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Discussion

DR. ROBERT E. HERMANN (Cleveland, Ohio): Dr. Reemtsma, Members and Guests of the Association, I enjoyed this paper by Dr. Cady very much and I congratulate him on his continuing studies on variations in the treatment of small or early breast cancer.

Our group at the Cleveland Clinic has continued to explore conservative methods for treating early stage breast cancer, the studies started by Dr. George Crile, Jr., in 1955. We have questioned the necessity to treat all patients who have had a partial mastectomy with postoperative adjuvant radiation.

Routine postoperative radiation therapy for all patients after partial mastectomy has not improved survival in any reported study. It increases the time of treatment, triples its cost, causes some early and late morbidity, and makes small recurrences in the breast more difficult to identify both mammographically and by clinical exam. Its only benefit, in past studies, has been to decrease local recurrence.

We have tried to identify or select a group of patients, as has Dr. Cady (patients with Stage 0 or Stage 1 breast cancer who have no evidence of multifocal disease by mammography or by biopsy), and treat these patients with partial mastectomy without postoperative radiation therapy. We attempt to have a 1- to 2-cm negative margin and do an axillary dissection in all of these patients.

From 1975 through 1988, we have treated 620 patients of a total group of 2020 patients by partial mastectomy without adjutant radiation therapy. Overall survival and disease-free survival were the same as in those patients treated by total mastectomy with an axillary dissection or by partial mastectomy with axillary dissection and postoperative radiation. Local recurrence in these selected patients at 5 and 10 years was not in the range suggested by the NSABP studies (i.e., 30% to 40%), but was only 11% at 5 years and 14% at 10 years.

Dr. Cady has stated that their local recurrence rate in patients after partial mastectomy without radiation therapy, I believe, was 18%. I wonder if he would clarify that? It was 16% in the abstract, but I think he showed it to be 18% on one of his slides.

Finally, I'd like to congratulate him and his colleagues on these studies.

DR. C. BARBER MUELLER (Hamilton, Ontario): Dr. Cady, while you've addressed the fact that mammography now brings a new group of patients into the Cancer Registries, they have smaller tumors, but as yet there is no direct evidence that they are earlier tumors.

It seems obvious to me and I think to most of us to conclude that these are early versions of garden variety breast cancer, but it is possible, maybe even probable, that they are a variant that is less lethal.

Could I have my slide, please? This is the survival curve of NSABP B-04. You saw it earlier in Dr. Cady's presentation. It shows the 10-year survival of Stage I *versus* Stage II. I have calculated that the half death time is different in these two. And, if there had been one disease with a delay in diagnosis, the slopes should have been parallel. But they are not. This slide represents two distinct variants, as distinct as two radioisotopes that decay with different half lives. These are two diseases, not early and late.

Now, the DCIS survival curve, a small curve that is published in several places, is somewhere up here. At 10 years we're looking at 85% or 90% survival. Tom Nealon had an article on this. Well, Dr. Cady, how do you make sure that the tumors you are finding are early versions of a true breast cancer, not just a pathologist's whim, which gives us a different entity?

I would remind you that in 1940 Shields Warren at your institution did this to us with papillary cancer of the thyroid. He identified a cancer that had measurable but minimal lethality. It took us 25 years to recognize that fact and to treat thyroids appropriately. Are we now going to have a repetition of

the thyroid exercise? Is it possible that you are finding a relatively nonlethal variant rather than an early stage? I'm sure you've thought about this.

DR. ROGER S. FOSTER, JR. (Atlanta, Georgia): Dr. Reemtsma, Members and Guests, Dr. Cady has made two points that I would like to relate to patient age.

First, he said that screening mammography is leading to the detection of smaller invasive breast cancers. I believe that's very true, but only for about two thirds of the women who are being screened.

We recently reviewed all of the breast cancers detected in Vermont during 1989 and 1990. We found that screening mammography had led to an impressive reduction in tumor size for women older than age 50; however, in women between the ages of 40 and 50, there was no decrease in tumor size in comparison to the premammography era despite a rate of utilization of screening mammography that was similar to that of women over the age of 50. I believe most of the smaller invasive cancers that are currently being found are being found in women over age 50.

Second, Dr. Cady has made the point that it's possible to limit local regional treatment. I'm in substantial agreement with Dr. Cady, but I've used age as the most important criterion for selection of patients for limited treatment.

This is for two reasons. The only established systemic adjuvant therapy for patients older than 70 years of age is tamoxifen and thus axillary node status is not important in the selection of patients for chemotherapy. Also, the available data suggest that in-breast recurrence rates are age related and that in-breast recurrence rates without radiotherapy are much less likely in the older patients.

I recently reviewed 157 patients with invasive breast cancer I have treated since 1980 who were older than age 70. Forty-eight of these patients were selected for treatment by lumpectomy without axillary dissection or breast irradiation, as described by Dr. Cady. The tumors were both T-1 and T-2. Only 2 of the 48 have had in-breast recurrence, and none has had axillary progression.

Dr. Cady, systemic therapy decreases both in-breast recurrence and contralateral breast primaries, whether it be tamoxifen therapy or cytotoxic therapy. I wonder what's your attitude towards this therapy for local regional control and what percentage of your patients currently receive systemic therapy after your conservative surgical therapy?

DR. WANEBO (Providence, Rhode Island): Blake, you've put together another provocative approach in your discussions of various cancer patterns of care and I think it's something certainly that's important to look at.

There are some questions in that you're talking about a disease less than one centimeter in the breast, and certainly in the group that are node negative the survival is extremely good, probably in the 95 percent range at 20 years if we look at Peter Rosen's (?) data. And indeed the concept of doing limited surgery in patients with small lesions is being addressed by an NSABP trial at least for mammographically defined lesions, which I think is local excision but I believe with axillary dissection. 182

I think the problem here is that there is a group, the group with nodal metastases, which probably does have a much impaired survival. As you pointed out yourself and which is obvious to everyone here, their survival is only in the 60 to 80 percent range, depending on the extent of disease. And indeed in your own study you showed that there was a 10 percent distant failure rate along with about a 15 percent nodal failure rate. But I think it's the distant rate that is still of concern.

So my question to you is: How would you define and discern that group of patients without a staged-in (?) axillary dissection? To my knowledge none of the biologic correlates such as ploidy, S-phase and so forth on a one-to-one basis actually identify those with nodal metastases.

But I would ask you whether you have defined a protocol that might at least conceptually identify most of the high risk patients so that what you are suggesting, a local treatment for the smaller lesions, would make sense?

And perhaps an added point might be that 183

certainly those with just the microscopic field involved of less than, let's say, one or two millimeters might be ideal for this where those that are larger might require an axillary dissection, which has a relatively low morbidity.

DR. R. ROBINSON BAKER (Baltimore, Maryland): I would like to compliment Dr. Cady on an excellent presentation of what I think is a very timely subject.

I would suggest that treatment decisions of small mammographic lesions can be based on tumor size, histology, estrogen receptor status, and possibly markers such as the number of cells in the S-phase of DNA synthesis. I would agree that an axillary node dissection is not necessary in a lot of these patients either as a therapeutic or as a staging procedure.

We (and "we" really means Dr. Paul Lin and Dr. David Allison) have recently reviewed the experience at Hopkins with a large number of patients who have undergone axillary node dissection. In 70 patients with tumors smaller than 1 cm, the incidence of axillary node metastasis was 6%, which I think indicates that for people with tumors smaller than 1 cm, it is not in their best interest to undergo an axillary node dissection.

I have one question. Have you had an opportunity to look at specific histologic types in your experience, specifically tubular cancers or papillary cancers, to see what the correlation with node metastasis is in that group?

DR. BERNARD GARDNER (Newark, New Jersey): I enjoyed the paper very much, Blake. I think it's an excellent study. I just want to make two short comments.

Number one, I agree that there are patients with these small tumors who have negative axillas and don't need to have the axillary nodes resected; however, I don't know who those patients are.

The question that I want to ask you is: Do you know of any case where you have an unresected breast cancer that was cured by chemotherapy?

DR. JOHN S. SPRATT (Louisville, Kentucky): You may recall the slide I showed earlier when I was discussing Dr. Gardner's paper about the extreme variance in the growth rates. You have

to remember that there's a real biological selection factor that goes into the discovery of cancers by screening mammography.

Only the very slow-growing indolent cancers are the ones that are picked up. These are picked up by a process that the epidemiologists call "length biased sampling." Patients also are going to live longer because the slower-growing cancers are more biologically favorable. The breast cancers that kill are ones that come up very quickly in-between annual screenings. The growth rates tend to be considerably faster in younger women.

I think the foremost student of the statistics that deal with this is Dr. David Eddy. He is Director for the Center for Health Policy at Duke. He has done some very beautiful simulation modeling on the computer of all the available studies and has concluded that there is no statistical justification for doing mammography in patients under age 50. Mammography does not lead to reduction in the probability of dying of breast cancer. Over age 50, the lifetime payoff for an annual mammogram between ages 50 and 74 is on an average an addition of about 30 woman-days of life (Eddy DM. Screening for breast cancer. Ann Intern Med 1989; 111:389–399.). The growth rates in young women are much, much faster, limiting the potential for effective screening.

DR. MONTSEUR (Cleveland, Ohio): I have two questions to Dr. Cady. One, was the axilla irradiated in those patients who received radiation therapy? Two, you pointed out that the incidence of nodal recurrence was higher among those who did not receive radiation, resulting in a worse survival. Would you consider in your proposed clinical trial an axillary biopsy or at least sampling to exclude these possibilities of microscopic lymph nodes metastasis?

DR. BLAKE CADY (Closing discussion): Dr. Hermann, I tried to differentiate between total local failure, which is 18% for the nonirradiated patients, *versus* local failure only, which I considered to be the biologically important one. Local failure only was 9% *versus* 6%, nonirradiated *versus* irradiated, in the whole group and 8% *versus* 5% in the T-1 group.

Dr. Mueller's studies are a model of thoughtful analysis of breast cancer and his paper entitled "Stage 2 Breast Cancer is Not Simply a Late Stage 1," is an extremely provocative paper that really gets to the nubbin of the issue.

Does this early disease that we're seeing have a different biological type or not? I can't tell. We had four patients without radiation therapy with small cancers, 5, 7, 8, and 10 mm in diameter, who had a recurrence that was very aggressive and resembled inflammatory breast cancer. I would infer from these cases that the very aggressive type can appear even at a very small size, too.

Dr. Foster has an interesting group of patients using older age as a criteria for an extremely conservative approach and I would commend that, since new studies that show reduced risks of local recurrence in the breast with excision only correspond to his report.

Systemic therapy in these small cancers could be used if we can find primary tumor characteristics that reliably give us the prognosis that we would otherwise get only with positive nodes. My point is that when you perform a large number of axillas to find a small number that are positive in order to use systemic therapy, you wind up with very poor cost-benefit ratios that produce a survival advantage of only 1%. If you do a hundred axillas at $10,000 a piece, that's a million dollars to save one life.

Dr. Wanebo asked about the primary features that might lead to systemic therapy. I would take lymph vessel invasion and perineural invasion to be the equivalent of a positive node, and some other features that have been reported to be poor prognostic signs.

I appreciate Dr. Baker's comments, particularly the data showing only 6% positive nodes in cancers smaller than 1 cm picked up by mammography. Specifically, some of our patients had tubular or papillary disease. Tubular carcinoma is very low grade and can be treated with minimal surgical procedures. I don't have specific data on node incidence in these cancers.

I don't know of any cure by chemotherapy alone in unresected primary cancer, to answer Dr. Gardner's comments.

Dr. Spratt brings up the perplexing issue of lead time bias. My particular concern is the cost, really. We need to start addressing some of the cost issues. We're having an extremely long run for a very short slide in some of these early cancers.

We need to make our risk-benefit ratios in cancer management rational. Some of our colleagues in medical oncology are treating everybody that walks in the door, and I think we need to address the appropriateness of that.

Keep in mind that all of the mammographic screening studies that have been reported so far in control trials have at least a 50% degradation of reported results because the experimental group doesn't all get mammograms and the controlled group has a significant proportion that does get mammograms. Mammographic screening programs may be even more effective than reported so far and we will see many more very small breast cancers.