patients will have a long-term, disease-free and overall survival comparable with those patients who undergo amputation.

Because of the improved survival that was observed in the early pilot trials utilizing chemotherapy in patients with soft-tissue sarcomas of the extremities,[19] the authors undertook a prospective randomized trial of the value of chemotherapy. The adjuvant chemotherapy regimen selected was a combination of doxorubicin, cyclophosphamide, and high-dose methotrexate that appeared successful in the early pilot trials.

A recent analysis of the results of treatment in the 26 patients in the pilot chemotherapy trial treated between May 1975 and June 1977 compared with our historical controls, with a minimum follow-up of four years, revealed an improvement in survival because of the adjuvant chemotherapy ($p = 0.001$). The prospective randomized trial comparing patinets receiving chemotherapy with those receiving no chemotherapy conducted between June 1977 and July 1981 revealed a marked improvement in disease-free and overall survival for those patients receiving chemotherapy. This trial has been analyzed in more detail elsewhere. It should be emphasized, however, that follow-up in this trial is short (one year, eight months), and further follow-up will be necessary to verify this conclusion.

In summary it appears that limb-sparing surgery plus radiation therapy is effective treatment for most patients with soft-tissue sarcomas of the extremities. Postoperative adjuvant treatment with the combination chemotherapy regimen that has been described appears capable of significantly improving disease-free and overall survival of these patients.

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Discussion

Dr. LaSalle D. Leffall, Jr. (Washington, D.C.): I would like to compliment Dr. Rosenberg and his colleagues on this paper, in particular for their continued study on a very important area in surgical oncology, and that is the management of soft sarcomas. Even though we don't see very many of these malignant tumors, very often when we do see them, some of these patients have been subjected to amputations, and I think, based on the study of Dr. Rosenberg and others who he has alluded to in his manuscript, we have evidence to show that we do not need to perform some of these amputative procedures.

In the manuscript, he gives recognition to the work of Suit and Lindberg; both of these men called attention to the role that radiotherapy plays in the management of soft sarcomas. At one time we

were taught that there were radiosensitive tumors, radioresponsive tumors, and radioresistant tumors, and I think that our radiotherapy colleagues have told us there is no such thing as a radioresistant tumor. They are either radiosensitive, or there are varying degrees of radioresponsiveness. Using that information, Dr. Rosenberg and his colleagues had the first prospective, randomized controlled trial, using limited surgery and radiation therapy.

In the second group, recognizing that histologic grade was the most important criterion affecting survival if all other things were equal, they added chemotherapy to the management of these patients, and that's something that we must keep in mind, histologic grade. Going back several years, we have come from the time of talking about round-cell sarcomas and spindle-cell sarcomas; we have come to specific histologic types, and now we have recognized the great importance of histologic grade. Pathologists usually will say either "low grade" or "high grade" or sometimes an intermediate grade.

The majority of patients in this series, as in most series, have high-grade tumors.

I think it's important, however, that we keep in mind that most recurrences occur in the first 12 to 18 months. I think that we probably will see what he has depicted here as being shown when the patients are followed for longer periods of time, that is, prolonged disease-free survival periods.

There are two questions that I would like to ask Dr. Rosenberg. Is there any role for intraoperative radiotherapy in patients in whom you suspect, because of the size of the tumor and the closeness of your margin, from a clinical point of view, that this treatment may have some adjuvant role?

What size must a tumor be, how small or how large, before you make the statement to yourself that this patient can have limited surgery, radiotherapy, and chemotherapy *vs.* having amputation?

DR. MURRAY F. BRENNAN (New York, New York): At my current institution, we see in excess of a hundred new soft-tissue sarcomas each year, and have been led by the insightful way in which Dr. Rosenberg has examined the problem. As a consequence, I have thought about his data a great deal. I really only have one question, and it is very different from Dr. LaSalle Leffall's.

The radiation therapy you deliver is not benign, particularly in the proximal thigh lesions. It can be extremely morbid, and it makes recurrence hard to detect. As I understood your data, both in the abstract and in your presentation, even in the positive margin patients the radiotherapy did not help, and all of the patients received chemotherapy, certainly in the first protocol.

My question is, can you comment on whether the radiation therapy is necessary at all? Eventually, you will have that data from your no chemotherapy arm.

DR. E. CARMACK HOLMES (Los Angeles, California): I too am concerned, as were the two previous discussants, regarding the morbidity of the radiation therapy, especially in the proximal thigh. Our group, which is led by Dr. Fred Eilber at UCLA, has employed the use of intra arterial adriamycin and preoperative radiation therapy, the dose being 3500 rads, with very low morbidity, to obtain equal or better control.

I would like to ask Dr. Rosenberg if he has any thoughts about other techniques that he could use to decrease the local recurrence in the proximal thigh lesions, in particular, the intraoperative radiation therapy modality that you have available to you at NIH that the rest of us do not have.

The second question has to do with the chemotherapy. I would like to compliment Dr. Rosenberg and his group for their very brave study, to prove with a prospective randomized trial that adjuvant chemotherapy is efficacious in these patients. I would, however, like to ask him to give us some idea of the morbidity associated with this chemotherapy. I happen to know that Dr. Rosenberg has decreased the dose of adriamycin from 550 mg per meter square to 350 mg per meter square, to minimize the toxicity. Our experience has been that when the patients do recur, it is almost never during the course of adriamycin but following its discontinuation, and I wonder if by decreasing the dose from 550 to 350, one might not see earlier recurrences, and indeed, if that will decrease the cardiotoxicity, or whether just discontinuing the cytoxan might diminish the cardiotoxicity.

DR. STEVEN A. ROSENBERG (Closing discussion): Our prospective randomized study of the role of adjuvant chemotherapy has a median follow-up of one year and ten months. This trial of adjuvant chemotherapy was based on our experience with 29 patients that were treated between 1975 and 1977 with chemotherapy in a pilot trial. We have updated follow-up of all of those patients with a minimum follow-up of four years. The overall survival in that patient population is 92%, which is quite remarkable for a patient population with high-grade soft-tissue sarcomas. In that experience as well in the reported studies of many others, over 80% of all recurrences in patients with soft-tissue sarcomas take place in the first two years; so, although the follow-up in our adjuvant chemotherapy trial is short, we have every expectation that these early results will be maintained.

Both Dr. Leffall and Dr. Holmes mentioned the possible use of intraoperative radiation therapy. This is a treatment modality that is being extensively evaluated at the National Cancer Institute by Drs. Sindelar, Kinsella & Glatstein of the Surgery & Radiation Oncology Branches. We're currently conducting three prospective randomized trials comparing intraoperative radiation therapy to conventional postoperative radiation therapy. The only one of these trials that deals with sarcoma patients deals with patients with retroperitoneal sarcomas and it is too early in the trial to draw any conclusions.

In answer to Dr. Leffall's question about which patients were eligible for our extremity trial, all patients with extremity soft-tissue sarcomas for whom we felt a limb-sparing operation could result in removal of all gross tumor, without elimination of function of that extremity, were included in the protocol. There is no evidence, to my knowledge, that size is an important prognostic correlate in patients with high grade soft-tissue sarcoma. I would estimate that about 85% of all of the soft-tissue sarcoma patients of the extremities referred to the National Cancer Institute were eligible for this trial because of the size of their lesion.

Dr. Brennan has raised a very important question concerning the necessity for radiation therapy for the treatment of these lesions. Dr. Holmes has referred to the morbidity of the radiation therapy, which tends to be magnified somewhat when simultaneous radiation-sensitizing chemotherapy, such as doxorubicin is used. I think this is an important point.

In our current trials, our three-year survival figures appear to be in the 85 to 90% range. It is, therefore, going to be very difficult to design trials that will look for improvements over that figure. Certainly, very large numbers of patients will be required.

It then becomes reasonable to attempt to reduce morbidity of treatment without losing therapeutic efficacy; in fact, this is the exact direction that our current clinical trials have taken.

Our next generation trial, which is a prospective randomized trial, is attempting not to eliminate radiation therapy, but rather to reduce the chemotherapy dose. The most serious toxic side effect of the use of this chemotherapy regimen is the cardiomyopathy associated with doxorubicin administration. About 11% of patients who receive full-dose doxorubicin will develop congestive heart failure. An additional 35% of patients will show decrease in left ventricular ejection fraction with this chemotherapy regimen, when this is looked at using ECG-gated radionuclide scans.

Our new protocol, therefore, is comparing the exact chemotherapy regimen I mentioned today with a chemotherapy regimen which limits the total doxorubicin dose to 350 mg per meter squared, a limit at which little clinical or subclinical cardiomyopathy would be expected. This prospective trial is in progress, and we have entered about 35 patients in this trial to the present time.

Another very reasonable trial would be to see if the radiation therapy could be eliminated. That will probably be our next trial.

I would only urge that when attempts to reduce the morbidity of treatment are evaluated in clinical trials, they be studied in well-designed randomized clinical trials. The differences that are being sought are small, and it will be extremely difficult to interpret trials that depend on comparison to historical controls.