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Discussion

Dr. John Daly (Philadelphia, Pennsylvania): Thank you, Dr. Thompson. Malignant melanoma is a disease that is increasing in frequency in the United States of America. But fortunately it appears as though both earlier stages and thinner lesions are being identified.

Dr. Morton and his group should be complimented on developing this mathematical model that may predict survival in patients with pathologically involved regional lymph nodes. Interestingly despite the fact that these are cases that already have metastatic disease, they have noted that characteristics of the primary, such as thickness, and patient characteristics such as gender, and the site of location of the primary continue to be important survival predictors. This probably explains the tremendous heterogeneity of survivorship in this series, from 76% to 14%.

He and his group also should be complimented on their use of node mapping, because it is a major contribution, and I think it will allow us to test various concepts of elective nodal dissection with much less morbidity.

I have several questions. In the manuscript you noted that the 5-year survivorship of patients in this series was 46%, compared with an earlier series of 37%. Is this due to a more biologically favorable group of patients such as we have seen with colon cancer, for example? Or is there some other cause? It did not appear as though adjuvant immunotherapy was borne out to be effective by the univariate analysis.

Second is there any explanation as to why the site of location continues to be a major predictor of survival, even though we are talking about cases that have already metastasized to regional lymph nodes?

Third you noted that synchronous and nonsynchronous metastases are not different, but is time to the development of nodal metastasis important? In the patient who develops nodal mets 3, 4, or 5 years after the primary has been resected, do they have a better survival?

Finally have you had the opportunity to prospectively test your model in a group of patients that were not actually included in the model that you developed?

Dr. G. Aranha (Maywood): Does your scan identify those patients with intransit metastases? If it does, would removal of these metastases at the time of simultaneous node dissection and wide excision of the primary further improve your survival rates?

Dr. J. B. Aust (San Antonio, Texas): This is a continuing report by Dr. Morton's group, who have long tilled in the vineyard of malignant melanoma, the chameleon of malignancies, with its bizarre course from patient to patient.

They present a very large database, and extensive statistical analysis of risk factors leading to a mathematical formula that forecasts prognostic risks. I would not touch that formula with a 12-foot pole. It is probably statistically sound, but it looks very difficult to apply.

The previous study had a poorer prognosis than the present study, and one worries that retrospective data may not forecast the future results of the next series of patients. There may be other factors, however, that account for the current better results.

One, the disease may have changed. I really doubt that has occurred. We see more patients and we see them earlier, but I do not think the disease itself has changed.

Two, patients may be getting better treatment, because we are seeing the patients earlier and operating earlier on them. It is certainly not because of effective immunotherapy or chemotherapy, because these modalities have not proved to be of significant benefit in malignant melanoma.

The third factor is probably the most important one, better classification. We may be moving a number of previous early stage cases into a more advanced stage. Dr. Morton's techniques of mapping and perhaps better pathologic examination of excised lymph nodes all tend to produce more lymph-node-positive cases than there were in the previous group, reducing the number of stage I cases and increasing the number of stage II with patients of lesser tumor burden, thereby improving the reported results of both stages.

So I think that what may be happening is that they are improving the final results by restaging the patients in a more effective way, and not because of better therapy.

I would like Dr. Morton to address that particular issue, and I wish him well in his continued studies. He has been one of the senior investigators of malignant melanoma over a number of years.

Dr. Edward Krementz (New Orleans, Louisiana): President Thompson, I take this occasion to rise to discuss Dr. Morton's report of his vast experience with melanoma in southern California. With the rising rates of melanoma in this country, he will soon be able to report more cases than the Australians.

I am concerned about the present tendency for surgeons to discount the good effects of chemotherapy, and particularly those obtained by regional chemotherapy. When I started in practice over 40 years ago, just about all of the solid tumors treated with chemotherapy were treated by surgeons. Now with the increasing numbers of medical oncologists, this case material is largely being referred to that group. Even in the field of regional chemotherapy, we are losing some of these patients to the interventional radiologists working with the medical oncologists.

Our group has treated over a thousand patients with limb melanomas

by chemotherapy and by regional perfusion. Although we cannot match the numbers of cases that Dr. Morton has presented, 1134 cases with regional lymph node dissection, we have had 129 patients with limb melanoma with positive lymph nodes treated by perfusion and regional lymph node dissection.

Our long-term cumulative survival rates at 5, 10, 15 years, are 52%, 51%, and 49%, respectively, which are better than Dr. Morton's reported rates for node dissection alone.

I would like to ask Dr. Morton, what is his therapeutic approach to melanoma patients with stage 3-A, satellitosis, or stage 3-AB disease, satellites and positive nodes? We find that with intransit disease excision alone, or systemic chemotherapy or immune therapy, do not provide long-term control. With intransit disease, our 10-year survival with chemotherapy by perfusion is 23%. If the satellites can be resected, it increases to 39%. With 3-AB disease, perfusion, and regional node dissection, the survival rate 28%.

There is one interesting point on which I would like to ask Dr. Morton to comment. When we did lymph node dissections for primary melanoma with positive lymph nodes, our 15-year survival rate was 30%, but if we had patients who had had previous resection of the primary disease, who showed up later with positive lymph nodes, perfusion and regional node dissection at that time produced a survival rate of 51%. I suppose the better survival had to do with a more favorable slowly growing type of melanoma, but I would like to hear his comments on this observation.

DR. BLAKE CADY (Boston, Massachusetts): This report continues the tradition of innovation that Don has established at UCLA, with over 5000 cases in 18 years and a 22% incidence of positive nodes; a 46% overall 5-year survival, which is clearly better, as he pointed out, than we are used to; and 41% survival at 10 years. Seven hundred thirty-seven patients form the basis of this report on the patients with positive nodes, which is 14% of the entire series but only about 65% of the cases with positive nodes, and I just wonder what type of subtle selection factors have gone into this subgroup of patients who had complete data.

There are some expected findings, such as the fact that there is no outcome difference with immunotherapy and no outcome difference, in my interpretation, from the time of the primary to death between immediate and delayed node dissection. There is no difference in survival based on the mathematical model, which you would not expect, because the mathematical model is derived directly from the data, and so when you reapply the model to the data you would not expect anything different; the real test of this model would be when it is applied prospectively.

There are some unexpected findings, however. There is no outcome difference in the number of positive nodes in melanomas between 0.76 and 4 mm in thickness in some selective groups. There is no difference in the incidence of positive nodes all the way from 0.76 to 4 mm in thickness, which is certainly different from what we have been led to believe and argues for selection bias in the analyzed group.

That unknown primaries behave like thin melanomas is another interesting aspect of his report. Twenty per cent of the clinical stage I had micrometastases, and about 20% of the clinical stage II had macrometastases, which would imply that all micrometastases eventually become macrometastases, quite different from breast cancer in the NSABP trials about untreated node metastases. Most remarkable of all is the selective low-risk group with positive nodes who have between 70% and 80% survival long-term with positive nodes. That is pretty remarkable, and it would be nice to be able to define that group very precisely.

I calculated, in trying to juggle with the figures, about a 3% overall impact on survival comparing prophylactic *versus* therapeutic node dissection, but it would be nice to know which selective risk group achieves that benefit. Is it the high-risk group or the low-risk group? I also calculated that the mortality rate in these patients is about 16% in the first year, 18% in the second year, 11% in the third year, 6% in the fourth year, 3% in the fifth year, 1%, as he noted, between 5 and 10 years, and about 0.6% yearly between 10 and 15 years. But is that mortality rate different with only micrometastases? And is this just another example of lead-time bias?

How many patients had deep groin nodes positive? And is that part of the regional nodal dissection policy? Do all such patients die and, therefore, deep nodes do not need to be removed? What is it about men that the number of positive nodes does not have an impact, and in women, why is it that the depth does not have any impact on survival when the nodes are positive?

Development of risk groups is critical in a sophisticated analysis of prognoses. Of course it only really helps if we have something to add in adjuvant therapy, and we do not have that in melanoma, but it would certainly be useful to help us make selections about who gets prophylactic node resection and who does not. There is an innovative technique that Don has developed of picking up the sentinel node, which will help us decide which nodes to dissect.

Thank you very much for asking me to discuss this and seeing the interesting data.

DR. E. COPELAND (Gainesville, Florida): Of the material presented, the so-called blue dye technique would be most likely to change my method of managing patients with melanoma, because the remaining data confirm my current treatment policies.

I was surprised, however, that there were no false-negatives, in other words, if the blue dye went to the "sentinel node" and it was negative, then no other regional lymph nodes contained metastatic melanoma. This conclusion would mean that no "skip metastases" existed in your dissected regional node specimens—a hard conclusion for me to accept because skip metastases in regional nodes have been noted for other surface malignancies such as breast cancer.

Explain to us why you think there were no false-negatives in your series.

DR. DONALD L. MORTON (Closing discussion): Dr. Daly wants to know why the survival is better in this series, 46% of 5-year *versus* our earlier series at 37%. We really do not have a good explanation for that. We thought it was because of immunotherapy, as there is about a 5% to 10% improvement at all points in the patients who got immunotherapy *versus* those who did not.

By univariate analysis, however, the differences were not statistically significant. And as we looked into the various heterogenous subsets, it is very clear that this type of comparison has to be very carefully done because of the huge difference in survival in the various subsets of patients.

Why is there a difference between the extremity and nonextremity sites in terms of the significance of numbers of involved nodes and the improved survival in women? I do not have an explanation for that. I think the fact that the unknown primaries paralleled the thin melanomas might be explained by the fact that if you have a thin melanoma, the host is more likely to reject it, and so that would not be surprising.

As Dr. Daly and several discussants brought up, the real test of our model is to apply it prospectively to our own series, and to other series, and we are now going about that. We have 2 years of patients currently being tested, and we hope to collaborate with those of you that have large data sets to compare survival in your series with that in ours.

The explanation for synchronous *versus* asynchronous metastasis and difference in survival is another point on which several people commented. And of course as you know, although about 85% of the patients who are going to develop lymph node metastasis from melanoma do so within the first 3 years, there is quite a tail of people that will go 10 and even 20 years before they develop clinical evidence of regional metastases. That probably indicates a tumor–host relationship that is much more favorable than that in patients who develop early metastasis. That may be one of the reasons for the improved survival of people with asynchronous metastasis in some series.

Dr. Aranha asked, will this technique identify intransit metastasis? And the answer is: It will not.

Dr. Aust has asked, again, why the improved survival? It is certainly true that some of this may be due to the fact that more of the patients in this series had elected no dissection. If we just look at those that have no dissections for clinically positive nodes, however, we have a 51% 5-year survival in that group compared with 37% in our prior series. And we cannot say that is the explanation.

Surprisingly if we look at all of our melanoma patients, and we are seeing about 400 a year now, the median depth of thickness of all of our patients has been remarkably constant over the last 20 years. And I can only assume that that is a result of the selection that occurs in the patients that are sent to us. The very thin early lesions are being treated in the local community hospitals, and they never find their way to a tertiary referral center such as ours.

Dr. Krementz has pointed out the extremely excellent results in people that have had limb perfusions and wants to know what our treatment of people with satellite disease is, and at present initially we treat with

90% of patients, and gives us a 25% 5-year survival. And in those that we cannot control with interlesional BCG, we perform a heat perfusion just as you, and we control 75% of those with perfusion.

So we have confirmed completely your experience with the effectiveness of heat perfusion in the management of this disease, but we have saved that for patients whom we cannot control with interlesional BCG.

Is the statistical model different from the group as a whole? The answer is that survival is exactly the same in these two sets of patients. The problem is that often the original primary lesion was not available for us for those 400 patients that we did not have complete data on.

Regarding the deep groin nodes, we have previously reported that patients' clinically negative but microscopically positive inguinal nodes have deep node dissections. They have the same survival at 5 years when deep iliac nodes are involved as do people who just have inguinal nodes involved. Therefore we still do a deep node dissection. In those that had clinically positive inguinal nodes, however, the 5-year survival of those have deep iliac nodes involved drops off dramatically. It is only about 15%.

Dr. Copeland asked, is it really possible that this technique has no false-negatives? The false-negative that we observed early on was due to the fact that we were not adequately injecting the dye. One must continue injecting the dye, because it goes right through the first echelon node to the second echelon node. If one does not keep injecting the dye every 20 minutes, the second node may be thought to be the sentinel node.

Once we learned that, we have not had any false-negatives. Now that is determined by two ways. Number one, all of the nodes in the lymphadenectomy specimen were examined both by standard hematoxylin and eosin (H & E) and immunohistochemical staining with S-100 and monoclonal antibodies. We did not find skip metastasis in melanoma. I think that melanoma is not the same as breast cancer. It is different.

Secondly, in the last 2½ years we have been doing just the sentinel lymphadenectomy. We have had no recurrences in a groin or axilla or neck when the sentinel node was negative. Although we need a little longer follow-up to be certain, it is encouraging that none of our sentinel-node–negative patients has developed a recurrence.