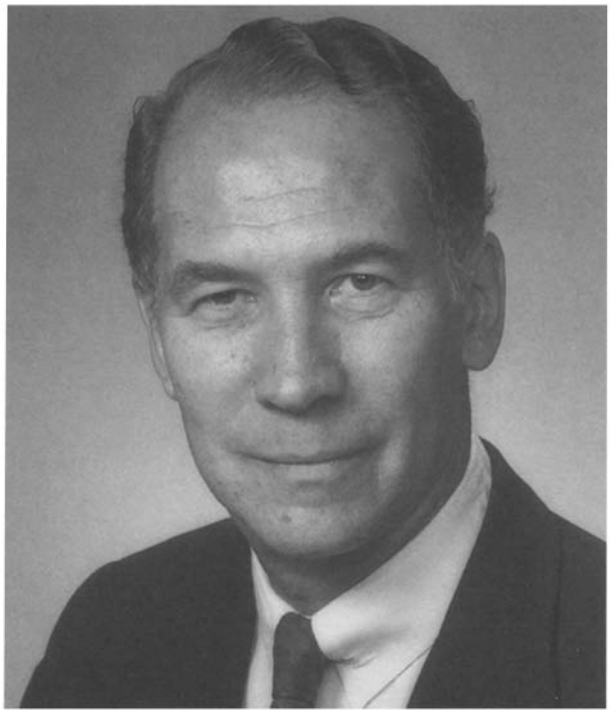
KARNOFSKY MEMORIAL LECTURE

Natural History of Small Breast Cancers

By Samuel Hellman

PROGRESS IN MEDICINE, like evolution, appears to occur in fits and starts, that is, there appear to be long periods of quiescence and then great bursts of insight into the etiology, natural history, and therapy of particular diseases. With breast cancer, the notion of the disease, its pathogenesis, and its treatment remained relatively static following the formulation of the Halsted paradigm for the disease and the acceptance of radical mastectomy as the logical therapeutic embodiment of this notion of disease spread.[1,2]

Fin de siècle or end of the century is used to describe the last decade of the nineteenth century, when this operation was described. It also connotes a time for reflection and taking stock. Since it has been just 100 years since the initial publication on this subject, it is appropriate to consider the state of the paradigm for breast cancer pathogenesis and its therapeutic implications. The acceptance of radical mastectomy was due both to the effectiveness and the attractiveness of the Halsted model. The underlying premise is that breast cancer is an orderly disease that progresses in a contiguous fashion from primary site, by direct extension, through the lymphatics to the lymph nodes, and then to distant metastatic sites. It implies that effective treatment must recognize this orderly, contiguous disease spread. In fact, in his original formulation, Halsted[3] suggested that even spread to the vertebra or to the abdomen was due to translymphatic contiguous extension. Its attractiveness lies in the en bloc approach to surgery, which came to be the guiding principle of cancer surgery. Despite a plateau in the effectiveness of radical mastectomy, it was not until recently that an alternative hypothesis was accepted. That hypothesis suggests that breast cancer is a systemic disease and implies that small tumors are just an early manifestation of such systemic disease, which, if it is to metastasize, has already metastasized. Nodal involvement is not an orderly contiguous extension, but rather a marker of distant disease. Local control, according to this theory, is unimportant to survival. This was first suggested by Geoffrey Keynes,[4] carried forward by George Crile, Jr[5], and fully explicated with both laboratory and clinical studies by a former president of the American Society of Clinical Oncology (ASCO) and Karnovsky lecturer, Bernard Fisher[6], who in that lecture stated "that breast cancer is a systemic disease involving a complex spectrum of host-tumor interactions and that variations in effective local regional treatment are unlikely to effect survival substantially." A third hypothesis considers breast cancer to be



a heterogeneous disease that can be thought of as a spectrum of proclivities extending from a disease that remains local throughout its course to one that is systemic when first detectable. This hypothesis suggests that metastases are a function of tumor growth and progression. Lymph node involvement is of prognostic importance not only because it indicates a more malignant tumor biology, but also because persistent disease in the lymph nodes can be the source of distant disease. This model requires that there are meaningful clinical situations in which lymph nodes are involved but there has not yet been any distant disease. Persistent disease, locally or regionally, may give rise to distant metastases and, therefore, in contrast to the systemic theory, locoregional therapy is important. This

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third, or spectrum, theory suggests that even if, as the systemic theory suggests, tumor cells spread distantly early in the natural history of the disease, metastases do not regularly occur. A most important parameter determining the likelihood of their presentation is tumor size. Therefore, there are significant times in the clinically relevant natural history of the disease when metastases have not occurred, but if tumor is left inadequately treated metastases will occur.

After this long period of acceptance of the Halsted hypothesis and radical mastectomy as the treatment we have had, like the rapid changes seen during certain periods of evolution, an abrupt alteration in our conception of this disease. This has been caused by the following three innovations in the diagnosis and treatment of breast cancer: (1) screening mammography, (2) lumpectomy and radiation therapy with breast conservation as an alternative local treatment, and (3) adjuvant chemotherapy as a curative treatment for subclinical disease. All three bear directly on the appropriate paradigm for breast cancer and the use of the Halsted operation. Screening mammography discovers tumors quite different in size with, I suggest, a more favorable biology than those detected clinically, and invites less radical treatment. While lumpectomy plus radiation is based on the Halsted model of disease pathogenesis, it is very different than en bloc surgical extirpation. Adjuvant chemotherapy emphasizes the importance of subclinical disseminated disease.

It is the purpose of this discussion to focus on the small breast cancers that we are seeing increasingly today—the result of active screening programs and a heightened public awareness—to determine which one of these models best fits with clinical experience. The 1990 SEER data indicate that breast cancer incidence is essentially flat except for the increase in stage 1 breast cancer, which has risen from 25% to almost 50% of all invasive breast cancers from 1983 to 1990. Almost certainly, this is the result of screening mammography. If one examines the data for screen-detected breast cancer in two large European studies, that from Nejmegen, Netherlands—a well performed screening project—and the two-county Swedish trial—a randomized trial[8,9]—one finds that small cancers are the large majority of those observed, even when one excludes the first screen. Such breast cancers are more likely to be node-negative and, as we shall see shortly, if nodes are involved they are likely to be limited in number. This is directly related to tumor size.

The first general question useful in distinguishing among the three hypotheses is at what time in the natural history of breast cancer do distant metastases occur? The systemic disease hypothesis suggests that these occur before clinical detection and argues that local eradication of disease makes little or no difference. The results from screening mammography argue strongly that this is not the case. There appears to be a 30% reduction in deaths due to breast cancer in mammographically screened populations. Again, as an example, let me use the two-county Swedish trial[8] for which the data have now been available for at least 11 years and continue to show a 30% reduction in deaths due to breast cancer. I emphasize breast cancer deaths as an end point, because reduction in this avoids the objections of lead-time bias or length bias to which incidence or survival rates can be subject. I believe the only plausible explanation for this 30% reduction is that, for those 30%, metastases would have occurred between the time of mammographic detection and routine clinical detection. Detection by screening mammogram has allowed effective locoregional treatment before distant spread of sufficient numbers of cells capable of metastatic growth. In my judgment, this is a strong argument against the systemic thesis.

Table 1. Clinical Appearance of Metastases as a Function of Tumor Size

Class	Diameter (cm)	Estimated Proportion of Initial Metastases (%)	Eventual Metastases (%)	Estimated Initial % per Year	No. of Cases
1	1 ≤ 2.5	3	27	2.5	317
2	2.5 ≤ 3.5	4	42	5	496
3	3.5 ≤ 4.5	7	57	7	544
4	4.5 ≤ 5.5	10	67	9	422
5	5.5 ≤ 6.5	16	73	12	329
6	6.5 ≤ 7.5	22	84	15	192
7	7.5 ≤ 8.5	22	81	15	136
8	≥ 8.5	35	92	22	212

NOTE. Data from Koscielny et al.[10]

Tubiana et al[10-12] have studied almost 3,000 patients with breast cancer who were seen at the Institute Gustave-Roussy before the routine use of adjuvant chemotherapy and have shown that metastases in that group is a continuous function of tumor size. For any tumor size, there is an eventual probability of metastases that increases with increasing tumor size. This never reaches 100%. The time to arrive at this plateau is inversely related to tumor size, that is, smaller tumors take longer to demonstrate their metastatic potential than do larger ones. This latter point is especially important when considering small breast cancers. I have taken the liberty of making a table based on a figure in one of their reports.[10] Table 1 indicates the increased proportion of initial metastases when patients are first seen, as well as the eventual percent of patients who develop metastases as a function of initial tumor size. It also estimates the initial slope of metastases as a function of tumor size. Note the smallest tumors in this study: class 1 tumors that are less than 2.5 cm. Patients

with tumors in this class develop metastastic disease at an estimated 2.5% per year, and half of the patients who eventually developed metastases did so by 42 months, as compared with only 4 months for class 8 tumors. This emphasizes the long follow-up duration required for small breast cancers and the limited value of 5-year data, even 5-year disease-free survival data.

What then are the possible natural histories of these increasingly frequent small breast cancers? I define small breast cancers for this discussion as those tumors $\leq$ 2 cm in size (T1) when first seen regardless of lymph node status. First, some of these may be incidental findings at mammogram of tumors with such benign or indolent natural histories as to have no significant effect on survival. The presence of such lesions is thought to elevate falsely survival calculations of mammographically screened populations. One technique that I find useful to avoid this bias is to consider only cancers found after initial screening. As a clinical issue when patients present to us, we cannot tell whether the tumor detected is one of these indolent and clinically unimportant cancers or not.

The second group would be those that have a localized cancer that, if left to grow, will become disseminated and result in the patients death. It is this group that must explain the success of screening in reducing breast cancer–related deaths. Also relevant to this group are the effects of locoregional therapy on outcome. If differences are found, they must be due to differences in the persistence of disease in the primary tumor or nodal site resulting in differences in distant metastases. The randomized trial performed in Stockholm of adjuvant radiation following mastectomy bears directly on this point.[13] The study is important since the treatment would be acceptable by today's standards, it was performed before adjuvant chemotherapy (1971 to 1976), and has the required long follow-up duration. This study shows the expected reduction in locoregional recurrences, but it also shows an accompanying decrease in distant metastases and deaths due to breast cancer. The overview analysis of all randomized trials of mastectomy with or without adjuvant radiotherapy has been updated by Cuzick et al.[14] They conclude, "The reduction of breast cancer deaths suggests that radiation therapy may have a value beyond the clearly established improvements obtainable for local control." That statement endorses the notion that distant metastases can be the consequence of persistant local or regional disease and that effective locoregional therapy can reduce their frequency. They point out that the National Surgical Adjuvant Breast and Bowel Project Study B-04, as well as the Stockholm results shows a significant mortality benefit. B-06 compared lumpectomy with lumpectomy and radiation.[15-17] There was a large difference in local control and, at 5 years, in distant metastases, but this was not true at 8 years. This study included all tumors up to 4 cm. Further study and follow-up evaluation of T1 tumors in this group would be interesting.

One study suggests that treatment of the axillary lymph nodes can affect survival. In the Guy's trial,[18] inadequate radiation treatment of the axilla resulted in more axillary recurrences and this was associated with a greater incidence of distant metastases and decreased survival.

Thus, we have considered those tumors that are destined to remain localized, those that metastasize as a function of size, and those that possibly disseminate from persistent lymph node disease. Finally, there must be some patients whose tumors have occultly disseminated by the time of diagnosis, since locoregional treatment is not universally effective in preventing metastases, even in those patients who have been rendered free of locoregional disease. It is, of course, the presence of this group that argues for adjuvant systemic therapy. Determination of the relative proportion of such patients when one is considering small breast cancers will inform any therapeutic strategy.

There is also the question of whether tumor progression occurs during the clinically observed portion of the natural history of localized breast cancer. There are two possible effects of tumor size. The first is that metastasic frequency increases directly as a function of tumor size because more cells are available to metastasize. A second possibility is that small tumors are intrinsically less malignant than large ones. The Gustave-Roussy series,[10,11] as well as the results of screening mammography,[7,8] shows an increase in grade as a function of tumor size. This may be due both to tumor progression and to selection of more malignant tumors by their more rapid growth. Thus, the reason that large tumors are more malignant may have to do with their having more cells to seed, by tumor progression with an increase in the malignancy of these cells, and by the more rapid proliferation of more malignant cells.

Analysis of survival data requires consideration of the consequences of different biologic events. Jay Harris and I have discussed this previously.[19-22] I would like to add a further distinction to that discussion. I propose that there are two components of malignancy. These are not necessarily completely independent, but current methods of analysis tend to confound them. For lack of better words I will call them virulence and metastagenicity. Virulence is the pace or rate of disease growth, dissemination, and clinical manifestation. Metastagenicity is the ultimate likelihood of distant metastases. Fixed-point survival estimates will confuse these when this point occurs before the full expression of metastastic potential. A class

Table 2. Percentage of T1N0 Patients Dying of Breast Cancer as a Function of Age at Diagnosis

Age at Diagnosis (years)	% of Patient Deaths		
	5 Years	10 Years	20 Years
< 50	14	14	20
≥ 50	6	11	19

NOTE. Data from Quiet et al (submitted).

of tumors that has a high virulence will demonstrate metastases quickly, even though the eventual likelihood for distant metastases may be no different than another group. An example of this is shown in Table 2, which comes from the Chicago experience to be described subsequently. The analysis at the usually accepted 5-year end point shows the expected and statistically significant effect of age on outcome; however, this disappears by 10 years. This, then, is a real difference, but it is in virulence not metastagenicity. Another possible example is seen in a review of breast cancers ≤ 1 cm or less reported by Stierer et al,[23] who showed a difference in virulence but not metastagenicity as measured by relapse-free survival when studying the prognostic significance of the number of mitotic figures in these tumors. Using a single point in time such as 5 years will not distinguish between virulence and metastagenicity. This should be especially important in trying to understand the effects of different types of systemic adjuvants. Hormonal manipulation may have quite different effects than chemotherapy. A soon to be published European Organization for Research and Treatment of Cancer (EORTC) trial (Bartelink H, Rubens RD, van der Schueren E, et al, submitted) showed quite different results when analyzed shortly after conclusion as compared with 8 years later. In this trial, which compared hormonal and chemotherapeutic adjuvant treatment for locally advanced breast cancer, the initially statistically significant benefit of chemotherapy disappeared, while the hormonal effect increased in size and significance with longer follow-up durations.

Informed by this formulation of the three alternative hypotheses—Halsted, systemic, and spectrum—and cautioned to observe the complete clinical evolution of small breast cancers, I should like to discuss two series with which I have been personally involved. These are both mature series of patients treated almost exclusively by local and regional methods and monitored for long periods of time. I shall try to ascertain from these data which hypothesis best explains their natural history. In both series, I will be discussing primarily these small tumors. One series comes from Memorial Sloan-Kettering Cancer Center and the other from the University of Chicago. Peter Rosen was the senior author on a study of the long-term survival of patients with T1,N0 and T1,N1 breast cancer who presented at Memorial Hospital from 1965 to 1970 and were analyzed 18 years later.[24] More recently, Coral Quiet (Quiet CA, Ferguson DJ, Weichselbaum RR, et al, submitted) has reviewed a series of patients with breast cancer, largely operated on and followed by Donald Ferguson, who were seen from 1927 to 1984 with a mean follow-up duration of 14 years and a maximum of 44 years. The node-negative patients were presented at the American Society of Clinical Oncology (ASCO) meeting last year and the node-positive patients are being presented this year. I shall first consider those patients without involved axillary lymph nodes. For those patients whose tumors were less than 1 cm without positive axillary lymph nodes in the Memorial Hospital series, 12% developed recurrence of their breast cancer, that is, for 88% of such patients locoregional treatment was effective. For those patients with tumors between 1 and 2 cm, 26% developed recurrence. Brinkley and Haybittle[25] have suggested a statistical definition of cure to be that proportion of the treated group that has the same survival as an age-adjusted peer population. For those patients with tumors ≤ 1 cm, 88% appeared to be cured and this appears to occur somewhere around 10 years. In those patients with larger T1 tumors, the curves do not become parallel until close to 15 years. The data from the University of Chicago series do not show this difference within T1 tumors, but the aggregate T1 results are similar. Seventy-nine percent of such patients are cured of their breast cancers. In this series, both the median time for recurrence and the time in which it takes 10% of the patients to relapse are inversely related to tumor size. Small tumors take a longer time to recur than do large tumors, and a 5-year end point will not capture many of the recurrences: in this series, almost half of the deaths occur after 5 years. This is consistent with the Tubiana-Koscielny data.[10,11] The results from screening also document the important relationship of size to survival. Tabar et al[9] show a difference within T1 tumors, as well as the high curability of such tumors as compared with larger lesions. Surely, these high disease-free survival data in the Memorial and Chicago experience before systemic adjuvant therapy argue strongly that stage 1 breast cancer is usually only a locoregional process. This is the case in approximately 75% to 80% of such patients. The data also suggest that even within stage 1 breast cancer, smaller tumors do better.

I should like to now consider those patients with involved lymph nodes. It is of interest that the number of nodes involved with such small breast cancers is limited. In a recent review of patients involved in European Organization for Research and Treatment of Cancer (EORTC)

Table 3. Percentage Disease-Free Survival at 20 Years as a Function of Tumor Size

	Tumor Size (mm)		
No. of Positive Nodes	1-10	11-20	≥ 20
0	79	79	64
1	95	78	59
2-3	73	73	53

NOTE. Data from Quiet et al (submitted).

trial of the role of a booster dose in breast-conserving therapy, 19% of patients had lymph node involvement (A. Ptaszynski, personal communication, March 1994). In 47% of such patients, only one node was involved, 22% had two nodes involved, 9% had three nodes involved, and only 22% had four or more lymph nodes involved; thus, in the entire group, only 4% had four or more nodes involved. In the Memorial series,[24] patients with one to three lymph nodes involved appeared to be cured by locoregional treatment 68% of the time. The curve became parallel with the age-adjusted peer population at approximately 13 to 15 years. The Chicago data emphasize the importance of small primary tumor size when there are only a limited number of positive nodes. In this series, size is important even when there is lymph node involvement. Small tumors that have only one positive nodes still have an excellent prognosis. This is also true when two or three nodes are involved. This does not appear to be true when four or more nodes are involved. Analysis of these 20-year data (Table 3) indicates that having only one node involved did not reduce survival for T1 breast cancer patients. Seventy-three percent of patients with two to three nodes involved survived 20 years without relapse. Only when there were four or more nodes involved was there a significant reduction in survival. These long-term data before adjuvant systemic therapy indicate that, in small breast cancers, lymph node involvement is not a marker of distant disease unless a large number of nodes are involved. When there are only a small number of nodes involved, there does not appear to be any higher probability of metastastic disease. Tubiana et al[12] show excellent results for these small tumors with limited nodal involvement and also show an independent effect of grade.

The curability, using locoregional treatment, of patients with small breast cancers and a limited number of positive lymph nodes speaks for the orderliness of disease progression in these patients. Such lymph node involvement is the first, or only, site of disease in the large number of patients cured by locoregional treatment. This suggests that the systemic hypothesis is not appropriate for patients with such small lesions. It also emphasizes the need for prompt and proper treatment, not only of the primary lesion, but of regional lymph nodes as well. While the systemic hypothesis may be correct in that tumor cells circulate very early in the natural history of the tumor, operationally it has quite different implications. Small tumors are usually amenable to local or regional treatment alone. This is true even when there is some axillary node involvement. Perhaps there is early distant dissemination of tumor cells, but, if so, presumably the host can deal with the small number of cells or these cells are insufficiently malignant to produce metastases. When tumors are larger, the likelihood for metastasis increases, perhaps both as a function of a larger number of cells seeding and possibly as the result of tumor progression.

Both the Halsted and the systemic hypotheses are too restricting. The hypothesis most consistent with the data is that breast cancer is best thought of as a spectrum of disease with increasing proclivity for metastasis as a function of tumor size, but for any tumor size there a proportion of patients with distant metastasis. Similarly, there is a proportion with local disease alone. While lymph node involvement can be a marker of increased risk of distant disease, it may be the only site of metastasis in many patients, especially those with small tumors. We have also learned that 5-year data can be misleading and should be used with caution.

What then are the therapeutic messages of this analysis of small tumors? The proportion the patients who present with such tumors is large and will increase with more widespread screening. The absolute curability of T1N0 breast cancer is quite high with effective locoregional treatment and this should not be compromized. To maximize uncomplicated cure, we must develop a strategy for adjuvant systemic therapy that recognizes the excellent prognosis of these patients. The increasingly recognized importance of chemotherapy dose-intensity requires a method of selecting those patients who require such treatment from the large majority cured by locoregional treatment alone. Different adjuvant therapies may affect virulence and metastagenicity differently, so that we need markers for both and should analyze mature adjuvant trials to determine which aspect of malignancy is most affected by the treatment.

This end of the century reflection on the natural history of small breast cancers then brings a synthesis to the contiguous–systemic dialectic. Both have some truth, but adherence to either alone is inadequate. The satisfactory synthesis recognizes both, within a spectrum in which for small tumors the disease is usually restricted to the primary tumor site with the possible involvement of a limited number of regional lymph nodes. Larger tumors are more likely associated with systemic disease when first observed. The lesson from all this is the value of clinical

investigation to study the natural history of disease. As the philosopher of science Karl Popper[26] has emphasized, the nature of scientific truth is conditional; progress is an increasingly satisfactory approximation of truth. I believe that this synthesis is a more satisfactory approximation of truth but it is only that, an approximation and it is conditional on more information. This brings me to the final lesson of this *fin de siècle* discussion: that of the inappropriateness of dogma in medicine and science.[27] Halsted became dogma and, more recently, the notion of breast cancer always being systemic has become dogma. Like all dogma in science, both are too restricting. They tend to limit our inquiries and deny the conditional and approximate nature of scientific knowledge.

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