have metastatic disease, but undetectable by current practice. We can actually find micrometastatic disease in many cases by using monoclonal antibodies that stain small amounts of cells with the right proteins, which are **epithelial markers** (science terms you can more or less ignore unless you see them elsewhere, and then you’ll understand that these markers are used to find cancer cells as needles in a non-cancer haystack). These markers are almost never false positives (almost never, ever seen in patients without a cancer, less than 2% of the time), and they light up on the actual tumor readily. In the few studies that have looked at aspirates of bone marrow in patients with clinical stage I – III NSCLC, about 40% of patients will show evidence of micrometastatic cancer cells in the bone marrow (see table below for references). The potential importance of micrometastases is that they have been correlated with a worse disease-free survival/higher recurrence rate than that seen among the patients who did not show micrometastatic disease in their marrow.

![Micrometastases in NSCLC](image)

(click to enlarge)

These are small trials, but the results have been consistent, and other types of cancer have shown similar patterns. Also, one of the studies (Pantel abstract here) demonstrated that patients who had increasing numbers of micrometastases present in marrow over time
demonstrated a particularly worse survival. This pattern of increasing micrometastases seems to predate the development of clinically visible metastases, at least in the modest amount of research done thus far in lung cancer.

In a few studies that have done multivariate analyses (looking at lots of factors as being potentially predictive of better or worse outcome, presence of micrometastases has emerged as an important independent predictor. The studies do not suggest that certain lung cancer subtypes, or tumor size, or even nodal stages are associated with occult micrometastases. The fact that nodal stage is not closely associated with micrometastases suggests that the mechanism of micrometastasis spread may be different from spreading through the lymphatic system through lymph nodes.

It is still debated whether these micrometastases really represent viable cancer cells about to create visible satellites of cancer on future scans. Some studies have shown that metastatic spread is inefficient, that many cancer colonies are started and subsequently die off without every becoming a viable, visible metastasis. Nevertheless, with the results from micrometastasis studies showing the association with survival, it appears at least that the presence of micrometastases reflects a higher likelihood of metastatic recurrence in the future, even if these micrometastases don’t all translate to a new metastatic focus.

Why hasn’t this idea taken off? Why are doctors not recommending that patients get bone marrow aspirations every few months as a routine surveillance technique? People who have had a bone marrow aspiration and biopsy might be able to explain. While some well-trained people can do them with a patient only experiencing mild discomfort, nobody finds them fun, and they can be pretty darn uncomfortable. You have to put a big hollow needle into the bone, usually at the top of the pelvis in the back, or occasionally from the sternum (breast bone). It may be more popular than a root canal, but it’s a lot less popular than a dental cleaning, and may be in the cavity filling range. It’s much easier to do scans and draw blood. In fact, there are some new techniques that are looking into detecting individual cancer cells traveling through the blood, but thus far, they aren’t especially reliable, with some not sensitive enough to find cancer cells in high risk patients (I participated in a trial in which the only patient in whom the blood-based metastatic cells were detected was a patient who turned out to have SCLC), or they pick up cells that the technique calls cancer cells from normal volunteers who don’t have cancer (and don’t develop it in the near future, just in case you were about to ask).

The technique of finding occult micrometastases in the marrow of a patient with early stage NSCLC would be very helpful in order to perhaps separate out the patients who need post-operative chemo from the ones who don’t. Or maybe we could try to detect micrometastatic disease in patients who have undergone chemo and radiation for locally advanced NSCLC or limited SCLC, to help us decide who might benefit from more treatment and who should stop and be watched, saving potential treatment for a time in the future when they show a rising count of micrometastases. However, it’s quite cumbersome and unpopular to seek repeated bone marrow samples from patients, and it would be far more feasible to look carefully for micrometastases in blood samples, if the science behind it becomes sensitive enough in the future. We’re not quite there yet, and in the meantime, people are generally much more inclined to get a CT scan regularly.