

MELANOMA CARE OPTIONS™

SURGICAL UPDATE

QUESTION-AND-ANSWER SESSION

from *The Three R's of Melanoma: Risk, Relapse, & Response*



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Question: Dermatologists in the community are treating lentigo maligna melanoma on the face with imiquimod. What do you think of this?

Dr Ross: Imiquimod is a reasonable option for a patient who has a lot of comorbidity and who would need a significant surgery. The problem with imiquimod in these cases is that these lesions are usually big, and you will often miss the invasive component that you cannot appreciate on physical exam. You may end up undertreating the patient by using imiquimod, and you won't get the penetration into the deeper part of the skin to get a full response. There is an anecdotal response with using imiquimod. However, it should be reserved for patients who wouldn't be candidates for other standards of care. There isn't any prospective data to look at the role of imiquimod in lentigo melanoma.

Dr Haluska: Using medical therapy when the standard of care is surgery may put you on shaky ground because you are not utilizing the therapy, diagnosis, and staging that is obtained with surgery.

Question: When should you do SLN biopsies for melanomas <1 mm?

Dr Ross: This is based on the fact that Clark level 4 melanoma changes the stage from 1A to 1B. There is not a lot of good data separately for Clark level 4 as being a great predictor for a positive sentinel node. There are actually better predictors for that in the thin melanoma group than Clark level 4. In trying to be consistent with the staging system, however, we would offer a sentinel node biopsy in a patient with a thin melanoma if the only other factor was a Clark level 4 lesion.

The other factor to look for is ulceration. However, the incidence of an ulcerated primary for a thin melanoma is about 6%. The incidence of a Clark level 4 lesion is about 14%. The two factors that we use the most are the vertical growth phase and a mitotic rate greater than zero, because they are the best predictors for positive sentinel nodes.

Question: What is the rate of regression in a melanoma less than 1 mm in thickness that would push you to do a sentinel node biopsy?

Dr Ross: This is a tough question because there's been so much controversy about what regression means in primary melanoma. Some people think it's a good thing, and some people think it's a bad thing. It is feared that you may be underestimating the thickness of the melanoma because of the area of fibrosis that is present. You can ask the pathologist to measure the area of fibrosis, or area of regression. If the thickness of the area of regression equals the area of a primary melanoma—for example, if the fibrosis extended to more than a millimeter—this would influence my decision to do a sentinel node biopsy.

Some practitioners use the extent of regression, which can be focal, partial, or extensive. Focal is a small area, partial is 50%, and extensive is greater than 50%. The Sydney Melanoma Unit looked at a small group of patients with thin melanomas who presented with gross nodal disease at the same time as their diagnosis. All of the patients had evidence of regression on their primary tumors. This shows that using extent of regression may not be the best course. I would have the pathologist measure the depth of regression to see if the area is similar to the area of a lesion without regression.

Question: Any suggestions regarding CLND in the field that has been disrupted because of the initial SLN biopsy? When do you perform deep nodal dissection?

Dr Ross: If the patient has disease in the superficial groin and CT scan shows disease in the iliac fossa, there's no question that the patient needs superficial and deep dissection. My personal opinion is that any time there's gross disease in the superficial system, regardless of the findings on the CT scan, the risk of finding microscopic disease in the deep system is pretty high. I have a relatively low threshold to combine superficial and deep because in my experience, most of the lymphedema is caused by superficial dissection. There's very little evidence from studies that the addition of the deep system actually significantly increases the incidence of lymphedema. It does increase the length of the operation and may increase length of recovery. There is very little in the data to suggest that the addition of the deep system increases long-term morbidity, especially when looking at lymphedema.



Some practitioners use Cloquet's node, which is the first kind of obturator node under the inguinal ligament, as the sentinel node of the deep system, in order to be selective about deep dissection. The problem is that there isn't a consistent anatomical description of the location of Cloquet's node. I would do a superficial dissection and Cloquet's node evaluation. This is the only time I would do a frozen section on a node to check for disease, so I wouldn't have to come back if it was positive. The only time I use Cloquet's node is in those patients who have microscopic disease of the superficial groin by sentinel node evaluation. If Cloquet's node is negative, I wouldn't do a deep dissection.

As far as handling a disrupted basin after a sentinel node biopsy, I ellipse out the area of skin as part of the incision and raise flaps around that so I don't get into the previous cavity. There doesn't seem to be a higher incidence of infection after a sentinel node biopsy, so I can do a complete dissection. The incidence of recurrence in basin failure after formal dissection for a positive sentinel node is around 5% or 6%, which is very low. Therefore, another utility of sentinel node biopsy is to improve regional control.

Question: Except for the groin, is there any reason not to use radiotherapy on the appropriate nodal basin when there are positive nodes? Wouldn't radiation plus interferon give the best overall control?

Dr Douglas: I still think the best overall control and the least amount of disease you can have is after a completion lymph node dissection. I think if the indicators are there, then the answer is yes. Local irradiation to the nodal bed followed by interferon would be what we'd recommend.

Dr Ross: I think the question was for any positive node, right?

Dr Douglas: The data have not been shown for any positive node. The risk factor really does appear to be a numbers game, much as it is in breast cancer: 4 nodes and above, or a single node that has extracapsular extension. Aside from that, it has not been shown that there is a statistically significant difference in control in that area.

Question: How frequently do you see a 1.8-mm melanoma in the neck, with a negative sentinel node, show up 7 years later with metastases to the brain and lung without local disease?

Dr Haluska: This is, in essence, the case I presented. I think we often underestimate the lethality of a thin melanoma with no other adverse features. Patients are frequently told by their primary dermatologists that they are clear and there is no chance this will recur. The risk is on the order of 15%. If you know the sentinel lymph node is negative, the odds improve. There are still failures, however. So I'd say that is probably a 5% to 10% occurrence.

Dr Ross: Yes, this is an important issue. I don't think people should walk away from any sentinel node discussion. It's the only prognostic factor that is important. It's currently the best one we have for the stage I and stage II patient population. But it certainly does not account for the 4%, 5%, or 10% of hematogenous spreaders that spread through the bloodstream without evidence of node involvement. I will say that's a relatively rare

case. Most of the patients who develop stage IV disease have some prior case of lymph node involvement.

Question: Can you comment on the role of neoadjuvant chemotherapy for lesions that pose a challenge for surgery, for example, eyelid tumors?

Dr Haluska: That's an interesting question because it's directed at using a systemic treatment for extensive local disease. That has not been well studied. In most cases the primary lesion is resectable. For the cases that are similar to the ones posed by Merrick, the issue of neoadjuvant therapy is one of local recurrence and is better substantiated. We have more information on how distant disease responds.

I think this is a practical issue, but there is very little data in the literature to guide us. It does open a whole discussion about our understanding of the genetics of different subtypes of tumor. In the last year there's been a lot of information that has come to be understood about the patterns of mutations that we see in acral, mucosal, and ocular melanomas that set them apart from the usual cutaneous melanoma on sun-damaged skin. In the near future, for a lesion like this that is most likely a mucosal melanoma (although it could be a cutaneous melanoma on the skin of the eye), there may be targeted therapies that will give us the chance to offer a response without toxic systemic therapy.

The direct answer to the question is that it's a "dealer's choice." If you think it might help, there's not a downside to doing something systemically, if you understand the response rates are typically fewer than 10%.

Dr Ross: I think it makes sense biologically; your surgical results may be better with a tumor that's responding to therapy. If you have a tumor that is responding, you will have less micrometastatic disease in the field. This may allow you to get a wider surgical resection margin.

Dr Douglas: That's assuming you have concentric shrinking of the tumor.

Dr Ross: It's interesting. We have more data for breast cancer that says the tumors respond in a concentric pattern. This is why we can do breast-conserving therapy with that type of response. It preserves the breast and produces negative margins. There is very little data on melanoma, however.

Question: How do you recommend therapy (surgery vs medicine) be directed with a patient presenting with stage IV melanoma?

Dr Haluska: 5% of patients with stage IV melanoma do not have an identified primary. If you look at the literature, there have been patients who were excluded from studies if they had a nondiagnostic or regressed lesion removed. Clearly there are patients with metastatic disease with no cutaneous precursor. Their disease will behave like cutaneous melanoma in one of two fashions: stage III or stage IV disease. If they present with a solitary lymph node basin that could have been from regional lymph node drainage, they behave like stage III melanoma. If a person presents with an axillary, groin, or supraclavicular node metastasis and no history of melanoma, the initial approach would be to treat it as if there were a cutaneous primary. We



would do a complete therapeutic dissection, consider radiation as necessary, and offer adjuvant therapy.

If they present with brain metastases or disseminated visceral disease without a primary site, however, they behave like stage IV disease. We typically treat them with clinical trial therapy or systemic therapy.

Dr Ross: Let me comment on that as well, because unknown primaries are an interest of mine. We have a paper that came out a couple of months ago that says patients should be treated according to how they present with metastases, regardless of whether a primary tumor was identified. If they have nodal disease, they behave like other stage III patients with nodal disease. The same is true for stage IV patients. If they have small-volume disease systemically, it's isolated. We would do surgery first, the same treatment as if the patient had a known primary melanoma. I think how a patient presents with the disease should dictate how they should be treated. Whether or not they have a primary diagnosis is probably not that relevant.

Question: What's the first treatment with or without CNS proven disease?

Dr Haluska: In my practice, I treat patients with CNS disease as if they have a completely different disease. This is because their outcome is almost exclusively dictated by how their brain tumors do. The limiting factor in their survival and morbidity is how their brain tumors are going to respond, whether or not they have systemic disease. If they have CNS disease, I typically treat them with an algorithm that starts with consideration of surgery, stereotactic radiation, and potentially palliative radiation therapy. I do not use temozolomide that often. There is a current paper in *Cancer* that shows temozolomide plus thalidomide had a 0% response rate in patients with metastatic melanoma in the brain.¹ I don't use medical therapies. I typically refer to the best specialist I can.

If they don't have CNS disease, my algorithm is based on whether or not the disease is resectable. If it is not resectable, they may be eligible for our clinical trial. If they are not eligible for clinical trial, they may benefit from some palliative chemotherapy, usually DTIC, or DTIC and platinum. It is not a mistake that I rank surgery over clinical trial. I feel there are very few clinical trials out there that have curative potential at the moment. You saw from the data that we gave you, up to 20% to 30% of patients with the right features in a solitary or oligodistribution of metastases could be curable. I subject those patients, somewhat unconventionally, to metastasectomy.

Question: Is there a need for a medical oncologist consult for a patient who has successful wide local excision for a melanoma of less than 1 mm? What is the appropriate follow-up testing for patients with thin melanomas who have not had SLN biopsies?

Dr Haluska: I would broaden that to something more generally applicable: what if it's greater than 1 mm and they still have negative SLN biopsy? There is a variation in local practice. Many of my colleagues, especially those who almost exclusively see melanoma, do follow these patients. I personally don't think a medical oncologist needs to be involved. We

talked about the fact that these patients can relapse, but their relapses are often delayed. The 7 years that was referred to in an earlier case is not unusual. Many of these patients have a longer natural history. They can be easily diagnosed by the dermatologic care that is necessary. Their chances of developing additional melanomas of the skin are high. They need to see a dermatologist at least every 6 months or maybe every year. I typically do not use medical oncologic follow-up if their sentinel lymph nodes are negative.

The details of a follow-up schema for thin melanomas without SLN biopsies have not been worked out. There's been a lot of controversy as to the necessity of follow-up CAT scans, chest x-rays, or blood work. There are data in the literature that suggest x-rays do not pick up metastases with any appreciable frequency and therefore do not affect outcome. In breast cancer and lymphoma there are randomized trials with large numbers of patients that are comparing intensive radiological schemes to routine clinical follow-ups. My personal view is that radiology does not have much to offer in this case. We do not have therapies that would benefit a patient if it were applied a month or two early. I recommend dermatologic follow-up for patients with negative sentinel nodes. If they have positive sentinel nodes, I'd base my follow-up on the natural history of disease. The median time to recurrence for most of these patients is about 3 years. I see them every 3 months for the first 3 years. I see them every 6 months after that, based on their lower rates of recurrence. I typically follow them for 5 or 6 years, then discontinue follow-up. If the patient wants to continue follow-up after that, it is their decision. I don't do routine radiologic testing; however, I do have a low threshold for imaging symptoms. If they have back pain, they get an MRI.

Dr Ross: The most important issue for patients with thin melanomas that don't have SLN biopsy because their risks are so low is the identification of a second primary. They are more likely to develop a new primary melanoma than to have a recurrence of the original melanoma. Dermatologic follow-up is the key.

Reference

1. Krown SE, Niedzwiecki D, Hwu WJ, Hodgson L, Houghton AN, Haluska FG. Phase II study of temozolomide and thalidomide in patients with metastatic melanoma in the brain: high rate of thromboembolic events (CALGB 500102). *Cancer*. 2006;107:1883-1890.