The Appropriate Breast Cancer Paradigm

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Perhaps no other disease or its treatment has evoked such strong feelings as has breast cancer. The reasons for this are to be found both in our culture in general and in medicine in particular. The breast, in certain contexts, is the symbol of motherhood, nourishment, and security while in others it represents beauty and femininity. There are equally compelling medical connotations which have made supporters of certain therapeutic alternatives act like religious zealots. Breast cancer has a long natural history; thus, early results may provide a misleading assessment of long-term outcome. Strongly held beliefs as well as the need for long-term follow-up have provided the ingredients for animated debate concerning the disease and its treatment.

In the middle of the 19th century, women with breast cancer typically presented to their physicians with locally advanced disease, not simply with a lump in the breast. These women sought attention for ulcerated lesions of the breast or for painful axillary involvement by the disease. There was no effective local therapy or any useful systemic anticancer treatment available at that time. Attempts at surgical extirpation generally resulted in a prompt return of the disease locally. The futility of therapy only reinforced the nihilistic attitude of the population regarding the advisability of prompt treatment for suspicious breast masses.

The introduction of the radical mastectomy by Willy Meyer (1) and W. S. Halsted (2) at the end of the 19th century not only was an important therapeutic advance but also provided the first important medical paradigm for this disease. The use of radical mastectomy was based on a model of cancer spread that was centrifugal. A tumor started locally, infiltrated via the lymphatics in a direct and contiguous fashion to the regional lymph nodes, and then spread distantly. In its most doctrinaire presentation, espoused by Halsted, this model explained even distant metastases by contiguous extension. This notion of the disease provided a rational basis for a radical operation designed to resect widely the tumor and contiguous tissues, including the regional lymph nodes. Thus, the primary appeal of radical mastectomy was that it was based on an important theory of disease spread. Secondly, the newly developed method coincided with the rapid improvement in surgical and anesthetic techniques, which was required if the operation were to be performed properly. This became the paradigm for much of cancer surgery and en bloc dissections became important in the treatment of a variety of other cancers. To disagree with the radical mastectomy, therefore, was to threaten the philosophical underpinning of all radical surgery.

It is in this context that one must consider what happened when McWhirter suggested that if postoperative radiation were to be used, the radical mastectomy might be replaced by simple mastectomy, thereby avoiding the morbidity associated with the radical operation (3). While this technique was based on the same model of disease spread, it threatened the notion of en bloc extirpative surgery. So intense was the latter conviction that McWhirter’s results were questioned; it was suggested that those patients cured by him probably never had cancer at all!

The radical mastectomy was expanded to “extended radical” and superradical operations, including dissections of the internal mammary lymph nodes and supraclavicular lymph nodes. Radiation was advocated as a further regional treatment to augment surgery in certain cases. While these techniques improved results for many, physicians became frustrated by the all too frequent presentation of distant metastasis despite proper application of this important regional treatment. Clinical observations and biological study suggested that perhaps such metastases were occult at initial presentation and unaffected by initial management (4). This new paradigm assumes that there are two types of cancer: one remains local and rarely spreads, while the other has occult micrometastases when the patient is first seen clinically. In either of these circumstances, local therapy does not alter outcome (5). If the patient is in the former group then only minimal local therapy need be applied. When and if the patient’s disease recurs, further therapy can be administered. For the latter group, local therapy has no effect on the distant metastases already present.

This new paradigm, taken to its logical conclusion, denies the existence of a circumstance in which an en bloc radical approach to the local area is important to survival. It suggests that metastatic spread never occurs during the clinical phase of disease evolution. Such an approach led to minimal local treatment of breast cancer and serious attempts to discern from pathological examination of the tumor the prognosis of individual patients. It was hoped that one could separate patients into two groups: those who already had occult disease; and those for whom breast cancer was at most a local disturbance. The pioneers of this new approach were surgeons whose views were considered by many to be heresy (6). In fact a recently published breast cancer textbook still rails against this approach and defends a doctrinal purity requiring regular use of the Halsted mastectomy (7).

The other form of local therapy developed in the 20th century is radiation therapy. At first, the same principles that governed the approach to surgery pertained: radical en bloc treatment was the goal. This was found by early investigators to be quite effective in eradicating the disease. The aim of successful radiation therapy is to return the patient as closely as possible to the premorbid state, and this could not be achieved with early external beam radiation therapy. While local control of the tumor might be gained, the cost for the patient was far too high. Changes in the irradiated tissues were severe, causing late tissue breakdown, fibrosis, and cosmetically and functionally unacceptable tissues. It is important to remember that even in the early years, radiation was found to be effective in many cases but was not used primarily because of these complications. An exception was the radium needle implant technique as applied by Keynes (8), which produced acceptable cosmetic

Received 7/30/86; accepted 8/14/86.

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results as well as local tumor control. However, the technique was not widely accepted because it was difficult and caused a significant amount of radiation exposure to the operator. Following the Second World War, the development of cobalt teletherapy units and linear accelerators which delivered megavoltage radiation and had "skin-sparing" capability allowed effective local treatment and produced cosmetically acceptable results (9-14).

The technique of radiation therapy has undergone a process of evolution. It is now appreciated that radiation is most effective and cosmetically most acceptable when high doses of radiation to large volumes of tissue are avoided. The amount of radiation required to destroy subclinical disease has been shown to be considerably less than that required to eradicate gross disease (15). Thus, the combination of surgical excision of the gross tumor with local-regional radiation has become the therapeutic approach increasingly used today (16).

The notion that surgery and radiation are largely complementary rather than competing modalities has evolved as the current paradigm of local cancer management. Whereas surgical treatment, when it fails, tends to do so at the margins of the resection where tumor is not appreciated or where vital structures prevent the extensive tissue removal required, these areas of subclinical microscopic foci of disease are quite amenable to moderate doses of radiation. Radiation fails in the large central hypoxic tumor mass itself or, if it is to succeed, requires very large doses. The cosmetic deformities associated with radiation are due to these high local doses, while the cosmetic deformities associated with surgery are due to the extensive en bloc removal of tissues containing only microscopic disease. Results from both retrospective and prospective randomized trials have shown that the combination of conservative surgery for the resection of the primary tumor, axillary dissection, and moderate-dose radiation to eradicate subclinical disease provides therapeutic results comparable to those of radical surgery while maintaining acceptable cosmetic results (9-14, 16-18).

An important aspect of current breast cancer management is the early detection of tumors. Organizations such as the American Cancer Society not only provide public education but also encourage a greater openness about the disease coupled with optimism for its cure. As a result of their efforts, more women practice breast self-examination and present to their physicians for early diagnosis when they discover suspicious lumps in their breasts. Early detection has also been greatly facilitated by the introduction and refinement of diagnostic mammography. Mammography today is capable of detecting breast tumors which are not apparent by physical examination. Furthermore, only very small doses of radiation are needed, allowing the use of mammography as a screening procedure. Breast cancer is a paradigm in cancer management for the detection of cancer at a very early stage via public education, physical examination, and modern technology. Detection of cancer at an earlier stage does not necessarily imply an improved cure rate. There are a number of biases which can operate to provide misleading results. For example, screening may simply increase the time to cancer death (lead-time bias) or may simply identify patients destined to do well (length-time bias). The ideal method to evaluate the utility of a screening procedure is a prospective randomized trial in which patients are randomly assigned to be screened or not screened. Such studies have been performed and the published results indicate a significant reduction in breast cancer mortality for screened individuals (19-21). These studies have established the importance of mammographic screening and have provided important information regarding the natural history of the disease.

Is there any evidence that allows us to evaluate the two competing explanations concerning the natural history of breast cancer? Each explanation is based on a different theory of when metastases occur. One hypothesis suggests that breast cancer either is nonmetastasizing or metastasizes before the clinical recognition of the disease. The alternative explanation suggests that at least in some patients the disease is orderly, starts in the primary site, and spreads distantly only some time after clinical detectability. We should be able to assess the validity of each hypothesis by considering evidence as to when breast cancer metastasizes. Perhaps the most important single piece of evidence which suggests that there is a period in the clinical evolution of primary breast cancer before metastasis occurs is in the data derived from the screening studies. That mammographic screening of asymptomatic women will result in a 30% decrease (19-21) in the mortality due to breast cancer implies that metastasis can occur between the limits of mammographic detection and detection by physical examination. As tumors increase in size, the likelihood of metastases increases. A review of data from a large series of patients with breast cancer from one institution reveals that the likelihood of metastasis increased with a sigmoid distribution when plotted against the logarithm of tumor volume (22). This suggests that there is a critical volume for each tumor which must be reached before distant metastasis occurs. The correlation between the size of the primary and the probability of eventual distant metastasis allows the determination of a tumor diameter associated with a 50% probability of metastasis. This appears to be approximately 3.6 cm, surely well within the range of clinical appearance. If tumors are found at a smaller size, the likelihood of distant metastasis is decreased. One must conclude from this that many tumors have not disseminated when they are at a size easily detectable clinically but are more likely to do so with increased tumor size. These results provide strong evidence that early diagnosis and local treatment will improve survival. Further evidence is found in the results of the recent study conducted by the National Surgical Adjuvant Breast Project comparing local excision of the tumor with local excision plus radiation (18). That study demonstrated that local excision of the tumor alone, even with apparently negative margins, results in a high frequency of local recurrence (Table 1). This finding in itself emphasizes the need for wide-field local treatment. More importantly, however, the addition of radiation treatment not only increased local tumor control but also decreased the likelihood of distant metastasis. This provides direct evidence for the notion that persistent local disease gives rise to distant metastasis and emphasizes the importance of local control to survival. We believe that these studies support the breast cancer paradigm that stresses early detection and effective organ-conserving methods for local tumor control. The use of breast conserving methods provides an additional incentive for women to

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Table 1. Results at 5 years of National Surgical Adjuvant Breast Project trial comparing segmental mastectomy to segmental mastectomy and radiation therapy in patients without involved axillary lymph nodes (18)

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<th>Segmental mastectomy</th>
<th>Segmental mastectomy and radiation therapy</th>
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<tr>
<td>Local recurrence (%)</td>
<td>24</td>
<td>&lt;0.001</td>
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<tr>
<td>Distant metastases (%)</td>
<td>27</td>
<td>&lt;0.02</td>
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participate in early detection programs.

While these studies provide support for early detection and local control, they do not imply that these are the only problems in breast cancer management. Even among women in whom the earliest detectable tumor is effectively treated locally, a significant number of patients develop clinically evident distant disease, presumably from occult micrometastases present at the time of initial treatment. Approximately 25% of patients with stage I tumors (primary tumors smaller than two cm without axillary lymph node metastases) who receive radical treatment develop distant metastases (23), the likelihood of which increases with increasing tumor size and with increasing lymph node involvement. For patients with stage II tumors, the situation is far worse; approximately 75% of such patients develop distant metastases despite radical local and regional therapy (23).

Those statistics prompted the search for a treatment effective against such distant metastases. A recent strategy has been developed based on the idea that therapies which have some effect against clinically apparent disease might be even more effective against subclinical disease since the volume of disease is much smaller. Two major forms of therapy have been considered. The first derives from the observation that hormonal manipulation can have a profound effect on certain advanced breast cancers. The identification of the estrogen receptor present on the cell membrane of certain tumors gives a sensitive indicator of patients for whom such therapy might be effective. Cytotoxic chemotherapy has also been found to be important in the management of patients with advanced disease. While it has not cured metastatic disease, it has provided significant tumor regression in many patients.

Early adjuvant studies (24, 25) testing the use of a short course of chemotherapy after surgical excision were encouraging. More recent studies (26, 27) have produced a renaissance of interest in this technique. These newer studies, which have been carefully analyzed and regularly reviewed, provide a clear experimental underpinning for the notion that adjuvant therapy may affect the natural course of breast cancer. Hormonal manipulation has had a similar history. Studies of ovarian ablation used as an adjuvant to mastectomy have, in general, shown a prolonged symptom-free period but not an improvement in survival. The most important exception was a study by Meakin et al. (28) which showed a definite survival advantage in patients treated with hormonal ablation plus low-dose corticosteroids to suppress adrenal steroid production. Renewed interest in this technique is due to the identification of the estrogen receptor protein and the availability of the powerful anti-estrogen, tamoxifen.

These studies of adjuvant chemotherapy or hormonal manipulation will require longer follow-up to evaluate their effect on the probability of long-term survival. The considerations important in evaluating these data have been presented elsewhere (29). While not long-lived enough to allow conclusions as to mechanism, these trials have clearly demonstrated a significant alteration in the natural history of breast cancer.

The current state of breast cancer management appears quite encouraging. Cure rates can be increased by the use of screening procedures which allow the detection of the tumor at an earlier stage. Local control is important to outcome and is consonant with satisfactory cosmetic results when the proper combination of conservative surgery and radiation therapy is used. There is optimism that distant metastases can be destroyed in some patients by effective adjuvant hormonal therapy or chemotherapy. Data have begun to show improved survival rates, but the long natural history of breast cancer requires careful long-term evaluation of these data.

Because such treatments can be both harmful and beneficial, it is important to develop markers which separate those tumors which are primarily indolent from those which have a high proclivity for distant metastases and thus require early systemic therapy. Currently the best predictor of this is the involvement of regional lymph nodes, the detection of which requires axillary dissection. Despite this, 25% of patients without axillary lymph node involvement develop metastases while 25% of those with axillary lymph node metastases never develop distant metastases. Perhaps the most important problem facing clinical breast cancer research at this time is the development of more sophisticated markers within the primary tumor which predict for metastatic spread and which will allow the appropriate treatment for individual patients. That this is an important current concern emphasizes the progress made. Without effective treatment alternatives this distinction would be unnecessary. With our present understanding of breast cancer, utilization of the tools available should result in an improved cure rate while preserving function and cosmesis.

References


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