Localized Breast Cancer: Recent Developments Regarding Diagnosis and Management

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Both the incidence rate and the death rates for breast cancer remain high in the U.S. despite much public interest and public education in this area by the American Cancer Society and by cancer centers. No really hopeful methods have been developed for the prevention of this cancer that is now estimated to develop in approximately one of every ten women in the United States. However, data are accumulating that strongly suggest early diagnosis, if accomplished on a large scale, would decrease the mortality of breast cancer. Since a review of the breast cancer problem requires an appreciation of breast cancer staging, and its impact on prognosis, staging of breast cancer will be considered first. We will then update the reader on recent developments in both the diagnosis and management of localized and potentially "curable" breast cancer.

Breast Cancer Staging

A number of staging systems of varying complexity have been employed over the years for defining the extent of this disease at the time of diagnosis. The staging may be "clinical-diagnostic" or "pathologic," the latter being possible only after thorough assessment of excised tissues following definitive operation. Although staging systems vary somewhat, the key features of the staging process in each system relate to prognostically important characteristics of the primary cancer itself (T), the clinical status of the regional lymph nodes (N), and the presence or absence of detectable distant metastases (M). This spectrum of prognostic criteria is well-defined by the currently most utilized staging system, the TNM system (Table 1). Clinical-diagnostic staging is useful in predicting prognosis (Table 2), and both clinical and pathologic staging are used in the development of therapeutic choices.²

Diagnosis and "Work-up"

Mammography: The newest development in the field of breast cancer diagnosis over the last decade or two has been the proof of benefit from screening mammography.⁴ ⁵ ⁶ Earlier data from the Health Insurance Plan (HIP) study in the 1960's did demonstrate a decrease in mortality from breast cancer in a group of women over 50 undergoing annual screening mammography when their mortality was compared to that of a similar group without such a screening program. The results from the breast cancer diagnostic demonstration project of the American Cancer Society and the National Cancer Institute in the 1970's, and longer term follow up of the HIP data now demonstrate approximately a 25% decrease in breast cancer mortality from annual screening after the age of 40.⁷ These data on decreasing breast cancer mortality have been confirmed by randomized trials in Sweden, Holland and Italy where the decrease in mortality has reached an even greater level (40-50%).⁸ The technology of screening mammography has been improved from the standpoint of diagnostic accuracy and radiation dosage, the cost has been driven down, insurance coverage is being achieved and it is now clear that mammography has a real potential for reducing breast cancer mortality if it can be applied on a regular basis to a major portion of our female population. This is our challenge for the future.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor</th>
<th>Nodes (inc. SCL nodes)</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>T₁ (in situ)</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T₁ (≤ or &lt;2 cm)</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T₀ or T₁</td>
<td>N₁ (clin. positive)</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T₂ (2-5 cm)</td>
<td>N₀</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T₃ (&gt;5 cm)</td>
<td>N₀</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T₀ - T₂</td>
<td>N₂ (fixed)</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T₃</td>
<td>N₁ or N₂</td>
<td>M0</td>
</tr>
<tr>
<td>IIIIB</td>
<td>any T</td>
<td>N₃</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T₄ (ext. to skin or chest wall)</td>
<td>any N</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>any T</td>
<td>any N</td>
<td>M1</td>
</tr>
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</table>

Table 2

<table>
<thead>
<tr>
<th>Stage</th>
<th>5 Yr. Survival¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>85%</td>
</tr>
<tr>
<td>II</td>
<td>66%</td>
</tr>
<tr>
<td>III</td>
<td>41%</td>
</tr>
<tr>
<td>IV</td>
<td>10%</td>
</tr>
</tbody>
</table>
Although optimal guidelines given for age group to be screened and examination frequency for screening mammography have varied somewhat in the past, the recent statistical data referred to above have led now to a virtual consensus regarding proper guidelines for screening. Currently, the American Cancer Society, the National Cancer Institute, the American College of Surgeons, the American College of Radiology and the American College of Obstetrics and Gynecology all agree that screening should begin at age 40. While some groups recommend examinations every one to two years in the 40-50 year group, the current data are leaning towards a uniform concept of screening annually from age 40 on.

A study of cost effectiveness of screening mammography by Moskovitz and Fox1 calculates cost of care of “early” versus “advanced” breast cancer by taking into account the relative health care costs of cured breast cancer patients versus those that are unsuccessfully treated. Using these estimates, there is a marked financial saving to both society and the health insurance carriers, a factor that seems to support the provision of screening mammography services to the public. Eddy from the Center for Health Policy at Duke University does not dispute the decrease in cancer mortality resulting from screening mammography but has questioned the balance between the total cost of screening mammography in this country and the potential benefits that might be achieved.9 However, the finding of a decreased breast cancer mortality in these studies of screening mammography is considered by many oncologists to be one of the major breakthroughs in clinical cancer research of the last decade.

The American Cancer Society initiated a national breast cancer detection awareness program here in Virginia in 1987. This was a pilot program designed to educate both the public and physicians to the advantages of screening mammography.10 Also, an effort was made to establish quality assurance guidelines for the examination itself, as well to lower the cost. This demonstration project was useful from the public education standpoint, and from the standpoint of encouraging lower charges for this examination, but the lack of coverage for screening mammography in a number of health insurance programs has continued to be an obstacle to widespread utilization of this important new tool for lowering breast cancer mortality. Bills encouraging coverage for screening mammography have been introduced recently and passed in a number of states, including Virginia.

Pathology: When a palpable mass is present, or a non-palpable radiologically identified abnormality exists, some form of biopsy is required. With palpable masses, the approach of aspiration biopsy with a fine needle (FNA) is gradually developing more adherents than the much more involved open surgical biopsy. Aspiration biopsy is an office procedure but it does require the teamwork of a clinician and a pathologist who are both available and competent in the area of cytologic diagnosis.11 12 A negative aspiration biopsy does not rule out cancer unless there is both aspiration of non-bloody cystic fluid and the loss of the palpable abnormality. A positive aspiration biopsy by a pathologist experienced with this technique is certainly as reliable as an open incisional biopsy and has the added advantage of being a simple, relatively painless procedure leading to a definitive report in 15-20 minutes. Treatment options and plans can then be discussed with the patient prior to a more formal operation and, when “up front” non-operative treatment is considered, aspiration biopsy can establish the diagnosis.

When the “mass” in question is a non-palpable, radiologically identified shadow, aspiration biopsy can be employed, as well, but the frequency of achieving the true diagnosis is relatively low in some trials that have been carried out in this clinical situation. Most of us utilize needle localization of the radiologic shadow (by mammography) and then proceed with open surgical biopsy of the abnormality under local or general anesthesia.13

The assay of cytoplasmic estrogen and progesterone receptors (ER and PR) has now become standard whenever the primary tumor mass is large enough to allow this assay without interfering with adequate histologic evaluation.14 The presence of these receptors is the best indicator of the likelihood of the cancer being responsive to hormonal manipulations. The information obtained helps in planning for adjuvant therapy programs as well as providing information for the later management of recurrent or metastatic disease if this does occur. In addition, ER+ and PR+ cancers have a somewhat better prognosis than those which lack receptors. More recently, aspiration cytology has proved to be a feasible approach to obtaining similar receptor information.15

A more recent assay with great potential value for determining prognosis is the determination of DNA on a tumor cell suspension using flow cytometry.16 17 Cancers with primarily diploid (normal) cell populations have a significantly better prognosis than those with a prominent aneuploid (abnormal DNA) peak on the DNA histogram. Many commercial pathology laboratories have already added this assay to their analyses of various human cancer specimens, and tissue from paraffin blocks can be similarly analyzed, but guidelines for using this information in the choice of treatment strategy have not yet been developed.

Pre-Treatment “Work-Up”: Once the diagnosis of breast cancer has been established, standard chest radiographs and biochemical screening tests for evaluation of liver functions are relatively standard. Bone scanning is a sensitive test for detection of metastatic breast cancer, but patients with stage I and II breast cancers show an extremely low rate of abnormal bone scans unless they have specific areas of bone pain, and not all abnormal findings on bone scan are diagnostic of skeletal metastasis.18 Therefore, bone scans are not considered cost effective and are inappropriate unless there are suspicious symptoms or the clinical presentation is a more advanced cancer. The same objection applies to the use of computerized tomography (CT) and magnetic resonance (MR) when there are no specific indications. Serum tumor markers have not proven to be too useful, although many clinicians utilize carcinoembryonic antigen (CEA) for pretreatment and follow-up evaluation if CEA is found to be
elevated initially. Locally advanced breast cancer (stage III) has a higher yield from more complex tests and scans, and even bone marrow aspirates may play a helpful role in the pre-treatment assessment of some patients.

Local Management of Primary Breast Cancer

The goal of local treatment is to obtain adequate control of the local manifestations of the disease so as to avoid any needless future morbidity from the primary lesion. In some patients, local control is sufficient for "cure" of the disease. The acceptable loco-regional options for therapy vary somewhat, depending on the stage of disease at the time of clinical presentation.

In Situ Carcinomas of the Breast: The non-infiltrating forms of breast cancer may be discovered by biopsy of a clinically benign breast mass, by biopsy of an area of fibrocystic disease with a "chance finding" of in situ carcinoma in the adjoining tissue, or by biopsy of some non-palpable lesions discovered by mammography. The non-infiltrating carcinoma may be of duct origin (intraductal) or lobular origin (lobular carcinoma in situ). Until recently, both of these lesions have been considered relatively uncommon but their frequency has increased with the increasing sophistication of mammographic techniques. Intraductal carcinoma actually accounted for approximately 15-20% of all breast cancers among patients undergoing mammography in a screening demonstration project.

Considerable data has accumulated that demonstrates these patients are at high risk for developing invasive breast cancer if there is no active intervention. The problem in determining the choice of optimal treatment for this very early, essentially precancerous, process is that reliable information on the risk of progression of these lesions to invasive cancer in the ipsilateral or contralateral breast is extremely limited. In the past, most patients with either of these in situ types of carcinoma were treated by mastectomy, thereby eliminating the possibility of studying the natural history of this lesion in most patients. Many are now followed by frequent careful examinations and mammography but a host of factors enter into the decision process. This review will not cover this particular management problem since we wish to focus on the management of infiltrating breast cancer.

Stage I and II Breast Cancer: The management options for the local-regional management of clinical-diagnostic stages I and II are quite similar despite some differences in the systemic adjuvant treatments recommended once pathologic staging is complete. These are the breast cancers that everyone considers "operable" and cancers for which surgery is still considered the primary initial mode of therapy.

Excision of the entire breast, adjacent pectoral muscles and the draining regional lymph nodes ("radical" mastectomy) was the mainstay of the surgical treatment of "primary operable" breast cancer for many years. The oft-stated basis for mastectomy was the finding of multiple sites of in situ breast cancer in other quadrants of the resected breast in 30-50% of women. It was assumed that these sites would eventually progress to clinical breast cancer unless they were resected. Axillary dissection was considered a necessary therapeutic component of the operation based on the now disproven Halstedian concept that virtually all cancers spread to regional lymph nodes prior to distant metastasis. A large clinical trial of the National Surgical Adjuvant Breast Project (NSABP) comparing radical mastectomy and total (simple) mastectomy for clinical stage I breast cancer showed no therapeutic benefit from axillary dissection. Also, less than 20% of the total mastectomy patients required later therapeutic lymph node dissection. The axillary dissection does give valuable staging and prognostic information, however, and pathologic findings from this operation have proven useful in planning subsequent adjuvant therapy.

During the last two decades the classic radical mastectomy has been replaced by what is termed "modified" radical mastectomy, an operation that includes axillary dissection and total mastectomy, but preserves the pectoralis muscles to reduce cosmetic deformity. Several studies of stage I and II breast cancer have demonstrated that radical mastectomy and modified radical mastectomy are equal in terms of clinical control of disease. This shift from the classic Halsted radical mastectomy to modified radical mastectomy has been a nationwide trend as shown by some of the patterns of care studies that were reported from the American College of Surgeons. A brief period of enthusiasm for extending the operation of radical mastectomy to include internal mammary lymph nodes ended when clinical trials demonstrated no benefit from this approach. Following this logic, surgeons have generally accepted total mastectomy with axillary lymph node dissection as the "standard" treatment for operable breast cancer. Can we still justify this approach for most patients with breast cancer, or can breast conserving treatments actually produce equal results?

For a number of years there have been proponents of the use of radiation therapy as either an alternative to operation or as part of a combined treatment for breast cancer. Actually, radiation therapy after radical mastectomy was in vogue for many years until the lack of impact on survival was appreciated. Dr. Vera Peters, and many others, then championed wedge resection of the breast cancer and subsequent radiation therapy to the entire breast to allow breast conservation. However, the results—often comparable to those obtained by radical operation—were never really considered valid by most surgeons due to the impression that these patients were especially chosen for this approach. The value of conservative surgery plus radiation was convincingly demonstrated as equally effective therapy for early cancer by a randomized prospective trial reported from Milan. Patients with breast cancers, less than 2 cms. and without palpable lymph nodes, were randomized to radical mastectomy or to quadrantectomy (local segmental resection), axillary dissection and radiotherapy to the residual ipsilateral breast tissue. The conclusions of this study for very small breast cancers were supported for somewhat larger tumors (<4cm.) and for cancers with clinically involved axillary lymph nodes by the NSABP protocol (B-06) comparing segmental mastectomy and axillary dissection with or without breast radiation to our "standard," modified radical mastectomy. Conservative surgery was
equal to mastectomy in terms of both local and distant control if radiation therapy to the breast was included in the treatment plan.

All of these considerations of local resection of breast cancer in some patients are of prime interest but how do they affect our overall approach to the patient? The answer to this question depends on several factors: how large is the lesion?, where in the breast is the lesion located?, how large is the breast?, what is the patient’s attitude? Conservative surgery with a reasonable cosmetic result usually is not feasible if the lesion is large in relation to the size of the breast. Such a patient is best managed by total removal of the breast, without radiation. A guiding principle, however, is that total gross excision of the local lesion is necessary, even if supplementary radiation therapy is to be employed. The possibility of local failure following conservative surgery and radiation is increased if gross cancer is present after operation or if microscopic margins of excision are involved. Some feel local failure is more frequent if there is an extensive intraductal component identified in the breast.30

Many patients can now be safely considered for a conservative approach since there is much evidence to show that the end results of this conservative approach are truly equal to those following the more standard modified radical mastectomy approach when segmental resection is anatomically feasible. Almost half of women with breast cancer are now choosing breast conserving treatment when presented with the options. This choice between modified radical mastectomy and conservative surgery plus radiation clearly depends on other factors than local control or survival expectations. These include cosmetic considerations, body image, cost and that broad concept, “quality of life.”31 The emotional needs, the commitment, and the feeling of the patient all play a role in this selection.

Stage III Breast Cancer: This clinical presentation may be “operable” or “inoperable,” depending on the local manifestations of disease. In contrast to stages I and II, those patients undergoing operation may require classic radical mastectomy and/or skin grafting to close the operative defect. Conservative surgery is not indicated in this group of patients, but adjuvant radiation and chemotherapy are frequently employed prior to or following operation to help achieve control of the disease. This approach will be discussed in the subsequent section on the role of adjuvant therapy for breast cancer.

Systemic Adjuvant Therapy

Several different local treatment options available for primary breast cancer produce essentially equivalent results in terms of survival, as outlined above. In part, this is because they are nearly equal in achieving local control, but it also reflects the fact that survival is determined primarily by the presence or absence of distant metastatic disease rather than by local or regional recurrences. Thus, in order to improve the chance for survival for patients with breast cancer, treatment must be directed at the eradication of occult metastatic disease that is present but not detectable at the time of diagnosis. The systemic treatment regimens now available can be grouped into hormonal manipulations, cytotoxic chemotherapy, and combined chemohormonal therapy. When used as adjuvants to primary surgery and/or irradiation, these modalities may increase the duration of disease-free survival (DFS) and, in some instances, overall survival (OS). In order to select patients at risk for developing distant disease, prognostic factors need to be evaluated before deciding on the most appropriate form of adjuvant treatment. The primary determinant of prognosis, in addition to the clinical staging criteria described earlier, is the presence or absence of metastatic cancer in the axillary lymph nodes on histologic examination. In fact, the prognosis worsens with each additional lymph node positive for cancer (Table 3).32 It is primarily on the basis of pathologic nodal status, rather than other prognostic indicators that most trials of adjuvant therapy have been organized.

<table>
<thead>
<tr>
<th># of Histologically + Nodes</th>
<th>% Disease Free (10 Years)</th>
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<tbody>
<tr>
<td>0</td>
<td>80%</td>
</tr>
<tr>
<td>1-3</td>
<td>53%</td>
</tr>
<tr>
<td>4-6</td>
<td>41%</td>
</tr>
<tr>
<td>7-12</td>
<td>31%</td>
</tr>
<tr>
<td>≥13</td>
<td>13%</td>
</tr>
</tbody>
</table>

The presence or absence of cellular hormone receptors (ER and PR) have been important factors for stratifying patients for clinical trials in recent years. These assays are the key determinant for predicting the likelihood that the patient’s cancer cells respond to sex steroid hormones. At the present time, hormonal manipulations should not be employed for patients with laboratory evidence of low or absent receptors. Endocrine ablation by surgical means (e.g., oophorectomy or adrenalectomy) is infrequently utilized in modern practice, since various non-operative alternatives are available. More recently, adjuvant hormonal manipulation has been primarily accomplished with tamoxifen, an anti-estrogen agent with minimal toxicity.33 34 35

Node-Positive Breast Cancer: Over the past three decades, numerous prospective randomized trials have been carried out to determine the worth of adjuvant chemotherapy and/or hormonal therapy in the treatment of primary breast cancer. It should be stressed here that the optimal recommendation for a breast cancer patient at the present time is participation in an ongoing, carefully designed clinical trial.

During the mid 70’s and early 80’s, two of the largest and most well-publicized studies, from the NSABP and the National Cancer Institute of Milan were reported, and the results were remarkably similar. Using either a single agent (L-phenylalanine mustard, NSABP B-05) or multiple agents (cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), Milan), significant improvements in DFS and OS were observed in the treated patients as compared to observation alone.36 37 In both studies, this benefit was confined largely
to premenopausal women or women <50 years old. Among premenopausal women, approximately 60% of the treated patients were alive at 10 years versus about 40% in the control group. Similar results have now been reported in numerous other trials.35 38 39 40 Therefore, adjuvant chemotherapy should be considered as routine management for premenopausal women with node-positive breast cancer, regardless of the receptor status. Although it has been suggested by some that premenopausal women benefit largely because the chemotherapy produces a "chemical oophorectomy," this observation remains controversial and has not been generally supported by analyses of amenorrhea in patients receiving chemotherapy nor by the much more modest results of surgical ovariablation.44 45 46 The use of CMF-based adjuvant chemotherapy regimens has now become standard for this subset of patients, and it has also been shown that 12 months of adjuvant chemotherapy are no better than 6 months of the same treatment.47 In contrast to the results in postmenopausal women (see below), there has been little if any benefit in most trials from using tamoxifen as an adjuvant in premenopausal women who have positive nodes; hormonal manipulations cannot be considered routine in this subgroup, although they are probably worthy of additional investigation.

More recent trials suggest additional benefit from more aggressive adjuvant chemotherapy regimens, such as combinations containing doxorubicin (Adriamycin).38 40 The use of more potent drugs and higher drug doses also adds significantly to toxicity, but these more aggressive regimens do seem to be more striking in extending the benefits of adjuvant chemotherapy to postmenopausal women as well as younger women.38 39 40 48 49 50 51 52 Therefore, in postmenopausal patients with node-positive, ER- cancers, the use of adjuvant chemotherapy should be considered, particularly for those patients <60 and if there are no serious limiting medical problems.

For postmenopausal patients with positive nodes and ER+ cancers, the use of tamoxifen alone or when added to chemotherapy has clearly been shown to increase DFS (by 10-15%) and, to a lesser extent, OS (by approximately 6%).33 34 35 Moreover, the beneficial effect of tamoxifen appears to increase with increasing levels of hormone receptors.53 54 Since tamoxifen has minimal toxicity, its use should be considered routine in this group of patients, unless participation in a clinical trial is feasible. It appears that giving tamoxifen for 3 years is better than 2 years;55 whether even longer use will be even better is currently under study. The addition of chemotherapy to hormonal therapy in these patients has not been shown to be more advantageous than hormonal therapy alone. There is even some experimental evidence to suggest that tamoxifen may decrease the efficacy of cytotoxic agents, by altering the tumor cell kinetics.56 Thus, the place for combining hormonal and cytotoxic therapies remains unclear.

Node-Negative Patients: At the time of the NIH Consensus Development Conference on Adjuvant Chemotherapy for Breast Cancer in 1985, the conference concluded that neither adjuvant chemotherapy nor hormonal therapy was standard treatment for node-negative breast cancer.57 However, the results of three recently published studies have shown that the use of cytotoxic chemotherapy can produce modest reductions in the incidence of recurrence in patients with node-negative breast cancer, particularly those with negative ER.58 59 60 As yet, no survival benefits have been demonstrated in any of these clinical trials. For several reasons, we do not feel that these results are compelling enough to recommend the routine use of adjuvant chemotherapy for all node-negative breast cancer patients. Aside from the DFS benefits being fairly small and the lack of a survival advantage, the patients studied in these particular trials had tumors that were somewhat larger than those seen in many groups of node-negative patients. At this time, it seems difficult from these data to justify the toxicity and cost of routine cytotoxic chemotherapy in all node-negative, ER- breast cancer patients. However, a number of factors have recently been shown to increase the risk of recurrence of breast cancer, and these may be useful in individualizing the choice of treatment in specific patients. Indicators of a worse prognosis include high nuclear grade,61 lack of differentiation,61 62 several features from flow cytometric analysis of tumor cell DNA content (high % of cells in S-phase, high degree of aneuploidy or abnormal DNA content, and high DNA index),63 64 65 66 67 as well as expression of certain oncogenes and oncogene products.58 68 70

A fourth study, also run by the NSABP, indicated that tamoxifen increased the 4-year DFS of women with node-negative, ER+ cancers, regardless of age, although no survival benefit has been demonstrated as yet.71 In contrast to the toxicity of chemotherapy, the minimal risks and side effects associated with the use of tamoxifen make it less objectionable, particularly in postmenopausal women, and its use seems quite reasonable in these patients. In younger women, the side effects of estrogen blockade tend to be more disturbing, and ER+ cancers less frequent. Thus, the role of tamoxifen as an adjuvant for premenopausal women, with or without nodal involvement, is less clear. Our current recommendations for adjuvant therapy are summarized in Table 4.

Table 4

<table>
<thead>
<tr>
<th>Negative Nodes</th>
<th>Postmenopausal</th>
</tr>
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<tbody>
<tr>
<td><strong>Premenopausal</strong></td>
<td><strong>Postmenopausal</strong></td>
</tr>
<tr>
<td>Adjuvant therapy only</td>
<td>ER+ : Tamoxifen</td>
</tr>
<tr>
<td>for selected patients</td>
<td>ER- : No routine adjuvant therapy; may be</td>
</tr>
<tr>
<td>at high risk for</td>
<td>considered for patients at high risk for recurrence</td>
</tr>
<tr>
<td>recurrence</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Positive Nodes</th>
<th>Postmenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Premenopausal</strong></td>
<td><strong>Postmenopausal</strong></td>
</tr>
<tr>
<td>Adjuvant cytotoxic</td>
<td>ER+ : Tamoxifen</td>
</tr>
<tr>
<td>chemotherapy for all</td>
<td>ER- : Adjuvant cytotoxic chemotherapy, if no</td>
</tr>
<tr>
<td>medical contraindications</td>
<td></td>
</tr>
</tbody>
</table>
Questions for the Future: One of the key challenges for future clinical research in the area of adjuvant therapy will be to predict more accurately the risk of recurrence and the likelihood of benefit from treatment. The use of doxorubicin may increase the efficacy of adjuvant chemotherapy and may extend its benefits to additional groups of patients (e.g., postmenopausal and/or patients with high risk of recurrence), but these results are not yet mature. Likewise, the addition of other agents or alternating between non-cross-resistant regimens may improve overall end-results. One of the more intriguing possibilities is that making treatment more “dose-intensive” may markedly increase its efficacy. If so, then it may be worthwhile to use various new methods for ameliorating toxicity, allowing the doses of some agents to be increased to higher levels than have been used previously. For example, higher total doses of doxorubicin may be able to be given by continuous infusion or in liposomes with less cardiac toxicity and greater anti-tumor effect. Through recombinant DNA technology, growth factors which stimulate the growth and differentiation of bone marrow cells have become available. These can be used to hasten recovery of peripheral blood cell counts and thus, allow the use of higher doses of certain drugs which are limited by their bone marrow toxicity.

The most appropriate way to combine or sequence hormonal and cytotoxic treatments remains an open question. It is not known at present whether using both methods simultaneously is synergistic, or actually antagonistic. However, experimental and some clinical data suggest that hormonal manipulations can be used to synchronize cancer cells and make a larger proportion of them sensitive to later attack by chemotherapeutic agents.

Finally, the use of chemotherapy prior to local treatment has been advocated as a more logical and possibly more effective sequence of therapies than the more common practice of giving systemic treatment after surgery. Certainly, for locally advanced breast cancers, especially those which are technically inoperable or inflammatory, the use of “neo-adjuvant” or “up-front” chemotherapy has resulted in marked improvement in our ability to treat these patients. Compared to historical controls in which only 10-20% of patients with such advanced cancers survived 5 years, we are now seeing 5-year survivals for this stage in the 40 to 60% range. While it is obvious that the use of induction chemotherapy is appropriate for inoperable disease, there has been no completed prospective trial that effectively tests the hypothesis that pre-operative chemotherapy is better than chemotherapy given after operation and/or irradiation. There are compelling theoretical and biological reasons to predict that either sequence may be better.

The answers to these and other questions must await the results of clinical trials which are currently underway or being planned. In the meantime, it is essential that as many physicians and patients as possible participate in clinical trials so that the answers can be obtained in the shortest time possible and therefore, allow the benefits of advances in treatment to reach more patients.

References


