MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

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The Use of Molecular Testing at a Diagnosis of Melanoma

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H&O What are the limitations of using traditional clinical and pathologic factors to assess melanoma risk?

VS We know that on occasion—in perhaps 5% to 10% of cases—a tumor that is considered relatively low risk by all known criteria winds up being very aggressive and killing the patient. In addition, approximately 50% to 60% of patients with high-risk melanoma never have a recurrence. The greater the number of informative factors we are able to build into our definitions of low and high risk, the better our predictions will be. For example, a patient with a thin melanoma may have a 90% chance of cure initially, but if a sentinel node biopsy is positive for cancer, that chance will be smaller. Conversely, if a patient is initially classified as being at high risk but the sentinel node biopsy is negative, the chance of a cure might increase from 50% to 80%. However, we will never be able to say with certainty whether a particular patient with melanoma will have a recurrence solely on the basis of clinical and pathologic factors. Looking through a microscope does not provide all the information we need to know about a tumor; ideally, we would also be able to learn about the genes contained in that tumor.

Variations in pathology are an additional source of problems. Back in 2010, we conducted a study at Moffitt (with Santillan as the first author) of 420 patients with thin melanoma or melanoma in situ who had been referred to our center. We found that when we reviewed the patients' outside biopsy samples, our pathologist made a change that influenced management in more than 20% of cases—a change in surgical excision margins in 12% of patients and a change in the decision about whether to perform a sentinel node biopsy in 16% of cases.

H&O What molecular tests are in use for patients with newly diagnosed melanoma?

VS Pathologists can run a number of tests that go beyond standard microscopy, including immunohistochemical staining evaluating the rate of mitosis and proliferation, fluorescence in situ hybridization (FISH) analysis, cytogenetic testing, and comparative genomic hybridization (CGH). We often use FISH and CGH tests to confirm diagnoses in pediatric melanoma, which is an area of particular clinical interest to me; they are less commonly used in the management of melanoma in adults. Increasingly, we are seeing the use of genomic testing such as targeted mutation analysis or next-generation sequencing, but this is more commonly done for evaluating treatment options in metastatic melanoma than in primary melanoma diagnosis.

Pathologists sometimes use the myPath Melanoma gene expression profiling test from Myriad, which can be helpful in determining whether a patient has a mole or melanoma. However, although this test has a reasonable track record for discriminating benign nevi from typical melanomas, it remains unproven in challenging melanocytic neoplasm subsets such as those that are Spitzoid in histology. So in the toughest cases, we do not always know what to do with the test result. With FISH and CGH, the greater the number of genetic abnormalities found with this test, the more likely the sample is to be melanoma. But with proprietary gene expression tests like myPath, we really do not know what the test score means on a biological basis or how it is derived. That is not to say it cannot be useful, just that we are not able to understand and learn from the test having given the result it did.

After we are certain that we are dealing with melanoma, we decide whether to conduct a sentinel node

biopsy. That decision is made on the basis of the pathology results; we currently do not have a validated test that will provide further information to guide the decision. Right now, the sentinel node biopsy result is negative 85% of the time, on average. If we could cut our biopsy rate in half without missing any of the 15% of patients with a positive biopsy result, that would be a significant advance. It is a big ask, however, to expect a test to have a sensitivity of 100%. Some oncologists have tried to use existing tests for this purpose, but I think that is a dubious approach.

> We need to have a validated test before oncologists and surgeons can feel comfortable skipping the sentinel node biopsy in even a subset of patients.

H&O What about the use of molecular tests to determine prognosis in melanoma?

VS That would be the next step—to know not only which patients need a sentinel node biopsy but also which have tumors that are going to spread widely and lead to death. This outcome is more difficult to predict and depends on a greater number of underlying factors. Complicating matters is that some of those factors are within the tumor and some are within the patient. For example, one person's immune system might be better than another's at fighting an aggressive melanoma even if the genetic profiles of the 2 tumors are identical, so any test that looks only at the tumor looks at only part of the problem.

Another problem arises when one is trying to predict the future on the basis of a tumor biopsy: what if the tumor is heterogeneous? Sometimes the biopsy sample shows indolent cells while cells in other areas of the tumor are aggressive. What if just 1% of the cells are aggressive—is that enough to be a problem? Must 10% of the cells be aggressive to be a problem? We do not know the answers to these questions, and they have not been raised nearly often enough in relation to gene expression profile testing and other molecular tests. The first biopsy specimen might not be identical to a subsequent wide excision, and obtaining the wrong sample can lead to the wrong prediction. I think that it has to be proved in an organized, rigorous fashion that any test marketed for predictive purposes can provide the same information regardless of where the biopsy sample is taken—in the most invasive central portion, at the noninvasive peripheral margin, or in an area of regression. If such were the case, we could feel very comfortable with any biopsy specimen obtained for use in a given test. However, if samples from different parts of the tumor produce different results, we are back to where we started in terms of uncertainty.

The other standard we still need to meet is proof that these tests work in a real-world setting. Most existing studies identify patients who died within a year or two and those who were still alive after 5 years and examine their biopsy specimens retrospectively. However, real-life tumors are not black and white like that; we see tumors that fall across the entire spectrum of outcomes. And because the tests are never perfect, we do not want to risk withholding treatment from people who need it. The rates of false positives and false negatives are very important. For example, consider a thin melanoma for which the chance of the patient having a positive sentinel node is only 10%. As a surgeon, I am willing to do 100 sentinel node biopsies to find those 10. But what if I did only half as many biopsies, on the basis of molecular testing, and found only 8 of the 10 positive nodes? My success rate would be higher, but I would have missed 2 cases.

For all of these reasons, here at Moffitt we do not use any commercially available tests, such as the DecisionDx-Melanoma test from Castle Biosciences. These tests have not been adequately validated, they are not endorsed by the American Academy of Dermatology or the National Comprehensive Cancer Network outside of clinical trials, and we do not consider them to be clinically valuable. Despite this lack of validation, Medicare and Medicaid sometimes cover the cost of these tests in eligible patients, and they are becoming more commonly used. However, no agreement has yet been reached on what exactly to do for a patient according to the results of the tests.

H&O What are the arguments in favor of using a commercially available molecular test to determine prognosis in melanoma?

VS Proponents will argue that it can be worthwhile to tell 20 people among 100 that something terrible will happen to them, even if it will happen to only 5 of them, so that we can be super-aggressive in screening and following them. My response is, how does that help? Some may respond that the sooner we detect a recurrence, the better. But we have no proof that this is true. We know that early detection of the primary melanoma is better, but this is not early detection per se because we have already detected the melanoma. This is intensive surveillance for

metastatic disease in a patient you think is at high risk but nonetheless might not be.

H&O Are additional tests in development?

VS Several companies are working on gene expression profile testing to predict sentinel node positivity. I view this as low-hanging fruit because researchers can find out if someone has a positive sentinel node much sooner than they can know whether that person will live or die in the next 10 years.

I am involved in a trial, which is still in the planning stages, that will look at a test developed by SkylineDx. The goal is to validate this test for use in predicting which patients with clinically node-negative melanoma can skip the sentinel node biopsy. If we are able to proceed with the trial, it will take at least a year and a half to see results. I cannot predict whether this test will work, but we need to have a validated test before oncologists and surgeons can feel comfortable skipping the sentinel node biopsy in even a subset of patients. We are not close to being there yet, but I think that this is an achievable goal with currently available technology.

H&O Is gene expression profiling useful in other types of melanoma besides cutaneous melanoma?

VS Melanoma of the eye is a different situation. Gene expression profiling and other forms of genetic testing are much better established for use in the eye than in the skin, for several reasons. First, taking a large biopsy sample is unacceptable in the eye because you may damage vision or even need to remove the entire eye. In addition, the eye contains no lymphatics, so we are without the additional information that the sentinel lymph nodes provide in skin melanomas. As a result, standard clinical evaluations and pathologic tests are less useful for predicting prognosis in eye melanomas than in skin melanomas. So scientists began using cytogenetic testing very early on in ocular melanoma and learned that the presence of 3 copies of a particular chromosome (trisomy 8) or just 1 copy of another (monosomy 3) can be associated with bad outcomes. Now we are able to draw fluid from the eye with a needle and test that fluid with gene expression profiling, which has led to the development of a test from Castle called DecisionDx-UM for predicting metastatic risk in uveal melanoma. This is a better prognostic test than any of the ones that exist right now for skin melanoma, and it has been prospectively validated in clinical trials. Even so, we still struggle to know how to use the information the test provides because treatment options for uveal melanoma are limited compared with those for cutaneous melanoma. This emphasizes that we need to take molecular testing beyond biology and learn how to make sound clinical decisions based on test results, if we want to make these tests a cost-effective part of the management of melanoma.

Disclosure

Dr Sondak is a compensated consultant for Bristol-Myers Squibb, Eisai, Merck, Novartis, Pfizer, and Regeneron. He is working with SkylineDx to develop a prospective validation trial of a gene expression profile but is not compensated by SkylineDx or any other company involved in the development or marketing of gene expression profiling.

Suggested Readings

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