Eur J Cancer Clin Oncol, Vol. 22, No. 1, pp. 123–128, 1986.
Printed in Great Britain.

0277-5379/86$3.00+0.00

Sounding Board

Some Changing Concepts of the Natural History of Human Mammary Cancer and their Effect on Diagnosis and Treatment*

H. J. TAGNON
Institut Jules Bordet, Boulevard de Waterloo, 125, B-1000 Bruxelles, Belgique, Belgium

FOR THE clinician and also for the patient and his/her future, metastases represent the central problem in the treatment of cancer. Without metastases, a cancer is easy to cure by the presently available local treatments, surgery and radiotherapy. There have been two diametrically different concepts concerning the metastases of breast cancer, and they have influenced treatment [1].

In an early concept of the natural history of breast cancer, which was proposed by the American surgeon, Halsted, around 1900, breast cancer remained a localized disease for a long time, growing by invading surrounding tissues and giving metastases only through the lymphatic system, not through the blood. Tumor cells moved in successive steps from the primary tumor to the proximal lymph nodes, then to the regional and more distant nodes. Halsted held the opinion that the nodes represent a natural barrier to the dissemination of cancer cells. Putting these ideas into practice, he devised the treatment of breast cancer by the surgical operation called the 'Halsted radical mastectomy'. Essentially, this is a resection *en bloc*, without dissection, of the whole affected breast together with all axillary nodes and tissues, and all surrounding tissues, including several important muscles. This was a mutilating operation based on the concept of breast cancer as initially a localized disease with local extension and therefore curable by an aggressive local or regional type of treatment. Halsted was a forceful, energetic man and his treatment was not really questioned by oncologists up until around 1950. The patient with breast cancer was treated as an emergency, immediately admitted to the hospital and operated upon the following day, all this to avoid dissemination, which might occur at any minute. Thereafter, the patient went into her post-mastectomy period with often a considerable degree of invalidity, mental and physical, and the perspective of future generalization. Yet a few patients had their metastases late in life, and this, with the few real cures, confirmed the value of the treatment. Also, the practice of estimating the value of treatment at 5 yr postoperatively gave a false opinion of the value of the treatment. This treatment has been administered to hundreds of thousands of women, perhaps millions. The Halsted operation was adopted under various names in all parts of the world.

After 1950, dissidents from the true religion began to appear, mostly because of the development of new ideas on cancer and metastases, but also because of the impact of the controlled clinical trials, which made clinicians sceptical of accepted ideas and which represent probably one of the important advances in modern clinical investigation. Finally, oncologists began to extend the follow-up of patients beyond 5- and the 10-yr periods, with surprising results. As a result of all this, the Halsted concept was re-examined: careful clinical observation and comparative analysis of the end results of treatment demonstrated the lack of objective evidence to support the idea of breast cancer as a localized disease protected from dissemination by a barrier of lymph nodes. Comparative clinical trials showed that the Halsted operation was no

Accepted 13 September 1985.
*Adapted from a seminar given in Bethesda, MD in 1981 as Senior Fellow in residence of the Fogarty Foundation.

more effective than a limited, non-mutilating tumor resection.

Contrary to earlier views, clinical and histological examinations have shown that tumor cells are transported by venous channels as well as by lymphatic vessels, and that there is an intricate communication between the two systems. A few minutes after the Halsted operation, tumor cells can be recovered from the vascular system. Lymph nodes are not a barrier since lymphatic vessels from the tumor area will enter a lymph node without stopping there but continue through it and into the thoracic duct and the vascular system. There are cases of breast cancer with distant metastases in which the regional lymph nodes are entirely free of tumor cells. The presence of tumor cells in lymph nodes is just a lymph node metastasis which will or will not develop into a new tumor. Removal of these invaded lymph nodes has been shown to have no influence on the prognosis, survival or recurrence. However, the presence of invaded lymph nodes is of great prognostic significance. Yet the effectiveness of the radical mastectomy in prolonging life was not immediately challenged: failures were attributed to delay in treatment and much work was done to try to demonstrate that early diagnosis was the answer to the challenge.

Let us now consider the much debated question of the early diagnosis or screening of symptomless healthy females for the discovery of early cancer in the hope that treatment of early lesions will prolong survival. For purposes of discussion let us consider two phases in the evolution of breast cancer: the preclinical and clinical phases. The preclinical phase is the evolution from the first modified cell to a size which is recognizable by the physician using the presently available diagnostic methods. This minimally recognizable tumor is a mass approximately 1 cm in diameter. This size varies with the volume of the breast, the skill of the diagnostician, etc., but in general a small tumor, let us say below ½ cm, can hardly be identified. Such a 1-cm tumor contains a maximum number of 10^9 tumor cells in addition to connective tissue, blood vessels, blood cells, etc. To produce 10^9 cells from one replicating cell, 27 reduplications are needed. The interval between each replication is variable among tumors and variable between the beginning and the end of the development. The time interval has been estimated at between 50 and 150 days. Taking the lower value as an average, such a barely palpable tumor, when clinically diagnosed by palpation and mammography, may have existed for approximately 1350 days, or more than 3½ yr. If there is cell loss, and there may be as much as 90% of the total cell mass, the length of the interval from the beginning of the preclinical to the clinical phase may even be longer. It is true that proliferation is faster at the beginning of the growth. On the other hand, there may be long dormant phases. These are necessary to explain the appearance of metastases in patients whose cancer was removed 15–20 yr before. Such late recurrences are not infrequent [2–4].

Taken together, these data suggest that the age of a barely palpable tumor is such that this tumor is not an early tumor. It has been there for months and probably for years, during which, in this symptomless and silent phase, it has had time to metastasize. The present view of breast cancer is that it probably is never a localized disease during its clinical phase and for some time before this. When diagnosed with the best methods now available, there are already distant, blood-borne metastases in the majority of the patients. The evidence for this is the development of late tumor metastases, up to 10–20 yr after resection of the primary tumor in 40% of patients with stage I small tumors, clinically localized and without clinical lymph node invasion. Metastases may be found in distant sites in apparently cured patients dying in accidents or operated upon for other causes. All this is confirmed by the fact that 40% of patients with stage I breast cancer, this means small and clinically localized, die of generalized breast cancer 10–20 yr after operation [1].

This long duration of what is called the silent phase, that is, the interval between the discovery and treatment of the primary tumor and the appearance of metastases, is quite consistent with numerous observations of foci of metastatic lesions which never develop into clinical cancer during the life of the patient. These patients are 'cured' for 10 or 20 yr, although they have silent, dormant metastases which may at some time start growing; they will eventually kill the patient.

Let us now examine the validity of early diagnosis and mass screening by presently available techniques as methods to increase the effectiveness of the treatment. It is an intuitive notion that if a cancer is caught early and removed, then many instances of metastases will be avoided and lives will be saved. Everyone knows the programs of early diagnosis which have been set into motion for a number of years and also the recommendations for breast self-examination, etc. We may first examine the assumptions on which these recommendations are based. Thereafter we will examine whether these programs have been successful in reducing mortality.

Screening for breast cancer proposes to detect cancers small enough that the patient is unaware of its presence. In other words, screening addresses itself to symptomless women who are not complaining of disease or have not noticed anything

abnormal in the breasts or elsewhere and present themselves spontaneously to the screening clinic. Remember that the detection of a tumor 1 cm in diameter is not necessarily an early diagnosis; that this tumor may have had a hidden life, the preclinical phase, of several months or even years. It is well known that all screening procedures for chronic diseases identify those with a long symptomless course, with more benign disease and who live longer. The rapidly developing breast cancer is seen by the patient's physician and is not screened. The long-lasting benign cancer is the one which screening detects. Therefore a subgroup of more benign cancers is identified by the screening procedures and their prognosis is going to be good, as it would also have been without the detection by screening. A recent report seems to confirm this opinion: 'interval breast cancers', that is, those detected after a negative screening test and before the next annual screen test is due, are unusually aggressive and have a lower survival rate at 5 yr than those diagnosed by screening [5]. Therefore the assumption that mass screening as now practised will improve diagnosis may not appear more acceptable than the alternative assumption that it will have no or little effect. Effort in the direction of developing new methods of detection and intensified research in biological approaches to cancer research should replace much of the ineffective present mass screening. The results of mass screening on survival have been tabulated in a study initiated in 1964 by the Health Insurance Plan of Greater New York. Approximately 62,000 women aged from 40 to 65 yr were randomly distributed into two groups of equal sizes. One group, the study group, received an invitation to participate in the breast screening program. The other was simply observed. Screening was done by clinical examination and mammography. The women in the study group were offered an initial screening examination. Those who accepted were invited to three more screening examinations at annual intervals. Approximately two-thirds of the women in the study group accepted the offer of screening and about one-half received all five examinations. At a recent report, there were 301 breast cancers discovered in the study group and 291 in the control group [6]. The survival advantage was of 93 deaths in the first group over 133 deaths in the second. This difference is statistically significant, but only for women 50–59 yr old. There was no advantage in the younger or the older age group. However, if this result partially satisfies the statistician, it may not satisfy the oncologist or the public health officer. Even admitting the number to reflect a positive action of mass screening, the result in absolute terms is not substantial, consisting of 40 prolonged survivals from 31,000 screening examinations. Assuming a cost of $100 per examination, the total cost for prolonging 40 lives would be well over $50,000 per patient. We do not know how long this prolonged survival will last. Furthermore, we cannot be certain that the two groups of women are comparable; the very fact that one group submitted to the screening procedure might indicate a biased or selective process. Regardless of these reservations, although human life has no price, one may well wonder whether the cost of this project would not have been more effectively spent, even in terms of human life, on research on treatment or on new and original diagnostic methods.

Our assumption of over $50,000 per prolonged life greatly exceeds the Edinburgh study, where each cancer detected cost $8000 [7]. Of the 18 detected cases, six had positive lymph nodes and a bad prognosis. Therefore, in this study, the cost of a possible life-saving detection amounts to $36,000 [6].

A very interesting discussion by Zelen also underlines the limited value of early diagnosis for patients' survival [4]. There have also been comments in the literature on the risk of provoking or encouraging unnecessary surgical treatment, based on an uncritical interpretation of the results of mass screening.

Leaving now mass screening and the attempts at early diagnosis, and their effect on recurrence and survival, and realizing that this is not the solution, we should examine the end results of the treatment of breast cancer without specifying the methods used as they were practised up to 10 or 15 yr ago, with a considerable proportion of radical mastectomies followed or not by radiotherapy. Data indicate that radiotherapy as primary treatment of the tumor is probably as good as radical surgery. As adjuvant therapy after surgery, it prevents local recurrence without altering the ultimate prognosis. Radiotherapy and surgery have in common that they represent a local treatment for what is in a very high proportion of instances a disseminated disease.

The full impact of breast cancer on human life is realized when one takes cognizance of the prevalence of breast cancer in our population and of the mortality figures. In Western countries, the disease affects one woman in 14 and is the most important cause of morbidity and mortality in women. The largest number of patients are between the ages of 40 and 50. In the Syracuse study 88% of the women who died following a diagnosis of cancer of the breast of mixed stages died or are expected to die of the cancer [8]. These patients had surgical treatment of the primary cancer. The 50% mortality figure for the youngest group was 13 yr, for the middle group 8 yr and for the oldest group 5 yr. In the Israeli study 85% of the patients who died

following a diagnosis of breast cancer died of the cancer. In the Cambridge study similar figures are found [9]. As far back as 1951, an Edinburgh study concluded that

"it has not been proven that the survival rate of cancer of the breast using the 5 year survival rate as an index, is affected by treatment at all. If in any way effective, treatment effectiveness cannot be greater than that required to increase the overall 5 year survival rate by more than 5 to 10 per cent" [10].

Stages I and II patients had somewhat better results, but not remarkably so. These considerations on treatment effectiveness up to the present era are a most important factor for the motivation of clinical scientists to test alternative methods by clinical research and to have the courage to innovate [7–9, 11–13].

A short digression is perhaps in order here and has to do with the heterogeneity of tumors, all matching probably the heterogeneity of the aggressiveness of cancer for the host [14]. I have always been impressed by the unquestioned usefulness and at the same time the tyrannic power of morphology influencing our thinking in oncology. Only recently has it become apparent that identical-looking cells may be extremely different in function, potential for growth and differentiation, as well as biochemical equipment. The striking example is the lymphocyte, of course. But the same is true of breast cancer. No morphological difference distinguishes the estrogen-receptor-positive cell from the receptor-negative cell. The development of cellular markers in the last 10 yr forces us to get accustomed to the fundamental heterogeneity of tumor cells and the dissimilarity, evidenced by prognosis and response to treatment, of what seem to be morphologically identical tumors. Our treatments are still largely based on morphologically identified tumors, and we are just beginning to add biological and biochemical criteria to our identification of tumors and to our choice of treatment. Speaking in general terms, when we say that a type of tumor responds to treatment to the extent of, for instance, 40% of cases, we are in fact stating, without always being aware of it, that the 60% non-responders are either different tumors, or grow in patients who have no defense against the tumor. In our prospective clinical trials, a deficiency has been the intellectual concentration on the positive results, obviously an important aspect of the trial, but another rewarding study, which should be undertaken as often as possible, is the analysis of possible factors which make a subgroup of tumors resistant to the treatment. This subgroup of tumors is different from the responding one, and it seems to me that we have not given it enough attention and used the available material to institute in each trial a careful study of what makes these non-responding tumors different. In all publications of clinical trials, an enquiry into the possible factors of failure to respond should be added to the positive results and verifiable hypotheses expressed as the basis for future work. A well-known instance in the case of breast cancer is provided by the studies on estrogen receptors. Whatever effective sexual hormone treatment is used in the treatment of breast cancer in controlled studies, the positive results are always in the neighborhood of 30–40%. These represent the percentage of breast cancers seen in the clinic which contain enough ER-positive cells, therefore enough cells killed by the hormonal treatment, to produce a 50% shrinkage of the tumor mass, which is the definition of a positive result. Generally speaking, the heterogeneity of the cellular population of breast cancer has been amply demonstrated and is kept in mind by the oncologist when he makes his therapeutic decisions [15]. Pathologists and surgeons have observed the presence of histologically identifiable small cancers in the clinically normal contralateral breast of a woman with breast cancer or in the vicinity of a clinically detected cancer in the same breast [16]. They are discovered in biopsy specimens taken by the surgeon from the contralateral breast when doing a mastectomy. These microcancers, histologically unmistakably malignant, are found at examination of the removed breast, and at a distance from the main cancer. Yet it is rather unusual to observe a simultaneous development of clinical cancer in both breasts, and perhaps more unusual to observe two distinct clinically diagnosable cancers in the same breast. The explanation given for this seeming contradiction is that not all histologically authentic cancers develop into clinical cancers, at least not for a long time. There are, of course, similar situations in other types of cancer, such as prostatic cancer. The prostates of old men almost always contain histologically identified microcancers. These do not necessarily progress to the stage of clinical cancer during the lifespan of the individual. Modern surgeons consider that the multicentricity of breast cancer is not an objection to the limited resection of the growing mass: they argue that it is very uncommon to observe multiple clinically apparent tumors in the same breast. Therefore the multicentricity should not affect the surgical strategy. This attitude seems to be supported by the identical results obtained by the radical and the limited mastectomy. However, this cannot be considered a general rule and multicentric cancers may be seen developing simultaneously or successively in limited mastectomy breasts.

If one accepts the preceding considerations, one can try to replace the old hypotheses by new hypotheses and new tentative proposals, the validity of which should be tested by the scientific method. Medical treatments should rest on scientific evidence for ethical reasons. There is no reason why clinical science should be less exacting than any other science, except that our experiments, in addition to being scientifically correct, should also directly benefit the patient on whom they are carried out, a non-compelling condition when one is working on mice. This condition complicates clinical science and gives it a special intellectual flavor. Therefore, we shall say somewhat dogmatically that mammary cancer at the time of diagnosis is probably not a localized disease; therefore, it cannot, except rarely, be *cured* by surgery or radiotherapy. But many of these cancers grow very slowly and long-term survival is possible with or without local treatment. However local excision or radiotherapy may be justified by one or more of three considerations: firstly, it decreases the tumor burden, and this has the reputation, still hypothetical in human cancer, of facilitating a subsequent chemotherapy; secondly, the cancer may eventually ulcerate by invading the overlying skin or the underlying thoracic wall. Such an ulceration causes a great deal of suffering and the infection may eventually kill the patient. Surgical removal of the axillary lymph nodes provides information of prognostic significance. They may also ulcerate if not eliminated, and this is an added reason to remove them; and thirdly, to operate on the breast cancer or to treat it by radiation is political or sociological. The great majority of patients at the present time, whether treated or untreated, will eventually develop metastases and die of their disease. If the localized disease has not received the presently acceptable treatment of breast cancer, the metastases and death may be attributed by the patient or her family to failure to administer this traditional treatment, and this contention will certainly be accepted by a court in a lawsuit. A court of justice usually rules that the adequate treatment of a disease is the one prevailing in the community. In the courtroom there is no pardon for innovators. Clinical investigation has to make its discoveries acceptable, and that is why so much of clinical research is pedestrian and slow. It is not enough that innovation should be beneficial. It should also not dissent too much from accepted ideas.

None of the three reasons given above for removing the local cancer prior to any other treatment is compelling except the last one. But in a less litigious (= fond of going to law) environment, and considering that innovation is an ethical obligation in the treatment of a lethal disease, the time may have come to propose to the patient, when first diagnosed, to invert the order of succession of treatment and to begin with the general treatment, hormones and chemotherapy, before the local treatment, surgery or radiotherapy. There is justification for this order of succession: firstly, present-day chemotherapy used as the adjuvant formula as well as the therapeutic formula has shown effectiveness, limited and temporary, on metastases. This is reinforced by the additional use of tamoxifen, an antiestrogen active on a fraction of the tumor cells and shown to improve the results of cytotoxic chemotherapy [15–17]. On the other hand, the natural histories of treated patients seem to indicate that the local treatment (surgical or röentgenological) has little or no effect on survival, except perhaps that it may prevent ulceration of the chest wall and resulting pain and infection. Therefore there is no harm in postponing it by a few months, while there may be some, admittedly slight, advantage in advancing the general treatment by a few months. In any event, the time is ripe to institute a clinical trial on consenting patients, because there are two more definite advantages to be gained by this method. It is probable that the local tumor will respond to the treatment in a certain proportion of patients. It may either decrease in size or disappear completely. If so, after careful verification by biopsies, the local treatment may become unnecessary and the very painful psychological trauma represented by partial or complete breast amputation is thus avoided. The other advantage is that the clinician will be able to verify *in situ* the effectiveness of the chemotherapy formula he has adopted. If the local tumor does not recede, he will realize in a short time by direct inspection the inadequacy of his choice. This information will be helpful for planning of subsequent treatments. This will thus induce him to modify his chemotherapy program long before the effect of his postoperative adjuvant treatment becomes evaluable by the appearance or lack of appearance of a clinically detectable recurrence. Obviously, this new therapeutic approach should be tested in specialized institutions under adequate medical and statistical supervision in the form of a controlled medical trial. An explicit informed consent should be obtained from the patient. This trial should be conducted with the collaboration of the surgeon. It should be restricted to so-called operable patients, with stages I and II cancers. During the first clinical trial and at the end of the preoperative chemotherapy, all experimental patients should undergo a limited breast resection either to ascertain the disappearance of the tumor or to remove it if still present. For those patients in whom the tumor has disappeared

under chemotherapy, the resection should interest the area of the tumor as determined at the first examination. Prior chemotherapy should probably be given for 3–6 months and continue for another 3 months if examination shows disappearance or a definite reduction in tumor size. Surgical resection should be carried out after 3 months if there is no response to chemotherapy. If complete disappearance of the tumor, verified histologically, is obtained by prior chemotherapy, it will probably be advisable to administer additional chemotherapy in the form of the same or a different combination, with which there is no cross resistance for a period of 3–6 months. The same considerations apply if the local treatment is radiotherapy instead of surgery.

Obviously this is only an outline of an entirely feasible trial which may eventuate into a non-surgical, non-radiotherapeutic treatment, at least in selected cases of breast cancer. The very precise and detailed procedures of investigation and application can now easily be formulated in a protocol of clinical trial. That such a trial should be initiated as soon as possible is justified by what we know of the natural history of the patient with 'primary' breast cancer as treated in the last 100 years and what we have learned of the effectiveness of chemotherapy combined with antiestrogens.

REFERENCES

1. Fisher B. Laboratory and clinical research in breast cancer — a personal adventure: the David A. Karnofsky Memorial Lecture. *Cancer Res* 1980, **40**, 3863–3874.
2. Rozencweig M, Zelen M, Von Hoff D, Muggia FM. Waiting for a bus: does it explain age-dependent differences in response to chemotherapy of early breast cancer? *N Engl J Med* 1978, **299**, 1363–1364.
3. Moore FD, Breast self-examination. *N Engl J Med* 1978, **299**, 304–305.
4. Zelen M. A hypothesis for the natural time history of breast cancer. *Cancer Res* 1968, **28**, 207–216.
5. Degroote R, Rush BF, Milazzo J, Warden MJ, Rocko JM. Interval breast cancer: a more aggressive subset of breast neoplasias. *Surgery* 1983, **94**, 543–547.
6. Miller AB. Controversies in screening for breast cancer. In: Margolese R, ed. *Breast Cancer*. New York, Churchill Livingstone, 1983, 1–22.
7. Langlands AO, Pocock SJ, Kerr GR, Gore SM. Long term survival of patients with breast cancer: a study of the curability of the disease. *Br Med J* 1979, **2**, 1247–1251.
8. Mueller CB, Ames F, Anderson GD. Breast cancer in 3,558 women: age as a significant determinant in the rate of dying and causes of death. *Surgery* 1978, **83**, 123–132.
9. Brinkley D, Haybittle JL, Alderson MR. Death certification in cancer of the breast. *Br Med J* 1984, **289**, 465–467.
10. Park WW, Lees JC. The absolute curability of cancer of the breast. *Surg Gynecol Obstet* 1951, **93**, 129–152.
11. Brinkley D, Haybittle JL. The curability of breast cancer. *Lancet* 1975, **i**, 95–98.
12. Hibberd AD, Horwood LJ, Wells JE. Long term prognosis of women with breast cancer in New Zealand: study of survival to 30 years. *Br Med J* 1983, **286**, 1777–1779.
13. Mueller CB, Jeffries W. Cancer of the breast: its outcome as measured by the rate of dying and causes of death. *Ann Surg* 1975, **182**, 334–341.
14. Leonard RCF, Smyth JF. The heterogeneity of human cancers and its influence on metastases and therapy. *Eur J Cancer Clin Oncol* 1985, **21**, 1001–1004.
15. Tagnon HJ. Antiestrogens in treatment of breast cancer. *Cancer* 1977, **39**, 2959–2964.
16. Mueller CB, Ames F. Bilateral carcinoma of the breast: frequency and mortality. *Can J Surg* 1978, **21**, 459–465.
17. The Nolvadex Adjuvant Trial Organization. Controlled trial of tamoxifen as single adjuvant agent in management of early breast cancer. Analysis at six years by Nolvadex Adjuvant Trial Organization. *Lancet* 1985, **i**, 836–839.