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Discussion

DR. ALFRED S. KETCHAM (Miami, Florida): I was privileged to discuss with Dr. Wanebo, over the telephone, the contents of his presentation, but I am somewhat astounded now that I hear the paper presented and see before me many of his figures and the analytical data.

Our most common cancer killers in women are lung and breast. We know what causes lung cancer, but preventing it interferes with our lifestyle, so the public does little or nothing about it. Breast cancer—we know nothing about its cause, so both of these lesions lead us to the mandate for early recognition, and an attempt at early recognition is the essence of this paper.

Although the Fisher National Surgical Adjuvant Breast Project (NSABP) study is not yet published, we hear rumors that there is an alarmingly high recurrence rate in the segmental mastectomy patients that did not receive postoperative radiation therapy. I understand that it is a local recurrence rate and not a new cancer or a manifestation of multiple primary disease. If this is local recurrence, then in my judgment, the surgery was not totally encompassing of the primary tumor. There is no other explanation for a recurrence rate of 10 to 20%, or whatever it will be shown to be.

The real question we would like to have an answer for is "What is the multiple primary identification rate for invasive tumors, occult or not, in these segmental and total mastectomy specimens and, very importantly, in the residual breast following partial mastectomy as well as in the opposite breast as identified by long-term follow-up? How alarmingly high is the incidence of cancer complication in the so-called normal breast tissue?

Dr. Wanebo gives us an astounding high rate of 26%. We believe that is somewhat higher than what the long-awaited NSABP B-06 three-armed study will show. A critical factor will be when these figures are differentiated for us as to whether we are dealing with invasive cancer or whether it will break down to about 90% noninvasive incidence in the contralateral breast, as compared to less than 10% of truly invasive cancer.

Are noninvasive cancers, intraductal cancers, carcinomas *in situ,* or even lobular carcinomas *in situ* really precursors of subsequent infiltration? This has never been unequivocally shown in the breast or, I believe, in the cervix, although Rosen and others certainly worry us with their reports. If it is true, and if Dr. Wanebo's figures hold up for the contralateral breast, then not only is contralateral biopsy indicated, but possibly more aggressive surgery than just biopsy might be considered on the opposite side.

The second part of Wanebo's studies demonstrate a seven per cent second primary in the opposite breast. In these cancer-aware patients, who supposedly are looking for early recognition signs, 41% had positive nodes; 59% developed distant metastases. These are not only astounding figures, but very, very alarming.

I routinely perform a contralateral biopsy with a 3-mm stab wound in the para-areolar complex and then use the pituitary biopsy forceps to remove six to eight small specimens per breast. Our incidence is approximately eight per cent for contralateral abnormalities, of which only one per cent are shown to be truly invasive.

Dr. Wanebo, your figures suggest we should more often consider the possibility of performing prophylactic mastectomy. Is that what you would like us to consider?

What is the incidence of invasive cancer found in your total mastectomy specimens, occult or otherwise? On occasion, you perform segmental mastectomy with breast preservation and cosmetic acceptance. Is this for invasive cancers? However, your figures suggest, and you have been heard to say, that we might consider prophylactic mastectomy for noninvasive cancer. Harry, how can you consider doing a total mastectomy for something that has never been proven to be cancer,

when you are doing a segmental resection on selected patients who have microscopically, unequivocally proven invasive cancer?

Would your experience allow you to comment on one of the more commonly performed operations here in South Florida for cancer prevention—that is, subcutaneous mastectomy with transplant preservation of the nipple complex? How much breast tissue is being left on the skin flap in order to obtain cosmetic satisfaction (even when the implants are placed in the subpectoral position)? Did you find any of your cancers or the precancer lesions developing in the so-called nipple areolar complex?

DR. KIRBY I. BLAND (Gainesville, Florida): I too want to congratulate Dr. Wanebo for his timely and, as you can see, controversial subject. We all realize the major risk factors of breast carcinoma with an increased incidence of bilaterality. As mentioned briefly by Harry, the personal history of breast carcinoma is associated with approximately a 0.7 to 1.0 per annum incidence of carcinoma. When these data are applied in a screening clinic, such as in the National Breast Cancer Detection Demonstration Projects, one will see that the incidence rate is well over one per cent per annum, when you remove the prevalent cases. With a familial history of breast carcinoma, we would expect to see an incidence in excess of 45% over 20 years. Finally, another major issue is that of the lobular carcinoma, which has received the greatest amount of attention. As we know, bilaterality rates for lobular cancer can vary anywhere between 25 to 60%, and are totally dependent on the scrutiny and the interpretation of the pathologist receiving the tissue.

(Slide) This slide is courtesy of Dr. Bob Egan, at Emory Clinic, and confirms the incidence of bilateral breast cancer to be increased in a screening clinic. As you can see, for four series with over 4400 patients, Dr. McSweeney and Dr. Egan evaluated 1700 patients who were screened and identified 81 secondary carcinomas. These data are in accordance with Dr. Wanebo's study, and the range of secondary cancers was between five and eight per cent. Interestingly, of the total number of second primary cancers, the incidence of simultaneous, or synchronous, carcinomas was just over a quarter of the total cancers (27%); thus, of these 81 cases in which new breast carcinomas were detected, over two-thirds were metachronous lesions. Use of xeromammography often allows differentiation of a secondary from a metastatic carcinoma. We have applied this screening modality with physical exams in follow-up of the opposite breast without a false-positive study. Egan et al. observed the total incidence of false-negative carcinomas to be just slightly over six per cent, a very acceptable rate. However, these four series reflect a varying incidence of synchronous (bilateral) breast cancer (range 0.27–2.0%). The highest rate (2%) is expectant when high-quality serial mammograms are used together with physical exam in the screening process.

To my knowledge, there has not yet been a prospective study addressing the advantages of the contralateral biopsy over xeromammogram, especially the kind of xeromammograms we currently employ. Up front, the cost-effectiveness would strongly suggest that we use xeromammography for that individual who should be selectively biopsied, especially with major and minor risk factors, as I have just mentioned. In fact, in the Urban series from Memorial Hospital that Dr. Wanebo just mentioned, if *lobular carcinoma in situ* is removed from this study, there would be essentially no difference in the incidence for detection of synchronous lesions with regard to the contralateral biopsy technique.

My only questions to the authors would be: Do you recommend this technique in every patient? Should you apply the important selective prognostic criteria (particularly age, major and minor risk factors, etc.) when you plan these contralateral biopsies?

DR. RICHARD T. MYERS (Winston-Salem, North Carolina): I would like to thank Dr. Wanebo for adding yet another study in our attempt to determine what the incidence of carcinoma in the opposite breast is. We have done our own study, which indicates a much lower percentage of positive biopsies somewhere in the neighborhood of two per cent, which roughly corresponds to that reported by Martin and demonstrated to you in one of his slides.

We have abandoned the contralateral routine biopsy in our patients for two reasons. One is because of that lower incidence; and secondly, the outlook in our hands, at least in a small personal series, for bilateral carcinoma of the breast is not all that bad. I would like to show slides to demonstrate the data base on which I make these conclusions.

(Slide) The first slide shows the total number of patients in a relatively small personal series, patients on whom I have operated over the years, since 1950. I have kept close follow-up on 100% of them. Bilateral carcinoma has occurred in this series of over 300 patients in the magnitude of 7.5%.

(Slide) This shows that one of the aspects of bilateral carcinoma is that you must have a good carcinoma to begin with; and you will notice that the majority of these patients had a stage I carcinoma at the first operation, and also the second one as well.

(Slide) This slide shows that the interval between is rather long; the average interval between, ranging from 0.3 to 49 years, was 11.6 years.

(Slide) Finally, I would like to show you the results in these 22 patients. At the present time, 18 are living, with no evidence of disease. One is dead of a stroke. Three are living with disease; none have died of disease itself. Those three there are going to come up relatively soon, I am afraid, but at the moment this looks like a reasonably good outlook for bilateral breast carcinoma.

I would like to thank the authors for this paper. I enjoyed listening to it. I would ask one question: Are there really any special technical aspects of bilateral biopsy that might increase or enhance the productivity generally in our hands?

DR. J. SHELTON HORSELY, III (Richmond, Virginia): One of the series that Dr. Wanebo alluded to was from the Medical College of Virginia, where Roger King reported 109 cases that were looked at consecutively, in which the opposite breast had nothing suspicious on physical exam. Only a few patients had xeromammograms. This was reported in 1976. At the time they found only five cancers; four of these were carcinomas *in situ.*

Looking at larger series that were reported by Leis (561 cases, in which he had a 7.3% incidence of cancer in the contralateral breast) and Urban (who reported on 301 cases with essentially the same figure, 7.6% biopsy-proven cancer in the opposite breast), we discontinued this procedure.

We strongly agree that the opposite breast should be carefully evaluated clinically. You should also use xeromammograms, and anything suspicious should be biopsied.

Another important factor, which has already been mentioned, is that the cancer found in the opposite breast is most likely a carcinoma *in situ.* Anywhere from 56 to 80% of the cancers found with this technique in the asymptomatic opposite breast are carcinomas *in situ.* We know that less than two per cent of these have spread to the axillary nodes, so the prognosis is quite good.

The question I would like to ask Dr. Wanebo is: What do you consider the cause of your much higher incidence of cancer in the opposite breast, which you reported in your abstract as 26%, when compared to other series, which are somewhere between 4.6% and 7.6%?

DR. CARL SUTHERLAND (New Orleans, Louisiana): I thank Dr. Wanebo and his colleagues for this thoughtful study. The problem of bilateral breast cancer is a fascinating one, with multiple areas of scientific interest for surgeons. However, for the women with breast cancer, two questions are of paramount importance: How does breast cancer, either unilateral or bilateral, affect my survival? What morbidity must I endure?

The NSABP has analyzed the stages I and II breast cancer cases treated in Protocol B-04; 1578 women were treated between 1971 and 1974, and now have an average of 116 months' follow-up. Multiple findings have come from this study, but of importance to the current discussion is that (1) there has been a clinical appearance of invasive cancer in 3.7% of the cases, and 0.5% of noninvasive cases; and (2) most importantly, there are *no* differences in survival, either overall or adjusting for nodal status, in the group with a single cancer *versus* those with a subsequent cancer.

Therefore, it seems from the Wanebo study, and others that have

been mentioned today, there is approximately a 15 to 20% range (perhaps even a little higher) incidence of microscopic disease in the opposite breast that can be discovered by contralateral biopsy. The questions are: (1) Is this of significance for survival? (2) Does therapy at time of diagnosis of the recognized primary affect survival in any way? (3) How much morbidity must women endure related to the benefits (if any)? I have three questions for Dr. Wanebo.

1. Have you examined your data base, controlled for the known prognostic factors, including nodal status and tumor size, and determined if there are survival differences in patients with bilateral disease?
2. Do you recommend contralateral biopsy for all or subsets of patients, in the absence of proven survival benefits from randomized controlled studies? If you believe this should be done, I would like to know the parameters. The NSABP study did not totally exclude differences in survival in unilateral *versus* bilateral disease, or treatment at primary would give survival differences, but it is highly suggestive that major benefits are not to be expected. Finding such a difference, if it exists, must require an enormous study. I would like to know what assumptions of treatment differences would have to be made and what would the sample size, length of entry, and follow-up be for such a study.
3. Finally, quality of life issues are being considered more and more. Significant differences have been found in patients treated with local resection and radiation therapy, compared to modified radical mastectomy. Have you done quality of life studies in these patients? If not, what would you expect to find, compared to a group of patients receiving either local excision and radiation therapy or a unilateral mastectomy?

DR. GREGORY SENOFSKY (Closing discussion): I will do my utmost to answer these most challenging questions.

Dr. Ketcham, you asked what the multicentricity rate is in our group. Out of our 62 contralateral biopsies, there were four patients with a multiplicity of tumors, essentially multifocal lesions. These were all noted in the ipsilateral dominant side. Out of the 13 positive contralateral biopsies, two patients had multifocal cancers. In the actual biopsy site, there was no multifocality noted by our pathologist, Dr. Fechner.

Dr. Ketcham, you asked the question: Is noninvasive cancer a precursor to invasive cancer? We think it is. (Slide) This work reflects Dr. Haagensen's work, in which 280 patients with lobular carcinoma *in situ* were followed for up to 40 years. He found that, beyond twenty years, approximately 23% of these patients developed invasive cancer. Other authors, such as Rosen at Memorial Hospital, have also commented that lobular carcinoma *in situ* is seen as the precursor lesion to invasive cancer.

You asked the question: Are our figures high for contralateral biopsy? Yes, they are quite high. (Slide) There are reasons for this. One of the reasons we think our figures are high is because our biopsy sites are large. The study at the Mayo Clinic, for instance, had a small biopsy site, about 3 cm. Our biopsy site tended to approximate that of Dr. Urban, almost a quadrant excision.

Another reason for our high numbers is the large number of slides prepared per biopsy and the assiduous examination by an experienced and committed pathologist. All of this probably contributes to the high rate of cancer we found in our contralateral biopsies.

I would like to point out that in the studies by Dr. Urban and Dr. Leis, they found high rates of atypia, along with the carcinomas *in situ*. If you add their rates of atypia to their carcinomas, the numbers become very similar to our own. As I have already stated, we had a very low number of atypias diagnosed by our pathologist in the contralateal biopsy site. Perhaps different pathologists have different thresholds for diagnosing atypia and carcinomas *in situ*.

Finally, in regard to the question asked by Dr. Bland about the mammogram and contralateral biopsy. You will note that in our paper we had seven out of 62, or 11% of our patients, that have clinically and radiologically undetected cancer. These are the patients that we hope to pick up with contralateral biopsy. Most of these will turn out to be *in situ* cancers. These are the ones that we particularly are looking for, the ones that will show up as being negative in the mammogram.

Who do we recommend contralateral biopsy for? We recommend contralateral biopsy, basically, for any patient who is at risk for contralateral cancer: patients who have early cancer, such as *in situ* cancer, favorable stage I and, perhaps, stage II cancers, and cancer with low metastatic potential; patients with a close family history of breast cancer; patients with multifocality; patients who are under 50; patients with dense breasts that are not amenable to mammographic interpretation; and, of course, patients with positive mammograms. These are the particular patients for whom we recommend contralateral biopsy.

Dr. Myers asked the question about our technique of performing the biopsy. We recommend doing outer quadrant biopsies for dominant lesions in that quadrant. For medial lesions, we recommend an adequate mirror image biopsy if technically feasible; if not, we would do an upper outer quadrant biopsy and include subareolar tissue as suggested by Fracchia.

Regarding one of Dr. Horsley's questions, all of our patients had mammograms. We have already answered the question about high numbers.

Dr. Sutherland raises a very controversial and difficult question: How do you compare the survival rate in patients with unilateral cancer compared to that in patients with bilateral cancer? We have thought about this quite a bit. If you think about it, the patients who develop bilateral cancer are patients who have to do well enough and live long enough after their first cancer to get to the point where they can develop a second cancer of their contralateral breast. Sometimes this may be quite a long interval. If you look at a group of patients—just a random group of patients with unilateral breast cancer—and compare them to a group of patients with bilateral breast cancer, it is not surprising in many studies to find that the actual time of survival from the first lesion is comparable in both groups, and sometimes even better in patients who develop a second breast cancer. The patients who present with unilateral advanced breast cancer, *i.e.*, stage IV metastatic disease, usually do not live long enough to develop a second, contralateral breast cancer, unless it presents synchronously. Development of a second cancer does impair further long-term survival.

I refer you to the classic study by Robbins and Berg, which we feel is the most eloquent comparison of patients with unilateral *versus* bilateral breast cancer. In their review of 1500 breast cancer patients, 90 of them over a 20-year period developed bilateral breast cancer. Eighteen were excluded because of questionable follow-up. For these 72 patients, they developed a matched control group consisting of patients matched according to the patient's age at the time of initial cancer, the tumor histopathology, the tumor size, and the lymph node status. They compared the survival of these two groups, 72 people who had bilateral cancer and 72 matched controls within their own group, and noted a 20% deficit in survival at 5, 10, 15, and 20 years, comparing their bilateral patients with their own matched unilateral controls. We felt that, of all the studies we had looked at with this type of comparison, this was the most eloquent and thoughtful type of comparison by far.

Dr. Sutherland, we believe in contralateral biopsy in view of the current data, especially in patients who have high risk of developing a second cancer. As far as large-scale studies (sic), we would have to discuss this with our statistician. Obviously, a prospective randomized trial with significant and substantial numbers would be needed to provide an ultimate answer, and hopefully this will be done in the future.