III lesions who receive WLE and RL compared with WLE alone. Neither of these differences was significant, but probably because the numbers were too small. The authors' regional node recurrence rate of 1.6 per cent is superior to those who do perfuse but do not perform RL.[28] The authors believe this supports the use of prophylactic RL.

Conclusions

The authors are of the opinion that the prognosis of Stage I melanoma of the extremities can be favorable and can be improved with an aggressive approach to the disease initially. Microstaging techniques have allowed the authors to identify patients at high risk for recurrence of disease. It is recommended that all patients with level III to V lesions greater than 0.76 mm undergo wide local excision with regional lymphadenectomy and regional hyperthermic perfusion and that with this regimen 90%, or better, five-year survival can be achieved.

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Discussion

Dr. Watts R. Webb (New Orleans, Louisiana): Dr. Krementz, who could not be here, asked me to present a few of the relevant data from the Tulane series, which started with the pioneering work of Dr. Oscar Creech in June of 1957, when he perfused the extremity (slide) of the man shown here, who had satellitosis (slide) of the extremity on the medial aspect of the thigh.

(slide) Nine years later there was total absence of any recurrent melanoma, and this man lived for a total of 16 years, dying at the age of 92 without any evidence of recurrence.

(slide) To pick a couple of pertinent points from this, you will notice that over the 20-year survival curve of all patients with Stage I having perfusion therapy, you notice that at five years the survival is 87.7%, very similar to that presented today; at ten years, 78%; and then at 15 and 20 years very little drop-off. Essentially, there is a plateauing at eight years, and essentially nothing except a very rare, dramatic recurrence after ten years.

Looking at the Stage II, perfusion results in better survival than non-perfusion, but nowhere near as good as Stage I.

(slide) Here we see the 161 patients that have been done in the past decade, during which time the perfusion has been standardized with a very high oxygen concentration, pO_2 of over 500, and hyperthermia. This technique has been very safe, with no drug-related death or problems of significance since 1964, and only four deaths total, primarily in cardiac patients.

The work of Dr. Krementz has centered on utilizing wide local excision and perfusion, without doing lymph node excision; and in 161 patients, there has only been a 12% recurrence rate in that group. There have been only fourteen deaths total, so that there is approximately 88% freedom from recurrence and a 91% overall survival.

We feel that the experience here, as well as that from many other centers, now indicates that regional perfusion, essentially, adds about 20% survival to surgery alone, or to surgery plus systemic chemotherapy.

I certainly enjoyed the paper, and thank you for the opportunity of discussing it. (Applause)

DR. RONALD A. MALT (Boston, Massachusetts): The question, basically, is: Why is malignant melanoma no longer a death sentence—but why can we tell some patients that it's almost no worse than the common cold? It could be that there is a great deal more effective therapy that's been developed recently, and, in fact, we use hyperthermic perfusion rarely for patients who have satellitosis or intransit metastases.

However, on balance, we use only simple excision of the primary malignant melanoma, with resurfacing with a skin graft or a local rotation skin flap. So the question is: How do our results with that technique compare with the much more elaborate technique?

(slide) Looking at the MGH/NYU combined survival data for Stage I malignant melanoma, Dr. Cal Day from the Dermatology Department and I came up with these calculations. For melanomas of less than 0.15 cm—these don't fall under the five-year category; these are percentages—we have 55% of our patients in that group, and the Oregon group had 51%; but we have a 99% ten-year survival, and they have a 100%.

Likewise, for the 1.5 to 2.99, we have a 91% five-year survival, versus a slightly lower one of theirs, and insignificantly different ten-year survival rates.

The same data apply to the thicker lesions in all categories.

So, really, one just has to inquire; and the question I'd like to ask is: Since sex and all other variables are the same in both groups, can one really demonstrate increased efficacy from this elaborate program, when all factors are being taken into account? (Applause)

SIR MICHAEL F. WOODRUFF (Edinburgh, Scotland): It may seem a little like nit-picking after hearing these excellent results both from Dr. Janoff and the previous discussant, but I think it is relevant to ask the question: Why are they not even better? Why do we still occasionally get recurrences with small and early melanomas, with negative lymph nodes, even when they are treated by such an elaborate method as we heard of from Dr. Janoff?

I think the question is important, and I think the answer lies largely in the heterogeneity of tumor cell populations, and in particular of populations in malignant melanoma. We have been reluctant to accept this concept of heterogeneity in tumor cell populations; firstly, we have been hypnotized by the dogma that nearly all tumors are monoclonal throughout the whole period of their life history, and secondly, because we found it difficult to conceive of the idea that a monoclonal population can diversify. But all tumors are not monoclonal, and monoclonal tumors can diversify.

I would like to draw attention to two observations, one clinical, one experimental, to illustrate this.

In the Journal of Experimental Medicine towards the end of last year (1981; 154:1764), a paper was published from Lloyd Old and his colleagues in which they established cell lines from three metastases of malignant melanoma in the same patient. They showed that the cells in these three metastases differed in respect to their growth rate, their morphology, their pigmentation, and in a whole variety of cell surface markers.

The second is an experimental observation of the mouse B-6 melanoma, published in Proc. Natl. Acad. Sci. (1981; 78:6226) by Poste and his colleagues, in which they showed that this is a very heterogeneous tumor. If you clone the tumor you can obtain uniform populations, but if you then take one of these clones, and you maintain it in tissue culture, or you grow it by transplanting it, then within a month or two you end up with a population just as heterogeneous as that of the original tumor.

I was discussing this with Dr. Francis Moore during the coffee break, and he said to me, "We are always telling ourselves that cancer is not one disease, but many, but what you are saying is that one tumor is many diseases."

Well, that is a typical Frannie aphorism. At first hearing it may sound far-fetched, but I think that we have to face up to the possibility that one tumor, and one melanoma, is indeed many diseases.

DR. MATTHEW N. HARRIS (New York, New York): I feel obliged to comment on this paper for two reasons. The first is that we now have a series of over 1800 primary malignant melanomas at NYU, and the second is that Dr. Janoff presented some of our results in his talk, so that I feel I have the right to rebuttal.

Our approach to malignant melanoma of the extremities differs from the one presented today. At the NYU Medical Center, Dr. Daniel F. Roses, Dr. Stephen L. Gumport, and I recently reported on 739 patients with extremity malignant melanoma. All patients had a wide and deep excision of the primary site, and regional lymph node dissections were done either therapeutically and electively for lesions of Clark's Level III or deeper. Four hundred and ninety dissections have been done, with a follow-up rate of 93%.

(slide) This is the lymph node status in the patients, and you can see from this slide that of the 490 lymph node dissections that were done, no lymph node dissections were done for Level I and Level II lesions; only for Level III and deeper. If Level II lesions are included, it will skew your statistics toward excellent results.

(slide) We performed lymph node dissections in 66% of the patients, indicating that the remainder had Level I or II lesions or the patients had refused surgery. Histologically positive nodes were found in 22% of the patients, a figure that is generally recorded in many series; about 25% will have positive nodes.

(slide) This is a life-table survival curve, comparing patients with histologically negative nodes with those having histologically positive nodes; and to briefly summarize it, the patients with histologically negative nodes do much better than those with positive nodes.

(slide) This is a life-table survival curve for patients with histologically positive nodes according to clinical nodal status. There is a longer median survival time in patients with histologically positive nodes only, as compared with patients with histologically positive and clinically positive nodes.

(slide) Finally, this slide shows the cumulative survival rates. This is a critical slide, because the results compare well with the group presented by Dr. Janoff that had regional perfusion. At five years, the cumulative survival rate for the histologically negative group was 91%; at ten years, 81.5%, and at 15 years, 72.2%.

At five years, the cumulative survival rate for patients with clinically negative, histologically positive nodes was 57.5%, and 32.8% for those patients who had clinically positive, microscopically positive lymph nodes.

The therapeutic advantage of performing elective lymph node dissection for extremity malignant melanoma is, admittedly, modest, but it does identify patients at high risk who may benefit from adjuvant therapy. Surgical oncologists today are questioning the efficacy of lymph node dissection. In this regard, the addition of regional perfusion, except in instances of multiple cutaneous metastases in an extremity, seems excessive to us, particularly when, in spite of this therapy, the authors reported six of seven patients with positive lymph nodes died of their disease.

Our efforts should be directed toward adjuvant therapy, identifying the high-risk patients, and treating them with modalities other than more extensive surgery.

My question for the authors is: Is it the hyperthermia, the chemotherapy, or the combination with surgery that accounts for the

reported good results, particularly when considering this is a nonrandomized group, as, admittedly, is ours?

DR. HIRAM C. POLK, JR. (Louisville, Kentucky): I'd like to speak in general support of the hypothesis presented by Dr. Fletcher and Dr. Janoff this afternoon.

Some eleven years ago we presented some work before this Association that suggested that there was merit in sparing patients with extremely favorable melanomas very, very aggressive treatment. (Ann Surg 1971; 174:402-413) On the other hand, I think this paper is a rational exposition of how useful it can be to concentrate your aggressive treatment on those patients with unfavorable tumors.

We have had an experience now that exceeds 150 perfusions for aggressive melanomas, and I would like to briefly refer to it.

First, in all but one of the 50 patients undergoing treatment for recurrent disease, there has been an objective regression of visible disease. That is a rather remarkable sign of efficacy.

Secondly, in those patients who have undergone prophylactic, or elective, perfusions for unfavorable, relatively thick Stage I disease, we have had a very low frequency of local recurrence, just exactly as shown by the essayists this afternoon.

On the other hand, I think the added lymph node dissection that has been done in these patients, to harken back to an old hypothesis, is not of value. By definition, their abstract shows that six of seven patients having that treatment died anyway. The treatment of metastatic disease involving the lymph nodes has not been very effective. The addition of the perfusion is extremely helpful, for the reasons dictated by many of the other discussants.

I would remind the authors that the World Health Organization Comparative Study did go through eight years, and that some of the alleged, suspected benefit of prophylactic node dissection was not shown there. We continue to try to find such benefit, and it is seldom able to be verified.

I would concur fully with the authors in the sense that the aggressive treatment is confined to the relatively thick level Clark lesions, and the thinner lesions, according to Breslow, are spared aggressive treatment. We then concentrate on a specific group. Among these perfusions we have not lost a limb, and not lost a life, although it can occasionally be a morbid process. Based on that, we would think, on balance, as Dr. Webb presented from Dr. Krementz's group, that there is a place for perfusion in certain lesions, and that this high level of improvement in long-term survival is not a unique change in disease, but is the result of more effective treatment.

More especially, whether we like to admit it or not, I think our colleagues in dermatologic medicine are doing an infinitely better job around the world, not just in North America, in presenting much more treatable and much more favorable disease.

DR. R. KENNEDY GILCHRIST (Chicago, Illinois): I have been interested in hyperthermia for many years, at least 25, and I rise primarily for a couple of questions.

First, what is the temperature of the injected blood? Second, how long is the treatment continued? Third, most importantly, what is the temperature in the tissue perfused?

It is perfectly obvious that some of these patients had metastases at the time when you thought that they were I's, and you cured some of them.

It would not be difficult to determine the temperature in lymph nodes, muscle, and fat by inserting very thin thermisters during treatment. There is ample evidence that a temperature around 107 F will kill many cells.

It is important to know how much of the favorable results produced here are due to the drug and how much to the temperature rise or to a combination of the two. Of equal importance is determining the maximum temperature that the various tissues can tolerate safely.

DR. WILLIAM S. FLETCHER (Closing discussion): In 1961 after I returned from a conference at which Dr. Creech, Dr. Krementz, Dr. Ryan, et al., had showed us how to do perfusions, Dr. Creech's instrument maker made our first heat exchanger. When that finally became obsolete, I had it made into a lamp to remind me of that history. This pioneering has brought us a long way, in not only isolation perfusion but hyperthermia.

I cannot answer Dr. Malt's question. Both our series are small. They are surprisingly equivalent, and they do not correlate whatsoever with very large numbers of series in the literature in which the results are not nearly as good. Maybe there is an evolution in the disease.

Professor Woodruff, there is no question that this tumor does clone the longer it grows. This can be seen on the slides of the more advanced lesions. There will be, clearly, subpopulations; I am sure that, were we able to culture those, there would exponentially be more subcultures. When we understand that and how to turn it off, we may make further progress against the disease.

I agree that we no longer need to do node dissections in the less aggressive disease forms, at least less than 1.5 mm, and possibly 2 mm.

I think, to answer both Dr. Harris' and Dr. Polk's questions, what we really need is a very large randomized cooperative trial, concentrating on lesions greater than 1.5, and perhaps less than 4 mm. I think the ones less than 1.5 do not need a node dissection. I am not sure whether they need a perfusion. The perfusion has little or no morbidity. It is the node dissection that has the morbidity; if the perfusion precludes the node dissection, especially in the thinner lesions, then we would have better results with less morbidity.

Dr. Gilchrist, as always, I think, has put his finger directly on the problem. The perfusate in the pump is run at 41 C. There is a certain loss between the pump and the patient, no matter how close to the operating table we try to get the machine. The tissue temperature of the extremity, without external heating, runs about 32 to 33 C. This can be raised to 36 or 36.5 C, with external heat, such as a K-pad, with the extremity wrapped in a plastic drape.

I think that is the direction in which we should go, increase the heat and decrease the node dissection.