Objective: To determine indications for the use of postmastectomy radiotherapy (PMRT) for patients with invasive breast cancer with involved axillary lymph nodes or locally advanced disease who receive systemic therapy. These guidelines are intended for use in the care of patients outside of clinical trials.

Potential Intervention: The benefits and risks of PMRT in such patients, as well as subgroups of these patients, were considered. The details of the PMRT technique were also evaluated.

Outcomes: The outcomes considered included freedom from local-regional recurrence, survival (disease-free and overall), and long-term toxicity.

Evidence: An expert multidisciplinary panel reviewed pertinent information from the published literature through July 2000; certain investigators were contacted for more recent and, in some cases, unpublished information. A computerized search was performed of MEDLINE data; directed searches based on the bibliographies of primary articles were also performed.

Values: Levels of evidence and guideline grades were assigned by the panel using standard criteria. A “recommendation” was made when level I or II evidence was available and there was consensus as to its meaning. A “suggestion” was made based on level III, IV, or V evidence and there was consensus as to its meaning. Areas of clinical importance were pointed out where guidelines could not be formulated due to insufficient evidence or lack of consensus.

Recommendations: The recommendations, suggestions, and expert opinions of the panel are described in this article.

Validation: Seven outside reviewers, the American Society of Clinical Oncology (ASCO) Health Services Research Committee members, and the ASCO Board of Directors reviewed this document.

The management of patients with invasive breast cancer has changed substantially over the past few decades. A large proportion of such patients is now treated with breast-conserving surgery rather than mastectomy. Increasing numbers of patients (including those with histologically negative axillary lymph nodes) receive systemic therapy. However, there are still many women in North America and elsewhere who require or choose mastectomy as their primary surgical treatment.

There are several reasons or end points that might justify the use of postmastectomy radiotherapy (PMRT) for patients with invasive breast cancer. These include a reduction in the risk of local-regional failure (LRF), with its potential physical and psychologic morbidity, as well as a reduction in the risks of distant relapse and death. There is little doubt that PMRT substantially reduces the risk of LRF (usually defined as the appearance of tumor on the ipsilateral chest wall or in mastectomy scars and/or in the ipsilateral supraclavicular nodes, infraclavicular nodes, axillary nodes, the interpectoral nodes, axillary soft tissue, or internal mammary lymph nodes). However, whether PMRT directly affects the risk of distant failure and, ultimately, death due to breast cancer has been much more controversial.1-8

This issue was highlighted by the publication in October 1997 of long-term results of the two largest trials conducted on this question for premenopausal node-positive patients treated with chemotherapy.9,10 These studies showed that PMRT not only reduced LRF rates but also improved disease-free and overall survival rates in premenopausal patients receiving chemotherapy. However, a meta-analysis which included these as well as other trials (some of which enrolled patients treated with breast-conserving surgery or mastectomy without axillary node dissection) found that in general there was no improvement in overall survival resulting from the use of irradiation after surgery.2 The applicability of the results of the Danish and British Columbia trials to patients treated in other centers and the
degree of benefit obtained from irradiation in more narrowly defined patient subgroups have been debated.8,11 Issues of concern with these two trials include the very high rates of LRF in the control arms compared with other reports (discussed in detail below) and the absence of statistically significant improvements in overall survival rates in other trials of PMRT. Also, there has been substantial disagreement regarding the optimal technical parameters of PMRT, particularly with regard to the value of specific nodal irradiation.

Therefore, in 1998, the Health Services Research Committee of the American Society of Clinical Oncology (ASCO) commissioned a panel to evaluate the evidence with regard to the value of PMRT in patients treated with systemic therapy. The panel restricted its attention to patients with involved axillary lymph nodes or locally advanced (T4) primary tumors, as no trials have compared the role of PMRT in addition to routine systemic therapy in patients with T1 to T3 node-negative tumors.

Our report examines several aspects of this question. First, what is the evidence (and its quality and strength) regarding the impact of PMRT on LRF, disease-free survival, and overall survival? Second, is there evidence with regard to differences in such effects with regard to tumor size, the number of involved axillary nodes, and other tumor-, patient-, or treatment-related factors? Third, what information is available with regard to determining the broad technical parameters of PMRT, including its integration with systemic therapy? Finally, what are the potential side effects of PMRT, particularly in the long term, and how should these be integrated into decisions to use PMRT?

PRACTICE GUIDELINES

"Practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances."12 Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation.12 Guidelines may be useful in producing better care and decreasing its cost. Specifically, utilization of clinical guidelines may provide (1) improvements in outcomes, (2) improvements in medical practice, (3) a means for minimizing inappropriate practice variation, (4) decision support tools for practitioners, (5) points of reference for medical orientation and education, (6) criteria for self-evaluation, (7) indicators and criteria for external quality review, (8) assistance with reimbursement and coverage decisions, and (9) criteria for use in credentialing decisions.

In formulating recommendations for radiation therapy after mastectomy, ASCO considered these tenets of guideline development, emphasizing review of data from controlled clinical trials. However, it is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. Accordingly, ASCO considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient’s individual circumstances. In addition, these guidelines describe administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease for which better therapy is sorely needed. In that guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.

METHODS

Panel Composition

The panel was composed of experts in clinical medicine, clinical research, and outcomes/health services research, with a focus on expertise in breast cancer. A patient representative was also included on the panel. The clinical experts represented all relevant medical disciplines, including surgery, medical oncology, and radiation oncology. Both academic and community practitioners were included. A steering committee under the auspices of the ASCO Health Services Research Committee chose panel participants for the clinical practice guidelines development process. Panel participants are listed in the Appendix.

Process Overview

In evaluating the evidence regarding the role of PMRT, the panel followed the process for guidelines development established by the Canadian Medical Association.12 The process included a systematic weighting of the level of the evidence and a systematic grading of the evidence for making a recommendation (Table 1).13,14

Literature Review and Data Collection

Pertinent information from the published literature was retrieved and reviewed for the creation of these guidelines. Searches were done of MEDLINE (National Library of Medicine, Bethesda, MD) and other databases for pertinent articles as of May 1998, with additional articles and abstracts added as they appeared until July 2000. Directed
There is little or no systematic empirical evidence.

There is evidence of type II, III, or IV but findings are generally inconsistent.

There is evidence of type I or consistent findings from multiple studies of type II, III, or IV.

Evidence from case reports.

Evidence obtained from well-designed, quasi-experimental studies such as nonrandomized, controlled, single group, pre-post, cohort, and time or matched case-control series.

Evidence from well-designed, nonexperimental studies such as comparative and correlational descriptive and case studies.

Evidence from from case reports.

Table 1. Levels of Evidence and Grade of Recommendations13,14

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence obtained from meta-analysis of multiple, well-designed, controlled studies. Randomized trials with low false-positive and low false-negative errors (high power).</td>
</tr>
<tr>
<td>II</td>
<td>Evidence obtained from at least one well-designed experimental study. Randomized trials with high false-positive and/or negative errors (low power).</td>
</tr>
<tr>
<td>III</td>
<td>Evidence obtained from well-designed, quasi-experimental studies such as nonrandomized, controlled, single group, pre-post, cohort, and time or matched case-control series.</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence from well-designed, nonexperimental studies such as comparative and correlational descriptive and case studies.</td>
</tr>
<tr>
<td>V</td>
<td>Evidence from case reports.</td>
</tr>
</tbody>
</table>

Grade | Grade of Recommendation |
------|-------------------------|
A     | There is evidence of type I or consistent findings from multiple studies of type II, III, or IV. |
B     | There is evidence of type II, III, or IV and findings are generally consistent. |
C     | There is evidence of type II, III, or IV but findings are inconsistent. |
D     | There is little or no systematic empirical evidence. |

Development Based on Evidence

The entire panel met twice. The first meeting was intended to identify topics to be addressed by the guideline, to develop a strategy for completion of the guideline, and to do a preliminary review of the initial literature search; the second meeting was intended to review the developed guideline and to evaluate more critically the recommendations and supporting evidence. The guidelines were circulated in draft form, and all members of the panel had an opportunity to comment on the levels of evidence as well as the systematic grading of the data supporting each recommendation. Final text editing was performed by Stephen Edge and Abram Recht.

Guideline and Conflict of Interest

The content of the guidelines and the manuscript were reviewed and approved by the Health Services Research Committee and by the ASCO Board of Directors before dissemination. All members of the expert panel complied with ASCO policy on conflict of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the expert panel completed ASCO’s disclosure form and were asked to reveal ties to companies developing products that might potentially be affected by promulgation of the guidelines. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The panel made decisions on a case-by-case basis as to whether an individual’s role should be limited as a result of a conflict. There were no conflicts of interest requiring such limitations.

Revision Dates

At annual intervals, the panel chairs and two panel members designated by the chairs will determine the need for revisions to the guidelines based on an examination of current literature. The entire panel will be reconvened every 3 years to discuss potential changes, or more frequently, if new information suggests that more timely modifications may be warranted. When appropriate, the panel will recommend revised guidelines to the Health Services Research Committee and the ASCO Board for review and approval.

Definition of Terms

The panel used specific language in the guidelines to reflect the type and strength of evidence available (defined according to Table 2). The term “recommendation” was used for guidelines based on level I or II evidence. The term “suggestion” was used for guidelines based on level III, IV, or V evidence, where there was panel consensus on the interpretation of the evidence. The phrase “there is insufficient evidence on which to base a guideline” was used when there was either little or no evidence on the practice in question or a lack of panel consensus on the interpretation of existing evidence or both.

Summary of Outcomes Assessed

The outcomes assessed, in accordance with ASCO policy on outcomes for oncology clinical practice guidelines,15 included LRF, freedom from distant failure, freedom from any relapse, overall survival, and treatment toxicity. Formal analysis of issues of quality of life, cost, and cost-effectiveness16-19 were not considered due to limited or no data existing on these subjects.

SUMMARY OF THE PANEL’S FINDINGS

The randomized trials clearly show that PMRT substantially reduces the risk of LRF in patients with involved axillary nodes undergoing modified radical mastectomy who receive systemic therapy. They also show, though not as uniformly, that PMRT improves disease-free and overall survival rates. For the population of node-positive patients taken as a whole, the magnitude of these improvements is sufficient that they substantially outweigh the potential benefits.
Table 2. Summary of Postmastectomy Radiotherapy Guidelines

| 1. Patients With Four or More Positive Axillary Lymph Nodes |
| PMRT is recommended for patients with four or more positive axillary lymph nodes. |
| 2. Patients With One to Three Positive Axillary Lymph Nodes |
| There is insufficient evidence to make recommendations or suggestions for the routine use of PMRT in patients with T1/2 tumors with one to three positive nodes. |
| 3. Patients With T3 or Stage III Tumors |
| PMRT is suggested for patients with T3 tumors with positive axillary nodes and patients with operable stage III tumors. |
| 4. Patients Undergoing Preoperative Systemic Therapy |
| There is insufficient evidence to make recommendations or suggestions on whether all patients initially treated with preoperative systemic therapy should be given PMRT after surgery. |
| 5. Modifications of These Guidelines for Special Patient Subgroups |
| There is insufficient evidence to make recommendations or suggestions for modifying the above guidelines based on other tumor-related, patient-related, or treatment-related factors. |
| 6. Chest Wall Irradiation |
| In patients given PMRT, we suggest that adequately treating the chest wall is mandatory. |
| 7. Details of Chest Wall Irradiation |
| There is insufficient evidence for the panel to recommend or suggest such aspects of chest wall irradiation as total dose, fraction size, the use of bolus, and the use of scar boosts. |
| 8. Axillary Nodal Irradiation |
| We suggest that full axillary radiotherapy not be given routinely to patients undergoing complete or level I/II axillary dissection. There is insufficient evidence to make suggestions or recommendations as to whether some patient subgroups might benefit from axillary irradiation. |
| 9. Supraclavicular Nodal Irradiation for Patients With Four or More Positive Axillary Lymph Nodes |
| The incidence of clinical supraclavicular failure is sufficiently great in patients with four or more positive axillary nodes that we suggest a supraclavicular field should be irradiated in all such patients. |
| 10. Supraclavicular Nodal Irradiation for Patients With One to Three Positive Axillary Lymph Nodes |
| There is insufficient evidence to suggest whether a supraclavicular field should or should not be used for patients with one to three positive axillary nodes. |
| 11. Internal Mammary Nodal Irradiation |
| There is insufficient evidence to make suggestions or recommendations on whether deliberate internal mammary nodal irradiation should or should not be used in any patient subgroup. |
| 12. Sequencing of PMRT and Systemic Therapy |
| There is insufficient evidence to recommend the optimal sequencing of chemotherapy, tamoxifen, and PMRT. The panel does suggest, given the available evidence regarding toxicities, that doxorubicin not be administered concurrently with PMRT. |
| 13. Integration of PMRT and Reconstructive Surgery |
| There is insufficient evidence to make recommendations or suggestions with regard to the integration of PMRT and reconstructive surgery. |
| 14. Long-Term Toxicities |
| The potential long-term risks of PMRT include lymphedema, brachial plexopathy, radiation pneumonitis, rib fractures, cardiac toxicity, and radiation-induced second neoplasms. There is sufficient evidence for the panel to suggest that, in general, the risk of serious toxicity of PMRT (when performed using modern techniques) is low enough that such considerations should not limit its use when otherwise indicated. However, follow-up in patients treated with current radiotherapy techniques is insufficient to rule out the possibility of very late cardiac toxicities. |
| 15. Toxicity Considerations for Special Patient Subgroups |
| There is insufficient evidence to make recommendations or suggestions that PMRT should or should not be used for some subgroups of patients because of increased rates of toxicity (such as radiation carcinogenesis) compared with the rest of the population. |

Nonetheless, our findings do not imply that all patients with positive axillary nodes should receive PMRT. The panel believes the evidence shows that, as for systemic therapy, PMRT will likely cause comparable proportional reductions in LRF for various patient subgroups, and hence similar proportional improvements in disease-free and overall survival. Treatment decisions should be based on absolute differences in outcome, which may vary depending on factors such as tumor size, number of involved axillary nodes, and others.

There is much less information available as to the absolute benefits of PMRT in specific patient subgroups of patients. Data on changes in outcome resulting from PMRT for subgroups of patients from randomized trials are limited. The decision as to what may constitute “sufficient” benefit to justify systemic or radiotherapeutic treatment from the breast cancer patient’s viewpoint has been examined in several studies. There exist substantial differences probably exist between patients’ attitudes in this regard and that of other lay people or health-care professionals. Therefore, we did not believe it appropriate for us to set a “threshold” value of LRF or of improvements in

long-term risks of life-threatening complications from PMRT performed using modern radiotherapy techniques.
disease-free or overall survival rates which should trigger a decision to use PMRT.

The panel found that the weight of the evidence from randomized trials was sufficient to recommend the routine use of PMRT for patients with four or more positive axillary lymph nodes. It is much less certain that the benefits of PMRT are sufficient to justify its use in most patients with T1/2 tumors with one to three positive nodes. The available evidence is insufficient to make recommendations for this subgroup. Further randomized trials (such as a recently opened intergroup trial in North America) are justifiable for this subgroup of patients. There are few data from randomized trials for patients with T3 or locally advanced (stage III) operable cancers, but the evidence from retrospective studies is sufficient for the panel to suggest that PMRT be routinely used for such patients. While the consensus of the panel was to suggest the use of PMRT for most patients treated with neoadjuvant systemic therapy, the panel could not find sufficient evidence to determine whether all patients should be irradiated after neoadjuvant systemic therapy.

The panel did not find sufficient evidence regarding the impact of other tumor-related, patient-related, or treatment-related factors to make recommendations or suggestions for modifying these guidelines. For example, although PMRT is commonly used for patients with close or positive margins, the data supporting this practice are fragmentary and sometimes contradictory. The 1995 and 2000 Oxford Overviews of radiotherapy suggest that patients 50 and older may not derive a net benefit from PMRT, due to an increased risk of non-breast cancer mortality. This effect was not seen in individual trials of PMRT in which this factor was examined, however. Further investigation of this issue is needed.

The Early Breast Cancer Trialists’ Collaborative Group conducted two meta-analyses which did not show an advantage in overall survival at 10 years and 20 years for patients who received radiotherapy after surgery compared with those who did not. Although in both studies there was a statistically significant reduction in the risk of breast cancer–related deaths, it was counterbalanced by an increase in the risk of non-breast cancer mortality. The findings of these Overviews and those of this panel may diverge over particular points for a number of reasons. First, the populations of concern in these two efforts were somewhat different. The Overviews examined trials in which radiation therapy was given after breast-conserving surgery, simple mastectomy, radical mastectomy, or modified radical mastectomy. The panel dealt solely with PMRT for patients treated with mastectomy with axillary dissection. The Overviews included trials in which systemic therapy was routinely given to patients and trials in which systemic therapy was not used. The panel restricted its review to trials of PMRT containing systemic therapy. Finally, the Overviews did not separately address the role of PMRT in women with differing number of positive nodes or other prognostic factors, whereas the panel assessed the presence and size of an effect of PMRT in precisely such narrower subgroups.

The extent of radiation fields to be used for PMRT, when utilized, is controversial. Since the chest wall is the site at greatest risk of recurrence, we suggest that adequately treating the chest wall is mandatory. With regard to irradiation of regional lymph nodes, the situation is less clear. However, because the risk of axillary recurrence after a complete or level I/II dissection is very low, and because the combination of axillary dissection and full axillary irradiation markedly increases the risk of lymphedema, the panel suggests that axillary radiotherapy not be given routinely to patients undergoing complete or level I/II axillary dissection. There are insufficient data to suggest subgroups that might be exceptions to such a policy. The incidence of clinical supraclavicular failure is sufficiently great in patients with four or more positive axillary nodes that we suggest supraclavicular irradiation should be given to all such patients. There are insufficient data to state whether the supraclavicular nodes should or should not be irradiated for patients with one to three positive axillary nodes. Finally, there is insufficient evidence to suggest or recommend whether internal mammary nodal irradiation should or should not be used routinely. Although such treatment was routinely given in the majority of the randomized trials (including the two Danish and the British Columbia trials, which show the greatest impact of PMRT), data on the value of internal mammary nodal irradiation are limited and contradictory. When the internal mammary nodes are deliberately treated, efforts should be made to minimize the treated volumes of heart and lung. There are insufficient data for the panel to recommend or suggest such aspects of PMRT as total dose, fraction size, the use of bolus, and the use of scar boosts.

The optimal sequencing of chemotherapy, tamoxifen, and PMRT cannot be determined from the available evidence. The expert consensus of the Panel was that chemotherapy should be started soon after surgery, and hence the start of chemotherapy should not be delayed until after PMRT. However, in cases in which prolonged chemotherapy regimens are used, the panel could not reach consensus on whether it was better to use a “sandwich” approach or deliver all chemotherapy before PMRT or to give concurrent chemoradiotherapy. The panel does suggest that doxorubicin not be administered concurrently with PMRT.
There are insufficient data available to make evidence-based guidelines with regard to the integration of PMRT and reconstructive surgery. Where reconstruction can be done with a low morbidity, such that systemic therapy and PMRT will not be delayed in the large majority of cases, the consensus of the panel is that it is reasonable to perform immediate reconstruction in patients with clinical stage I or II cancers. However, there was disagreement within the panel regarding the use of immediate reconstruction in patients who may be candidates for PMRT, particularly those with stage IIIb tumors (ie, T4 or N2 disease) and larger T3 tumors.

The incidence of toxicities from PMRT can be difficult to assess. Many effects appear only after prolonged latency periods, and their incidence may be strongly related to the details of treatment technique as well as patient factors (such as age). The risk of carcinogenesis is so low in incidence that it should not be used in making treatment decisions. The risks of radiation pneumonitis, cardiomyopathy, brachial plexopathy, and clinically significant arm edema should also be acceptably low when state-of-the-art radiotherapy techniques are used, although follow-up in patients treated with current radiotherapy techniques may be insufficient to rule out the possibility of very late toxicities. “State-of-the-art” radiotherapy uses techniques to minimize excessive exposure of the heart and lung, pays attention to integrating the extent of nodal irradiation to the extent of axillary dissection (eg, avoiding treating a “full axillary” field in patients undergoing a complete axillary dissection), and uses daily radiation fraction sizes of 2 Gy or smaller. Data from the Oxford Overviews suggest that, when older radiotherapy techniques are used, patients may have increased risks of non–breast cancer mortality that may outweigh the benefits of PMRT for older individuals.2,3 There are few studies of this problem in patients receiving potentially cardiotoxic drugs, such as anthracyclines or trastuzumab (Herceptin; Genentech, Inc, South San Francisco, CA), as well as radiotherapy. Considering the available evidence and its limitations, however, the panel finds sufficient evidence to suggest that serious toxicity from PMRT in most circumstances is not sufficient to outweigh its likely benefits for the groups in whom we have recommended its use when current radiotherapy techniques are used. Similarly, there are insufficient data at present in the panel’s expert consensus to warrant not using PMRT for some subgroups of patients, such as those with BRCA1 and BRCA2 mutations, because of a fear of increased rates of radiation carcinogenesis, compared with the rest of the population.

The panel’s guidelines are summarized in Table 2. The following sections contain a detailed review of the relevant evidence with discussion of the panel’s rationales for its decisions.

### RANDOMIZED TRIALS COMPARING SYSTEMIC THERAPY TO SYSTEMIC THERAPY PLUS PMRT

There are at least 18 randomized studies containing over 6,300 patients which have compared systemic therapy to systemic therapy plus PMRT in (predominantly) node-positive patients treated with modified radical mastectomy (Table 3). Important aspects of each these trials, such as eligibility criteria, population characteristics, and treatment techniques, have been summarized elsewhere.5,7,26 The results given in Table 3 are generally taken from the latest publications of these trials. For the M.D. Anderson Cancer Center trial, results from the Oxford Overview of radiotherapy trials were used,3 as those were the only detailed ones available. Results in the British Columbia trial with 2 years of additional follow-up were reported recently in abstract form.27 However, only the overall survival rates were updated for the population as a whole (43% and 52% in the control and radiotherapy arms, respectively; P = .02). Two of these trials (Danish trial 82c and one of the South Sweden trials) treated patients with tamoxifen; the rest used chemotherapy. Two trials (performed in Helsinki and by the Eastern Cooperative Oncology Group) included only patients with operable clinical stage III disease.

All trials reporting LRF rates showed that PMRT substantially reduced the risk of such failure (by roughly two thirds to three quarters, proportionally). Given the large differences seen, it is clear that they had sufficient power to demonstrate this effect reliably (level I evidence).

Only one trial reported whether PMRT reduces the ultimate risk of having uncontrollable LRF.28 Fifteen (4%) of the 387 patients who received adjuvant PMRT and systemic therapy developed LRF that was “persistent” despite salvage therapy, compared with 28 such patients (7%) among the 387 who did not receive initial PMRT.

The chance that a benefit in relapse-free and overall survival rates was shown seems related to trial size. In the 10 studies with fewer than 200 assessable patients (which contained a total of 1,132 assessable patients), sometimes the control arm fared better, and sometimes the radiotherapy arm did. Eight of the nine trials that contained 200 or more patients (which together contained 5,214 assessable patients) showed trends favoring the radiotherapy arm, with absolute improvements of 2% to 17% in recurrence-free and 2% to 11% in overall survival rates in the irradiated cohort. Differences in relapse-free survival rates reached the conventional level of type I statistical significance (P < .05) in five of the eight trials that contained more than 200 patients. Only three trials (the Danish Breast Cancer Group trials...
82b and 82c and the British Columbia trial showed statistically significant improvements in the overall survival rate for the combined-modality arm. However, the power of the trials listed in Table 3 to show that such differences as were observed were statistically significant was limited, as only two of them contained more than 1,000 patients. Because of this finding, the conclusions of this panel concerning the impact of radiotherapy on relapse-free and overall survival were therefore predominantly supported by level II evidence rather than level I evidence. Although trends toward both relapse-free and overall survival improvements were seen in the large majority of the larger trials, the difference in the numbers of studies in which these differences reached statistical significance led the panel to find the evidence to be “generally consistent” (grade B) with regard to relapse-free survival and “inconsistent” (grade C) with regard to overall survival.

Proportional improvements in relapse-free and overall survival were substantial in the two largest trials in which patients received chemotherapy. In the Danish trial 82b, radiotherapy reduced the odds of any recurrence or death by 41%9; in the British Columbia trial, the reduction in the relative risk of any recurrence at 15 years was 33%. 10 The relative reductions in the risk of death due to any cause in these two trials were 29% and 26%, respectively. (In the update of the British Columbia trial, this reduction was 30%27) Reductions in other trials using chemotherapy or those using tamoxifen were not as large.

It also should be pointed out that comparison of the results of these trials is hampered by several factors. One is the substantial heterogeneity between their patient populations with regard to important prognostic factors, such as the number of positive nodes and tumor size. Subgroup analysis has been performed only for a few trials. It is therefore

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Table 3. Randomized Trials Comparing Mastectomy With Axillary Dissection Followed by Systemic Therapy to Mastectomy With Axillary Dissection Followed by Systemic Therapy and Radiotherapy

<table>
<thead>
<tr>
<th>Series</th>
<th>No. of Patients</th>
<th>Follow-Up (months)</th>
<th>LRF (%)</th>
<th>RFS (%)</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBCG 82b</td>
<td>1,708</td>
<td>114</td>
<td>32</td>
<td>9*</td>
<td>45</td>
</tr>
<tr>
<td>DBCG 82c</td>
<td>1,375</td>
<td>123</td>
<td>35</td>
<td>8*</td>
<td>36</td>
</tr>
<tr>
<td>S. Sweden-TAM</td>
<td>483</td>
<td>96</td>
<td>18</td>
<td>6*</td>
<td>61</td>
</tr>
<tr>
<td>British Columbia</td>
<td>318</td>
<td>150</td>
<td>33</td>
<td>13*</td>
<td>33</td>
</tr>
<tr>
<td>ECOG stage III</td>
<td>312</td>
<td>109</td>
<td>24</td>
<td>15</td>
<td>44</td>
</tr>
<tr>
<td>SECSG</td>
<td>295</td>
<td>120</td>
<td>23</td>
<td>13*</td>
<td>38</td>
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<tr>
<td>S. Sweden-cyclophosphamide</td>
<td>287</td>
<td>96</td>
<td>17</td>
<td>~</td>
<td>63</td>
</tr>
<tr>
<td>Glasgow</td>
<td>219</td>
<td>63</td>
<td>25</td>
<td>11*</td>
<td>43</td>
</tr>
<tr>
<td>Mayo</td>
<td>217</td>
<td>48</td>
<td>30</td>
<td>10*</td>
<td>48</td>
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<tr>
<td>German BCG</td>
<td>199</td>
<td>96</td>
<td>—</td>
<td>0.35*</td>
<td>—</td>
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<tr>
<td>DFCI-AC</td>
<td>123</td>
<td>45</td>
<td>20</td>
<td>6*</td>
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</tr>
<tr>
<td>Israel</td>
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<tr>
<td>Coimbra, Portugal</td>
<td>112</td>
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<td>—</td>
<td>7</td>
<td>56</td>
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<tr>
<td>M.D. Anderson</td>
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<td>24</td>
<td>7</td>
<td>56</td>
</tr>
<tr>
<td>DFCI-CMF/ME</td>
<td>83</td>
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<td>5</td>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>Piedmont-CMF</td>
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<td>132</td>
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<tr>
<td>Helsinki stage III</td>
<td>79</td>
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<td>Piedmont-LPAM</td>
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<tr>
<td>Köln, Germany</td>
<td>71</td>
<td>36</td>
<td>—</td>
<td>—</td>
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</tr>
</tbody>
</table>

Note: Follow-up is in median months, unless otherwise noted. Relapse-free survival and overall survival in the Helsinki stage III study were estimated from Figures 1 and 2 at 5 years. Relapse-free survival in the Cologne study was estimated from Figure 4 at 3 years.

Abbreviations: AC, doxorubicin-cyclophosphamide; BCG, Breast Cancer Group (also known as BMFT 03 trial); CMF, cyclophosphamide, methotrexate, and fluorouracil; DBCG, Danish Breast Cancer Group; DFCI, Dana-Farber Cancer Institute; LPAM, L-phenylalanine mustard; LRF, local-regional failure (includes patients with simultaneous distant failure, when reported in that manner by the study authors); MF, methotrexate and fluorouracil; OS, overall survival; RFS, relapse-free survival; RT, radiotherapy plus systemic therapy arm; SECSG, Southeast Cooperative Study Group; ST, systemic therapy arm; TAM, tamoxifen.

*Difference between radiotherapy and no-radiotherapy arms was statistically significant.
†Relative risk, radiotherapy vs control group; absolute rates not reported.
‡Trial data were not published or published only in part; results taken from 3.

82b and 82c showed statistically significant improvements in the overall survival rate for the combined-modality arm. However, the power of the trials listed in Table 3 to show that such differences as were observed were statistically significant was limited, as only two of them contained more than 1,000 patients. Because of this finding, the conclusions of this panel concerning the impact of radiotherapy on relapse-free and overall survival were therefore predominantly supported by level II evidence rather than level I evidence. Although trends toward both relapse-free and overall survival improvements were seen in the large majority of the larger trials, the difference in the numbers of studies in which these differences reached statistical significance led the panel to find the evidence to be “generally consistent” (grade B) with regard to relapse-free survival and “inconsistent” (grade C) with regard to overall survival.
difficult to assess the absolute size of potential disease-free and overall survival benefits in specific patient subgroups. There are also differences in the scoring of LRF between trials. Some trials scored only patients with “isolated” LRF, some scored LRF either with or without simultaneous distant relapse, and one trial scored LRF when it occurred at any time after randomization, even after the development of distant metastases.28

Differing treatment factors, such as the extent of axillary dissection, may be another important source of variability in the observed results of these trials. The LRF rates in the control arms in some trials were also higher than for patients in other randomized trials as well as many retrospective studies (see below). This has led some to question the generalizability (or external validity) of their results.

There have been few meta-analyses performed of these trials. The Early Breast Cancer Trialists’ Collaborative Group conducted a meta-analysis that did not show an advantage in overall survival at 10 years2 and 20 years3 for patients who received radiotherapy after surgery, compared with those who did not. However, this study included trials in which breast-conserving surgery, simple mastectomy, radical mastectomy, or modified radical mastectomy was used. Patients with both positive and negative axillary nodes were included. In addition, many of the trials used outdated radiotherapy equipment. Most importantly, this study did not segregate trials in which systemic therapy was routinely given to patients from those in which systemic therapy was not used. A meta-analysis using published data from only those trials in which all patients were treated with mastectomy plus axillary dissection and also received systemic therapy showed that PMRT reduced overall mortality, with an odds ratio of 0.83 (95% confidence interval, 0.74 to 0.94; \( P = .004 \)).30

To conclude, PMRT reduced the risk of LRF after mastectomy in patients receiving systemic therapy by a substantial amount in all trials. The majority of available trials, particularly the larger ones, also showed that PMRT improves relapse-free and overall survival rates to a lesser, but clinically relevant, degree.

GUIDELINES FOR SPECIFIC PATIENT SUBGROUPS: PROBLEMS OF AVAILABLE DATA AND ANALYSIS

As reviewed above, trials have shown that, for node-positive breast cancer patients as a group, aggregate, PMRT improves disease-free and overall survival in addition to local-regional control. This section will examine the evidence available to estimate the benefits from PMRT for patient subgroups defined by specific prognostic factors. As noted above, this process was hampered by limitations in the available data. Most importantly, the randomized trials of PMRT were not designed to have a high degree of statistical power to detect effects in patient subgroups, and patients were not always stratified by subgroup. None of these trials analyzed results in subgroups defined by combinations of prognostic factors, such as tumor size and the number of involved nodes. It is likely that such combinations of prognostic factors are more accurate predictors of outcome than are single factors considered in isolation.31-35 Finally, treatment-related factors (such as details of surgery or systemic therapy) not controlled for in these trials may affect the risks of LRF substantially.

As a result of these problems, it was difficult to make conclusions with regard to the role of PMRT in specific patient subgroups. Further investigation of this area is urgently needed.

Patients With Four or More Positive Axillary Lymph Nodes

Guideline: PMRT is recommended for patients with four or more positive axillary lymph nodes.

Level of Evidence: II.

Grade of Recommendation: B.

Patients With One to Three Positive Axillary Lymph Nodes

Guideline: There is insufficient evidence to make recommendations or suggestions for the routine use of PMRT in patients with T1/2 tumors with one to three positive nodes.

Only a few of the randomized trials reviewed above have examined patient outcome based on their pathologic nodal status (Table 4). The Danish 82b and 82c trials were the only one which included node-negative patients (who were eligible for this trial due to the presence of such “high-risk” features as invasion of the pectoralis muscle or skin by the primary tumor).9,29 There were statistically significant differences in LRF, relapse-free survival, and overall survival rates favoring the irradiated patient arm for patients with negative, one to three positive, and four or more positive nodes in the 82b trial. In the 82c trial, there were substantial differences between the two arms in these end points also, but the statistical significance of these differences was not reported. The initial report of the British Columbia trial showed statistically significant improvements in LRF in irradiated patients in the subgroups with either one to three or four or more positive nodes.10 In an update of this trial (with unstated length of follow-up), the difference in crude LRF rates for patients with one to three positive nodes was of borderline significance between the arms (20% in the control arm and 8% in the irradiated arm, \( P = .066 \)), while the difference between the arms for patients with four or
more positive nodes remained highly significant (LRF rates of 51% and 17% in the two arms, respectively, \( P = .004 \)).

In the initial report, a statistically significant difference in freedom from distant failure was seen only for patients with four or more positive nodes; these rates were not updated in their recent abstract. Overall survival rates in these groups were not reported separately in their original report. In their update, there was a borderline significant improvement in patients with one to three positive nodes (53% and 64% in the control and PMRT arms, respectively, \( P = .07 \)) but no significant difference in patients with four or more positive nodes (28% and 35% in the two arms, respectively, \( P = .27 \)).

Thus, all but one trial that examined nodal subgroups found trends toward improved disease-free and overall survival in patients treated with PMRT. Absolute improvements (when found) in disease-free survival rates and overall survival rates for the use of PMRT for patients with one to three positive nodes were 9% to 15% and 8% to 11%, respectively; for patients with four or more positive nodes, the respective rates were 11% to 13% and 7% to 12%. There seems to be consistent evidence of improved local-regional control for PMRT in patients with either one to three or four or more positive nodes (level II, grade A), but the evidence for improved disease-free survival rates and overall survival rates for the use of PMRT is more consistent for patients with four or more positive nodes (level II, grade B) than for patients with one to three positive nodes (level II, grade C).

However, there are strong reasons for questioning the generalizability (or external validity) of the results of these trials in these subgroups, based on retrospective (level III) data from other institutions, as well as discrepancies between the results in the randomized trials themselves. In particular, LRF rates in unirradiated patients with one to three involved nodes in the Danish 82b trial (crude rate of 30%), the Danish 82c trial (crude rate of 31%), and the British Columbia trial (10-year actuarial rate of 16% but 15-year actuarial rate of 33%) were substantially higher than in the few other published series with more than 5 years of follow-up that have reported results for patients with one to three involved nodes (6% to 13%).

Similar discrepancies may be noted for patients with four or more positive nodes between results in these three trials.
(crude rates of 42% and 46% in the Danish 82b and 82c trials, and 10- and 15-year actuarial rates of 41% and 46%, respectively, in the British Columbia trial) and those of other investigators (14% to 29%).

In summary, it is not clear that the LRF rates in the three largest trials reporting subgroup results (the Danish 82b and 82c and British Columbia trials) are representative of the results routinely achieved in North America. (Differences in surgical techniques may be responsible for this; see below.) However, in other studies, LRF rates for patients with four or more positive axillary nodes are still fairly high, even if lower than in these two trials. Although the benefits of PMRT in this subgroup may, therefore, not be quite as large as observed in the British Columbia and Danish trials, these retrospective data and the supporting data from two of the three other randomized trials lead the panel to recommend the routine use of PMRT in patients with four or more positive axillary nodes. However, given the much lower LRF rates in retrospective studies of patients with one to three positive nodes than in the Danish and British Columbia trials, it is much less certain to the panel whether the benefits of PMRT are sufficient to justify its routine use in most patients with one to three positive nodes. We therefore believe that the available evidence is insufficient to make recommendations or suggestions for this subgroup.

Patients With T3 or Stage III Tumors

Guideline: PMRT is suggested for patients with T3 tumors with positive axillary nodes and patients with operable stage III tumors.

Levels of Evidence: II, III.

Grade of Recommendation: C

Retrospective data suggest that the risk of LRF in unirradiated patients with operable T3 node-positive tumors is substantial (in excess of 25%), despite the use of systemic therapy and regardless of the actual number of involved axillary nodes. Only two reports of the randomized trials of PMRT specifically analyzed results by tumor size. In the Danish 82b trial, there were statistically significant improvements in local-regional control, disease-free survival, and overall survival in patients with T1, T2, and T3 tumors. In the 82c trial, there were again substantial differences between the two arms in these end points for each tumor size, but the statistical significance of these differences was not reported. However, the issue of whether tumor size independently affects the benefits of PMRT, controlling for nodal status, was not addressed. In several retrospective studies that did not use PMRT, the combination of tumor size plus the number of involved axillary lymph nodes was a more accurate predictor of the risk of LRF than axillary nodal status alone, but the effect of tumor size did not seem as great as that of nodal status.

Although the panel decided not to address the issue of PMRT in patients with negative axillary nodes in general, we made an exception for patients with T3 primary tumors. The largest study included 101 patients treated with mastectomy without PMRT. All patients had negative margins. Only 9% received systemic therapy. At a median follow-up time of 93 months, 15 patients (15%) developed LRF. In a retrospective study from Helsinki, three of five uniradiated patients had an LRF, compared with 9% (three of 33) of irradiated patients. (Adjuvant systemic therapy was given to 53% of all patients in this study, but the allocation of such treatment between these two subgroups was not reported.)

Two small randomized trial of PMRT performed specifically for patients with operable locally advanced (stage III) breast cancer showed that PMRT substantially reduced the risk of LRF but did not result in statistically significant improvements in disease-free or overall survival. The 5-year LRF rates (with or without simultaneous distant failures) among patients with such tumors in the first of these trials was 38% (five of 13) for patients receiving chemotherapy alone, compared with 7% (two of 27) for patients receiving either PMRT alone (none of 12) or chemotherapy plus PMRT (two of 15). No analysis of specific patient subgroups within this stage was performed for the second trial.

Retrospective studies from individual institutions have also shown high LRF rates for operable stage III patients. In one study, the risk of LRF in patients receiving chemotherapy was 18%, compared with 8% in irradiated patients. In other series, the risk of LRF in patients receiving PMRT was 10% or lower.

The poor prognosis for patients with locally advanced, initially inoperable breast cancers (including inflammatory breast cancer) has led most investigators to use multimodality therapy for these patients. Chemotherapy is used initially, and responding patients are then treated with mastectomy plus PMRT. Patients with more limited or no response often receive preoperative radiation, followed by mastectomy. There are no randomized trials addressing the role of PMRT in their treatment and only scant retrospective data on patients treated with chemotherapy and mastectomy without PMRT. In one retrospective series of patients with inflammatory breast cancer, those treated with chemotherapy plus mastectomy without radiotherapy had an LRF rate of 59% (16 of 27), compared with 15% (15 of 98) for patients treated with chemotherapy, mastectomy, and radiotherapy. In a similar group of patients in another series, the incidence of...
LRF was 31% (four for 13) for unirradiated patients, compared with 7% (three of 42) for irradiated patients.54

On balance, the panel believed that the benefits of PMRT in improving local-regional control for patients with operable stage III cancers seem to be reasonably well established. A consistently demonstrated benefit for overall survival has not been demonstrated. Therefore, based in part on the magnitude of the risk of LRF for such patients, the panel suggests the routine use of PMRT.

Patients Undergoing Preoperative Systemic Therapy

Guideline: There is insufficient evidence to make recommendations or suggestions on whether all patients initially treated with preoperative systemic therapy should be given PMRT.

There are no data from randomized trials or retrospective studies on the role of PMRT in patients with clinical stage I or II tumors who undergo preoperative systemic therapy. Therefore, the use of PMRT in this setting entailed vigorous discussions among the panel. The majority concluded that, in general, patients who require mastectomy after systemic therapy should receive PMRT. The rationale for this is based on the inability to accurately assess initial pathologic tumor size and axillary nodal status, because we recommended the use of PMRT for patients who undergo immediate surgery with four or more positive axillary nodes, and because the majority of patients who require mastectomy in this situation have more advanced cancers (clinically T3 or T4 noninflammatory cancer). However, we could not come to agreement that all patients should be treated with PMRT after neoadjuvant therapy. Further data on this issue are urgently needed, especially data on improved pretreatment staging and data correlating outcome with pathologic findings on mastectomy.

Modifications of these Guidelines for Special Patient Subgroups

Guideline: There is insufficient evidence to make recommendations or suggestions for modifying guidelines regarding the routine use of PMRT based on other tumor-related, patient-related, or treatment-related factors.

OTHER TUMOR-RELATED CHARACTERISTICS

There are very few studies of how other tumor characteristics affect the risk of LRF. Such factors include the presence of vascular or lymphatic invasion,55 tumor grade,9,29,33,55,56 HER2 expression,57 P53 expression,58 and estrogen receptor protein expression.35,37

One potentially important consideration is the surgical margin status, or the distance of tumor from the pectoralis fascia. Although PMRT is commonly used for patients with close or positive margins, the data supporting this practice are fragmentary and sometimes contradictory.59-61

The effect of the presence of extracapsular extension of tumor on the risk of LRF is uncertain. It did not seem to increase the risk of LRF in several series, when the number of involved nodes was accounted for.62-65 In one study, the presence of extracapsular extension did substantially increase the risk of chest wall recurrence for patients with one to three positive axillary nodes but not for those with four or more positive nodes.66 However, these studies were relatively small. Retrospective analysis of the British Columbia trial found that there was a substantial difference in the crude rates of overall survival for patients with one to three positive nodes when extensive extracapsular spread or extensive nodal involvement (defined as essentially replacement of the node by tumor) was found for the control arm (60% v 39% crude overall survival rates without and with this finding, respectively) but not for the PMRT arm (65% for both subgroups).67 For patients with such nodal findings, the improvement in overall survival resulting from PMRT was statistically significant (\( P = .04 \)). There were much smaller differences for patients with four or more positive nodes either in the control arm (overall survival rates of 41% and 25% without or with extensive extracapsular spread) or the PMRT arm (36% and 34%, respectively).

In summary, the panel found insufficient evidence to recommend or suggest how other tumor characteristics should be used to modify the decisions to use or not use PMRT for patients covered in the first three guidelines. Further investigation of the pathologic and molecular correlates of LRF and treatment efficacy should be vigorously pursued.

PATIENT-RELATED FACTORS

Evaluation of the role of PMRT relative to patient age at diagnosis or menopausal status is hampered by the lack of routine analysis of these factors in either randomized trials or retrospective series. In the Danish 82b trial (which included only premenopausal patients), there were no differences in the risks of LRF or distant failure among patients younger than age 40 years, those 40 to 49 years old, and those age 50 or older.5 The first two of these age groups had similar, statistically significant improvements in 10-year disease-free and overall survival rates resulting from PMRT. In the Danish 82c trial, patients age 59 or younger and those age 60 or older also benefited similarly to each other from PMRT.29 The 1995 and 2000 Oxford Overviews found that radiotherapy had almost the same proportional effects on breast cancer mortality and nonbreast deaths among women, regardless of age at diagnosis.2,3 However,
because the underlying risk of cardiac disease is higher in older patients, there was a net benefit to younger patients from radiotherapy but not for older ones. In the 1995 Overview, the odds ratios of death due to any cause (their Table 1) were 0.91 ± 0.05 for patients younger than 50 years old, 1.00 ± 0.05 for patients ages 50 to 59, and 1.01 ± 0.04 for patients age 60 and older. (Age-specific overall mortality statistics were not updated in the 2000 Overview.)

Patients over 70 years of age were not generally included in either prospective or retrospective studies of chemotherapy or tamoxifen.28,29 Hence, little can be stated about the use of PMRT in these women. Although most trials have included both pre- and postmenopausal patients, the impact of menopausal status was analyzed adequately only in the Scottish trial.37

In summary, the panel found insufficient evidence to recommend or suggest how age and menopausal status should be used to modify decisions to use or not use PMRT.

**TREATMENT-RELATED FACTORS**

Variations in surgical and systemic treatment might affect the risk of LRF and hence the value of PMRT. The panel therefore reviewed the evidence on this subject.

Differences in surgical technique may be responsible for much of the differences in LRF rates found between different studies. In particular, the extent of axillary dissection (roughly estimated by the number of resected nodes) was more limited in a number of the randomized trials of PMRT than routinely performed by many surgeons in North America and Europe. In the Danish 82b trial, where this factor was evaluated, the extent of axillary dissection seemed to have an impact on the LRF rate in patients not undergoing PMRT.9 The 10-year LRF rate was 40% for 133 patients who had an axillary dissection specimen from which only zero to three nodes were recovered, compared with 32% for 511 patients in whom four to nine nodes were recovered and 27% for 211 patients in whom 10 or more nodes were examined. Of importance, LRF rates were very similar in irradiated patients, regardless of the number of recovered axillary nodes. A recent study of patients treated in four Eastern Cooperative Oncology Group (ECOG) trials of systemic therapy without PMRT showed a similar trend that was statistically significant on multivariate analysis.35 The absolute impact of the number of recovered nodes on LRF rates was greater in patients with four or more positive nodes than in patients with one to three positive nodes. In the Danish 82c trial, there was no difference in the rates of LRF, relapse-free survival, or overall survival whether seven or fewer nodes or eight or more nodes were examined; however, results in patients with seven or fewer recovered nodes were not further subdivided.29

The use of such findings in making decisions about the use of PMRT is complex. In the Danish trial, all three subgroups (including the one with the lowest risk of LRF) had nonsignificant trends toward improved disease-free and overall survival rates when PMRT was used.9 However, the size of the benefit received seemed to decrease as the risk of LRF decreased. For the subgroup of patients with 10 or more recovered nodes, the use of PMRT resulted in a 4% increase in the overall survival rate at 10 years after irradiation, compared with 10% among patients with zero to three or four to nine recovered axillary nodes. Hence, improvements in surgical technique may not eliminate the benefits of PMRT, but they may reduce it. Nonetheless, even such reduced benefits from PMRT might still be large enough to be clinically worthwhile. Few institutions have up-to-date information on LRF rates in their patients recently treated with mastectomy and systemic therapy; however, such information is needed to assess the implications of the results from the randomized trials of PMRT to their own patients.

The impact of differing systemic therapies on LRF rates has not been well studied. However, regimens that are commonly used today seem to vary little from one another. For example, cyclophosphamide, methotrexate, and fluorouracil (CMF)-based and doxorubicin-based regimens were about equally effective in this regard in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-15 and Southwest Oncology Group 8313 trials.67,68 In a randomized trial performed in Canada in node-positive premenopausal women, the incidence of isolated chest wall failure (as the first failure site) was approximately the same in the patients receiving standard oral CMF (8%) and patients receiving cyclophosphamide, epirubicin, and fluorouracil (CEF) (10%), whereas the risk of distant failure was significantly reduced in the CEF arm.69 In the ECOG experience, there was little difference in LRF rates among premenopausal patients treated in trial E5181, whether doxorubicin and other agents were given in addition to CMF or not.35 Whether modifications of current regimens will reduce LRF rates substantially is uncertain. Increasing the dose-intensity of cyclophosphamide did not decrease LRF rates in the NSABP B-22 trial, compared with “standard” doses.70 Also, the risk of LRF was still substantial in unirradiated patients (three of eight), despite high-dose chemotherapy, in patients with 10 or more involved nodes in a pilot study performed at Duke University.71 There are no data yet on whether adding newer chemotherapy agents, such as the taxanes, or using altered schedules (such as “dose-dense” chemotherapy programs) will have an impact on LRF rates.
In theory, the routine addition of tamoxifen to chemotherapy for patients with estrogen receptor protein (ERP)-positive tumors might reduce the risk of LRF compared with that when chemotherapy alone is used. However, few data are available to evaluate this conjecture. The Italian Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group (GROCTA) trial I enrolled both pre- and postmenopausal patients with node-positive, ERP-positive tumors. The incidences of isolated LRF in patients receiving tamoxifen for 5 years, chemotherapy, or both were 12%, 13%, and 5%, respectively, at a median follow-up time of 5 years. However, these results included both patients treated with breast-conserving therapy and those treated with mastectomy; also, an unstated number of patients received PMRT. In the ECOG experience, trials E5177 and E6177 showed trends for modest reductions in LRF rates in patients who received both chemotherapy and tamoxifen, compared with chemotherapy alone, but the differences were not statistically significant. The duration of tamoxifen in these two trials (and in the two randomized trials examining the role of PMRT in patients receiving tamoxifen without chemotherapy) was only 1 year, which would be considered inadequate today. Still, longer courses of tamoxifen may not have substantial impact on the risk of LRF either. In ECOG trial 4181, ERP-positive postmenopausal women who received 1 year of tamoxifen plus chemotherapy had a 10-year risk of LRF (including patients with simultaneous distant failure) of 20%, compared with 15% for patients randomized to receive 5 years of tamoxifen in addition to the same chemotherapy. However, in ECOG trial 5181, ERP-positive premenopausal patients who received 1 year of tamoxifen plus chemotherapy had a 12% LRF rate, compared with 11% for patients who received 5 years of tamoxifen in addition to chemotherapy. The addition of chemotherapy to tamoxifen reduced LRF rates for node-positive patients age 50 or older with ERP-positive or progesterone receptor-positive tumors in the NSABP B-16 trial. However, no differences in LRF rates were seen in similar patients assigned to 2 years of tamoxifen (20%) or tamoxifen plus eight cycles of intravenous CMF (18%) in the MA.4 trial conducted by the National Cancer Institute of Canada.

In summary, the panel did not find sufficient evidence to recommend or suggest how treatment recommendations for the use of PMRT should be modified according to surgical or systemic treatment factors.

TREATMENT TECHNIQUES: RANDOMIZED TRIALS RELEVANT TO SELECTION OF RADIOTHERAPY VOLUMES

Few trials have examined the possible value of nodal irradiation in its own right, separate from that of chest wall or breast irradiation. Most of these suffer from substantial methodologic problems or accrued only very small numbers of patients. In a trial conducted in Oslo, Norway, from 1968 to 1972 (the so-called “Oslo II” trial), 265 patients were irradiated (170 patients with negative axillary nodes, 95 with positive nodes); the control group had 277 patients (186 with negative nodes, 91 with positive nodes). Local-regional recurrences occurred in 5% and 13% of the irradiated and nonirradiated groups by 10 years, respectively. These results were not subdivided by nodal status, however. There was a nonsignificant trend toward slightly worse relapse-free and overall survival rates in the patients with negative nodes who received radiotherapy, compared with the control group. The opposite trend was found in the node-positive patients (ie, favoring the radiotherapy arm), particularly for patients with medial or central tumors. (Trials that examined the value of internal mammary node dissection or irradiation are discussed below.)

Thus, there is little level I or II evidence on how selecting different treatment volumes for PMRT affects disease-free and overall survival. The panel’s guidelines on whether such treatment should be given (and how to do it) were therefore based on level III evidence regarding the risks of pathologic involvement and of developing clinical recurrence at specific sites (recognizing the potential limitations of detecting such recurrences), weighed against the potential morbidity of such treatment (discussed in the following section). Consensus on these guidelines was generally strong, however, where the available data were consistent or generally consistent (grade A or B).

Chest Wall Irradiation

Guideline: In patients given PMRT, we suggest that adequately treating the chest wall is mandatory.

Level of Evidence: III.
Grade of Recommendation: A.
Details of Chest Wall Irradiation

Guideline: There is insufficient evidence for the panel to recommend or suggest such aspects of chest wall irradiation as total dose, fraction size, the use of bolus, and the use of scar boosts.

The chest wall is the site at greatest risk of recurrence in patients undergoing mastectomy. Hence, treatment of the chest wall was considered mandatory by all panel members. There are few data available to resolve questions related to more detailed technical aspects of treating the chest wall, however.

There is no agreement as to what an “adequate” or “optimal” radiotherapy regimen for PMRT is. Different centers throughout the world use very different fractionation methods of chest wall irradiation in patients given PMRT.
schedules and total doses. Most institutions in the United States treat the chest wall to total doses of approximately 50 Gy in 1.8- to 2-Gy daily fractions, given five times weekly. There are no data on whether giving doses to the entire chest wall in excess of approximately 50 Gy are of additional benefit. However, the M.D. Anderson Cancer Center has used 2.5-Gy fractions to give a dose of 50 Gy in 4 weeks.84 Institutions in Europe and Canada have often used even shorter schedules. Twice-daily treatment has also been used at the M.D. Anderson Cancer Center to treat patients with locally advanced or inflammatory carcinomas after surgery.85,86 It is not clear whether one fractionation scheme has any advantages over another. A randomized trial of four different fractionation schemes (the START trial), which includes patients treated with PMRT, was begun in the United Kingdom in 1998. There are few data on whether or in what circumstances giving a boost dose (usually 10-16 Gy) to the mastectomy scar is of value in reducing the risk of local failure, compared with treating the entire chest wall uniformly without a boost.87,88

The relative effectiveness of photon-based and electron-based treatment schemes was similar in the only (retrospective) study comparing the two.54 The use of “bolus” (material with absorption of x-ray photons or electrons equivalent to that of tissue) placed on the skin surface to increase the skin dose is common, especially when photons are used to treat the chest wall. Whether it is necessary to apply bolus every day, less frequently, or at all is uncertain.50,87,88 For patients with locally advanced disease (stage IIIIB), achieving a high skin and subcutaneous dose may be more important.55

Axillary Nodal Irradiation

**Guideline:** We suggest that full axillary radiotherapy not be given routinely to patients undergoing complete or level I/II axillary dissection. There is insufficient evidence to make suggestions or recommendations as to whether some patient subgroups might benefit from axillary irradiation.

**Level of Evidence:** III

**Grade of Recommendation:** B.

Full axillary irradiation was used in nearly all the randomized trials that examined the role of PMRT. However, the value of routinely giving such treatment is not clear. The risk of clinical axillary recurrence after mastectomy varies depending on whether axillary nodes are involved (and how many are positive) and by the type of axillary dissection performed.89 In most series that used a level I/II or complete dissection of levels I to III, axillary recurrences occurred in a few percent of patients when only one to three nodes were positive, whether radiotherapy to the breast was a part of treatment or not.35,90-92 Such failures may be more common in patients with four or more positive nodes. In one recent retrospective series, axillary recurrence occurred in 7% of patients (nine of 133) when irradiation was not used or suboptimal doses (less than 45 Gy) were given to axillary or supraclavicular nodal sites but in none of 31 patients treated with adequate irradiation doses.92 In a series from Lund, Sweden, no axillary failures were seen among either 46 unirradiated or 52 irradiated patients with four or more positive nodes.93 In a small series of patients who underwent high-dose chemotherapy after complete dissection which revealed 10 or more positive nodes, there was no difference in axillary failure rates whether a supraclavicular field or full axillary field was treated.94

The extent of axillary dissection, as measured roughly by the number of nodes recovered from the specimen, seems to have an impact to some degree on the risk of recurrence.89 In a recent review of the experience of the ECOG, the 10-year cumulative incidence of axillary recurrence in patients who had one to three positive axillary nodes was 7.0% when two to five nodes were examined in the axillary dissection specimen (43 patients), 0.5% when six to 10 nodes were examined (215 patients), and 1.5% when 11 or more nodes were examined (758 patients) (P = .0009).35 For patients with four or more positive nodes, the 10-year cumulative incidence of axillary recurrence was 12% when four to five nodes were examined (18 patients), 8% when six to 10 nodes were examined (138 patients), and 6% when 11 or more nodes were examined (840 patients) (P = .63).35

It is not clear whether other factors play a significant role in the risk of axillary failure after surgery. The one that has been most closely examined is extracapsular extension, which does not seem to substantially increase the risk of axillary failure.62-65,92

The panel believed it important to note that the lower portion of the axilla (level I and part or all of level II) is ordinarily included in the same fields as are used to treat the chest wall when photon techniques are used. The so-called “supraclavicular field” (ie, lateral border at the coracoid process or medial border of the humeral head) ordinarily includes the level III nodes in most patients, as well as the true supraclavicular nodes more medially. The “full axillary field” (also called a “supraclavicular/axillary field”) extends the lateral border of the supraclavicular field to split the humeral head, thus including more soft tissue laterally.89 As discussed below, the distinction between these two fields is important with regard to the risk of lymphedema.

Therefore, despite the use of full axillary radiotherapy in the randomized trials, the panel suggests that axillary radiotherapy not be given routinely to patients undergoing complete or level I/II axillary dissection. The available data
are insufficient to suggest whether certain patient subgroups may benefit from specific axillary irradiation.

**Supraclavicular Nodal Irradiation for Patients With Four or More Positive Axillary Lymph Nodes**

**Guideline:** The incidence of clinical supraclavicular failure is sufficiently great in patients with four or more positive axillary nodes that we suggest a supraclavicular field should be irradiated in all such patients.

**Level of Evidence:** III.

**Grade of Recommendation:** A.

**Supraclavicular Nodal Irradiation for Patients With One to Three Positive Axillary Lymph Nodes**

**Guideline:** There is insufficient evidence to state whether a supraclavicular field should or should not be used for patients with one to three positive axillary nodes.

There are few surgical data on the risk of pathologic involvement of the supraclavicular nodes in patients with breast cancer. Occult supraclavicular node involvement was found in 18% (23 of 125) of patients with histologically positive axillary nodes (and none of 149 patients with negative axillary nodes) in one series in which supraclavicular node biopsies were performed routinely.95 The risk of clinical supraclavicular recurrence after mastectomy seems to depend mainly on the extent of axillary involvement. In most series, supraclavicular recurrences occur in 1% to 4% of patients when only one to three nodes are positive.95,96-92

Supraclavicular nodal failures are more common in unirradiated patients with four or more positive axillary nodes. In one series, supraclavicular nodal failure appeared in 17% of unirradiated or inadequately irradiated patients (17 of 102), compared with 2% of 56 irradiated patients.92 In another series, the risk of supraclavicular failure was 13% (six of 46) among unirradiated patients with four or more positive nodes, compared with 4% (two of 52) for those irradiated.93 However, in another recent study, the incidence of supraclavicular failure was only 3% (one of 36) without irradiation.96 Doses of 45 to 50 Gy in 1.8- to 2-Gy fractions seem adequate to achieve control in the great majority of patients.84,89

The appropriateness of giving supraclavicular nodal irradiation was discussed extensively by the panel. This subject has not been well studied. Some argued that such failures can be very difficult to control and can cause great morbidity.97 Others believed that the potential morbidity of irradiation itself (discussed in detail below) might outweigh the risk of uncontrollable supraclavicular recurrence, especially in patient subgroups with relatively low failure rates. Further, there are no clear data on the impact of supraclavicular irradiation on overall survival. Two trials (one conducted by the European Organization for Research and Treatment of Cancer, the other by the National Cancer Institute of Canada) are currently open in which patients are randomized to receive or not receive both supraclavicular and internal mammary nodal irradiation. These may someday help settle this contentious issue, but at present there are clearly substantial differences of opinion on this subject within the radiation oncology community, as well as among the panel members.

Therefore, based on these considerations of morbidity and the substantial observed incidence of clinical supraclavicular failure in patients with four or more positive axillary nodes, the panel suggests that a supraclavicular field should be irradiated in all such patients. However, there are insufficient data for the panel to state whether a supraclavicular field should or should not be used for patients with one to three positive axillary nodes.

**Internal Mammary Nodal Irradiation**

**Guideline:** There is insufficient evidence to make suggestions or recommendations on whether deliberate internal mammary nodal irradiation should or should not be used in any patient subgroup.

One of the most controversial issues regarding PMRT is treatment of the internal mammary nodes. Internal mammary nodal irradiation was used in the majority of trials of PMRT, including the two Danish and the British Columbia trials. However, the data regarding the value of routine internal mammary nodal irradiation are limited and contradictory.

In older studies, the incidence of internal mammary node metastases was approximately 10% in patients with a negative axillary dissection and 20% to 50% in patients with a positive dissection.97-100 More recent studies tend to show lower risks of involvement.101-104 Tumor size, clinical stage, and the number of axillary nodes involved affect the risk of internal mammary node involvement.101-105 The location of the primary tumor in the breast seems to have only a minor impact on the risk of internal mammary node involvement, when controlled for axillary nodal status and tumor size.98,99,105

Clinical recurrence in internal mammary nodes in patients with positive axillary nodes is rare in most series, even when radiotherapy is not given.35,62,106,107 Although a few studies have found higher rates of recurrence (9% to 10%).108,109 In one series in which 20 patients had biopsy-proven internal mammary node involvement but did not subsequently receive irradiation, only one patient had a clinical recurrence.109 The reasons for this discrepancy between the apparently large risk of pathologic involvement and this low incidence of clinical manifestation are uncertain.
One of the reasons why it may be difficult to show that specific internal mammary nodal irradiation improves outcome, at least in patients undergoing breast or chest wall irradiation, is the anatomic location of these nodes. The nodes most likely to be involved in breast cancer are in the upper three interspaces. These tend to be located less deeply than the ones located more inferiorly. Hence, in many patients, many or most of the internal mammary nodes will likely be included in tangential photon treatment fields, even if they extend only to the midline. Thus, techniques that attempt to more comprehensively treat the internal mammary nodes may add only a small degree of benefit (if any) to standard chest wall irradiation fields.

Retrospective studies of irradiated patients differ on whether there are any benefits to giving internal mammary nodal irradiation. A few randomized trials have focussed on whether internal mammary nodal treatment improves patient outcome. Two trials showed no improvement in survival in patients who underwent internal mammary node dissection in addition to standard radical mastectomy. However, systemic therapy was not used in these trials, and hence the applicability of these results to patients receiving systemic therapy is not known. A trial performed from 1985 to 1993 at the National Cancer Institute Hospital in Tokyo, Japan, randomly allocated 150 patients with biopsy-proven internal mammary node involvement to either radical resection of the internal mammary supraclavicular chain, irradiation of the supraclavicular and internal mammary nodes, or no further surgery or deliberate irradiation of these areas. All patients were treated with quadrantectomy and irradiation of the breast, as well as six courses of CMF. The 5-year disease-free survival rates were similar in the three arms (57%, 53%, and 51%, respectively), although the risk of supraclavicular and/or internal mammary recurrence was lowest in the irradiated group (12%, 0%, and 16%, respectively). A randomized study of internal mammary irradiation performed in Tampere, Finland, between 1989 and 1991 in patients treated with breast-conserving surgery showed no difference in relapse rates at a median follow-up of 2.7 years, but only 13% of the 270 patients included had positive axillary nodes and only 18% had centrally or medially located primary tumors. A trial was conducted from 1992 to 1997 in France in which 1,391 patients were randomized to receive either chest wall and supraclavicular radiotherapy or chest wall, supraclavicular, and internal mammary irradiation after modified radical mastectomy (axillary irradiation was optional). About half of these patients had primary tumors located in the central or inner quadrants of the breast and half had tumors in any location within the breast but had positive axillary nodes. No results are yet available for the individual arms of this trial. In early 1996, the European Organization for Research and Treatment of Cancer began a trial (protocol 22922/10925) of the value of internal mammary and medial supraclavicular chain irradiation for similarly selected patients undergoing either breast-conserving surgery or mastectomy, with an accrual goal of more than 4,000 patients. A similar trial began in Canada in 2000 (open only to patients undergoing breast-conserving surgery).

There is insufficient evidence for the panel to make either suggestions or recommendations as to whether deliberate internal mammary nodal irradiation should or should not be used in any patient subgroup. However, because of the potential increase in cardiac and pulmonary toxicity resulting from such treatment, the expert consensus of the panel was that irradiation of the internal mammary nodes should not be considered mandatory at present.

Sequencing of PMRT and Systemic Therapy

Guideline: There is insufficient evidence to recommend the optimal sequencing of chemotherapy, tamoxifen, and PMRT. The panel does suggest, based on available evidence regarding toxicities, that doxorubicin not be administered concurrently with PMRT.

There are few data defining the optimal sequencing of chemotherapy and PMRT. The interval between surgery and the start of radiotherapy may affect the risk of LRF. At the University of Washington in Seattle, the 8-year actuarial risk of LRF among 19 patients beginning radiotherapy within 6 months of initial diagnosis was 5%, compared with 23% among 35 patients beginning radiotherapy more than 6 months after diagnosis. Another group of 248 node-positive patients (50% with clinical stage III tumors) in Granada, Spain, were nonrandomly assigned after mastectomy to receive irradiation (50 Gy in 5 weeks) and chemotherapy in one of three combinations: radiotherapy followed by six cycles of CMF; six cycles of CMF followed by radiotherapy; or a sandwich regimen of three cycles of CMF, then radiotherapy, then three more cycles. The respective LRF rates were 10%, 18%, and 5%. However, this study has only been published in abstract form. Conversely, a retrospective review performed at the University of Pennsylvania of 221 patients receiving PMRT between 1977 and 1992 showed little, if any, impact of the interval between surgery and PMRT on the risk of LRF. Adjuvant chemotherapy was given to 151 patients (68%). With a median follow-up of 4.3 years, the LRF rates at 5 years were 13% for 82 patients beginning PMRT within 2 months of mastectomy, 4% for 50 patients beginning PMRT from 2.1 to 6 months after surgery, and 9% for 89 patients beginning PMRT more than 6 months after surgery ($P = .51$). PMRT was also highly effective in preventing LRF when given...
after chemotherapy in two randomized trials.39,48 Hence, the effect of delaying PMRT remains uncertain. One French randomized trial has directly examined this question of early versus delayed initiation of PMRT; results from this trial are not yet available.120

The impact of delaying the start of chemotherapy in order to give radiotherapy first is not certain. A number of randomized trials of PMRT gave radiotherapy before beginning chemotherapy.37,38,47,121,122 Despite the delay in beginning chemotherapy, patients in the radiotherapy arms had disease-free and overall survival rates as high or higher than that of patients in the chemotherapy-only arms. However, in a trial of the sequencing of chemotherapy and radiotherapy in patients treated with breast-conserving therapy at the Joint Center for Radiation Therapy (JCRT) and affiliated institutions, freedom from distant failure and overall survival rates were higher in patients randomized to receive chemotherapy before radiotherapy, rather than radiotherapy followed by chemotherapy.123 Nodal status seemed to modulate the impact of the sequencing of chemotherapy in this trial, but not in two retrospective studies in which the interval before starting chemotherapy had little, if any, impact.124,125

Another option in integrating chemotherapy and PMRT is the sandwich approach (ie, giving one or more chemotherapy cycles, then stopping chemotherapy to give radiotherapy, then resuming chemotherapy). The British Columbia and Danish 82b trials found reduced risks of distant failure and improved survival rates in the combined-modality arms, despite the use of sandwich approaches.9,10 The randomized International Breast Cancer Study Group Trial VI also found that interrupting a six-cycle program of CMF did not reduce its effectiveness.126 In the retrospective experience of the JCRT, the crude 5-year distant failure rates were very similar in patients with one to three positive nodes who received either sandwich therapy (19%) or concurrent chemotherapy (18%).127 In the study from Granada noted above,118 the 10-year actuarial disease-free survival rates in patients treated with CMF after radiotherapy, CMF before radiotherapy, and a sandwich approach were 41%, 46%, and 57%, respectively. The respective survival rates in these three groups were 48%, 47%, and 57% (P = .05). However, none of these trials or studies routinely used anthracycline-containing regimens or taxanes. Therefore, it is uncertain whether these data are relevant to newer regimens (particularly ones that are shorter than previously used CMF regimens).

Another issue relevant to the integration of chemotherapy and PMRT is toxicity. Toxicities for the treatment program as a whole (particularly myelosuppression and radiation pneumonitis) seem to be marginally greater in patients treated with chemotherapy after radiotherapy, compared with radiotherapy after chemotherapy,123,128 but the differences are of minimal clinical relevance with regard to delivered drug doses.123,129

Concurrent administration of chemotherapy and radiotherapy generally increases the risks of acute and subacute complications compared with sequential administration, unless steps are taken that may limit the individual effectiveness of either chemotherapy or radiotherapy.130,131 Doxorubicin and epirubicin cause unacceptable skin and soft tissue effects when given concurrently with radiotherapy, although mitoxantrone does not.132-135 Some investigators have reported substantially increased acute skin toxicity136 and rates of radiation pneumonitis137 with specific programs of concurrent administration of paclitaxel and radiotherapy. However, other schemes may not cause such a high incidence of complications.138,139 The acute toxicity of concurrent chemoradiotherapy may also be reduced by omitting some drugs during radiotherapy, such as methotrexate,140-142 or by giving reduced drug doses138,143 or by modifying radiation doses and/or using limited irradiation fields.144 Nonetheless, there is danger that such modifications might decrease systemic145,146 or local-regional tumor control.

The cardiac toxicity of doxorubicin and radiotherapy may be enhanced by their concurrent administration. No long-term data regarding this issue are yet available. However, subacute symptomatic congestive heart failure was reported in four (4%) of 114 patients (with one of these cases being fatal) with left-sided lesions who underwent breast-conserving therapy in a study in Milan in which patients received doxorubicin during radiotherapy.147 In a pilot study of concurrent paclitaxel and radiotherapy with subsequent fluorouracil/epirubicin/cyclophosphamide, two of 11 patients developed echocardiographic changes without clinical symptoms.148

There are no data available with which to decide whether hormonal therapy should be started before, during, or after PMRT. However, both trials examining the use of PMRT in postmenopausal women gave tamoxifen concurrently with PMRT, with no apparent loss of effectiveness in preventing local-regional failure.28,74

Thus, the panel concluded that there is insufficient evidence to recommend the optimal sequencing of chemotherapy, tamoxifen, and PMRT. What data are available are drawn from studies that make use of regimens (predominantly CMF) that are becoming less frequently used in clinical practice. It is unknown whether certain factors (eg, margin status) should influence the sequencing of treatment. On the basis of expert consensus, the panel agrees that it is prudent to start chemotherapy soon after surgery, and hence the start of chemotherapy should not be delayed until after PMRT. No agreement was reached on how long a period
PMRT can be delayed after surgery before its effectiveness is reduced. No consensus was achieved with regard to whether it was better to use a sandwich approach or deliver all chemotherapy before PMRT (as has been commonly done in trials and studies in North America) when prolonged regimens are used (anticipated duration > 4 to 6 months). The panel does suggest, on the basis of available evidence regarding toxicity, that doxorubicin or epirubicin not be administered concurrently with PMRT. The expert consensus of the panel was that tamoxifen may be given either concurrently with or after PMRT, but evidence is insufficient to make a clear recommendation or suggestion.

Integration of PMRT and Reconstructive Surgery

Guideline: There is insufficient evidence to make recommendations or suggestions with regard to the integration of PMRT and reconstructive surgery.

There are only limited retrospective data regarding how the use of PMRT affects the outcome of reconstructive surgery. These studies contain heterogeneous populations treated with multiple reconstructive techniques (both autologous and prosthesis-based) in which PMRT was given either before or after reconstruction. The incidence of LRF does not seem to be different for patients undergoing reconstruction (either immediate or delayed) than for patients not undergoing reconstruction. Performing immediate reconstruction also does not ordinarily seem to significantly delay or interfere with the use of chemotherapy or PMRT, even for patients with locally advanced breast cancers.

Reconstructions created using autologous myocutaneous flaps without a prosthesis tolerate PMRT well, with a risk of complications and cosmetic outcome similar to those in unirradiated patients. Patients who undergo reconstruction using prostheses and also receive PMRT have higher complication rates and worse cosmetic results than unirradiated patients, whether reconstruction is performed before or after radiotherapy is given. In a series of patients who underwent reconstruction using prosthetic implants at the M.D. Anderson Cancer Center, capsular contracture of Baker grade III or higher, pain, implant exposure, or removal occurred in 43% (six of 14) of irradiated patients who had implants without coverage by a myocutaneous flap, compared with only 12% (33 of 266) of unirradiated patients. When the prosthesis was placed beneath an autogenous myocutaneous flap, 40% (10 of 25) of irradiated patients had complications, compared with 8% (six of 72) of unirradiated patients. This increased risk of complications also seems to hold true for patients in whom tissue expanders are used.

Thus, the panel believed that there is insufficient evidence to make recommendations or suggestions with regard to the integration of PMRT and reconstructive surgery. Where reconstruction can be done with a low morbidity, such that systemic therapy and PMRT will not be delayed in the large majority of cases, the consensus of the panel was that it is reasonable to perform immediate reconstruction in patients with clinical stage I or II cancers. However, there was disagreement within the panel regarding the use of immediate reconstruction in patients who may be candidates for PMRT, particularly those with stage IIIB tumors (ie, T4 or N2 disease) and larger T3 tumors. In any situation, the panel agreed, the timing of reconstruction must be secondary to the oncologic treatment objectives (either local-regional or systemic). Since only a minority of patients who have reconstructions with prostheses will require major revisions as a result of PMRT, and reconstruction using purely autologous tissue is substantially more complex than prosthetic reconstruction for both patient and physician, it is not clear that patients and physicians will prefer autologous reconstruction solely due to the possible advantages it has with regard to PMRT. However, the expert consensus of the panel was that the type of reconstruction performed should not be allowed to interfere with delivering local-regional and systemic treatments.

COMPLICATIONS

Long-Term Toxicities

Guideline: The potential long-term risks of PMRT include lymphedema, brachial plexopathy, radiation pneumonitis, rib fractures, cardiac toxicity, and radiation-induced second neoplasms. Data would suggest that the incidence of many of these toxicities will be lower when modern radiotherapy techniques are used, although follow-up in patients treated with current radiotherapy techniques is insufficient to rule out the possibility of very late cardiac toxicities. In reviewing the available evidence with its limitations, however, the panel suggests that, in general, the risk of serious toxicity of PMRT (when performed using modern techniques) is low enough that considerations of toxicity should not limit its use in most circumstances when otherwise indicated.

Levels of Evidence: II, III.
Grade of Recommendation: B.

LYMPHEDEMA

Lymphedema of the arm results from interruption and damage to lymphatics by surgery and/or radiation or may result from blockage of lymphatics by advanced cancer. Lymphedema is usually mild or moderate, but it can be
severe and disabling in some cases. Lymphedema may develop immediately after treatment or after many years. There is no way to predict which individuals will develop lymphedema or when it will develop. If restriction of extent of radiation and/or surgical treatment can reduce the risk of lymphedema without jeopardizing cancer outcome, such restriction of treatment is warranted.

A major problem assessing factors affecting the risk and extent of lymphedema is the lack of a standard definition. However it is defined by different authors, the risk of lymphedema is increased by more extensive axillary surgery. The rate of lymphedema after axillary dissection without radiation is reported as between 5% and 15%, but individual reports range as high as 30%.89

The details of both surgery and radiotherapy are important in determining the risk of patients’ developing arm edema. In particular, giving full axillary radiation therapy to patients undergoing complete axillary dissection substantially increases the rate and severity of lymphedema, compared with other combinations of surgery and radiotherapy. A study from Switzerland found that the risk of lymphedema after axillary radiation without surgery was 3%, compared with 25% after complete axillary dissection plus axillary irradiation.165 In a series from the JCRT, lymphedema occurred in 36% of women treated with full axillary dissection plus irradiation of the axilla, compared with 6% of women who had limited axillary dissection (level I or levels I and II) plus axillary irradiation.166 Similar results were found after a complete dissection in a series from the Netherlands Cancer Institute (risk of moderate or severe arm edema was 6% without and 28% with axillary radiotherapy).167

There are few data on this issue from the randomized trials of PMRT. In the Mayo Clinic trial, in which patients underwent complete axillary dissection, the risk of arm edema in 108 irradiated patients (which included the axilla) was 54%, compared with 25% in 104 patients treated with the same chemotherapy alone.168 However, an increased incidence of arm edema was also seen in the irradiated patients in the British Columbia trial, in which a level I/II dissection was performed. The incidence of symptomatic arm edema (9%) and the number of patients who required intervention (3%) were higher among the 164 patients randomized to PMRT (which also included the full axilla), compared with the 154 patients treated with chemotherapy alone (respective incidences, 3% and 0.7%).10 Eighty-four patients in the Danish trials of PMRT living in Aarhus County were prospectively studied for complications.169 Ipsilateral arm edema occurred in 14% of the PMRT patients, compared with 3% of the control patients.

Other factors that affect the risk of lymphedema include body mass index. Women who have a large body mass index have an increased risk of lymphedema.89 There are no data on whether the use of chemotherapy or tamoxifen changes the risk of lymphedema.

Limiting the extent of radiation therapy after mastectomy (ie, not treating a full axillary field) may reduce the risk of lymphedema. The rate of axillary failure after mastectomy using either a level I/II or complete axillary dissection without radiation is very low (see above). The risk of arm edema does not seem to be increased by the use of a supraclavicular field, compared with patients undergoing axillary dissection alone. The risk of arm edema was only 3% in a recent series of 82 node-positive patients treated with a supraclavicular field at the University of Michigan after either level I/II or complete dissection.170 In a series of patients treated at the University of Pennsylvania with PMRT, there was no difference in the risk of arm edema between patients treated to the chest wall only or those treated with a supraclavicular field or axillary field.88 Similarly, in the Netherlands Cancer Institute series, the risk of moderate or severe arm edema in patients treated to a field including the supraclavicular and internal mammary nodes was 7%, compared with 6% for patients treated with complete dissection alone.167

In summary, the risk of lymphedema is increased by the addition of radiation to the axilla after complete axillary dissection. However, in most situations, the panel agreed, treatment of a full axillary field is not indicated after complete or level I/II axillary dissection (see above). Therefore, the risk of lymphedema should not preclude the use of PMRT.

BRACHIAL PLEXOPATHY

Injury to the brachial plexus resulting in transient or permanent brachial plexopathy is uncommon in breast cancer patients. Brachial plexopathy must be distinguished from neuropathies that are common after axillary dissection characterized by numbness and paresthesias.171,172 The risk of developing brachial plexopathy seems to be substantial only when doses above 50 Gy173 or large fraction sizes are used.173–177 Some cases of brachial plexopathy may be transient. For example, in the JCRT series, only four of the 20 affected patients had severe or permanent injuries.178 It has been estimated that a dose of 60 Gy in 2-Gy fractions given to the entire plexus is required to result in a 5% risk at 5 years of permanent brachial plexopathy; a dose of 75 Gy was estimated to be required to cause a 50% risk.179 Such doses are far larger than those routinely given patients with breast cancer postoperatively. Both the radiotherapy dose and the use of chemotherapy...
may affect the incidence of brachial plexopathy. In the JCRT experience,\textsuperscript{178} when the axillary dose was 50 Gy or lower, the incidence of plexopathy was 0.4\% (three of 724) when no chemotherapy was given and 3.4\% (10 of 267) when chemotherapy was used. When the axillary dose was more than 50 Gy, the incidence of plexopathy was 3\% (two of 63) when chemotherapy was not used, compared with 8\% (five of 63) when chemotherapy was given. The risk of brachial plexopathy also may depend on the volume of the plexus treated.\textsuperscript{167,179}

Therefore, with careful radiation therapy planning and limitations on the delivered dose and fraction size, the rate of permanent brachial plexopathy is so low that it should have no bearing on decision making with regard to the use of PMRT.

**RADIATION PNEUMONITIS**

Clinically, radiation pneumonitis is characterized by a chronic cough, fever, and nonspecific infiltrate on chest x-ray.\textsuperscript{180,181} It usually develops in the first few months after radiotherapy and (for breast cancer patients) is usually self-limited, with symptoms lasting an average of 4 weeks. Few patients require any specific treatment. Changes on x-ray may persist after the resolution of symptoms.

Chemotherapy may cause pulmonary toxicity independently of radiotherapy,\textsuperscript{182} and hence combining these modalities may result in enhanced lung damage. Both the sequencing of chemotherapy and radiotherapy, radiotherapy treatment technique (which affects the volume of lung treated), and the drugs used may be important in determining this effect.

In the JCRT experience, when a suprACLavicular or full axillary field was treated in addition to breast tangential fields, the incidence of symptomatic radiation pneumonitis in patients treated with concurrent chemotherapy (nearly always full-dose CMF) and irradiation was 9\% (eight of 92), compared with 1\% (three of 236) when chemotherapy and radiotherapy were given sequentially.\textsuperscript{183} Higher incidences of symptomatic radiation pneumonitis have been reported in series in which a photon “hockey-stick” field was used to treat the internal mammary lymph nodes concurrently with chemotherapy.\textsuperscript{168,184} This technique results in a much larger volume of lung being treated than in patients treated with “deep tangents,” as in the JCRT series. Symptomatic pneumonitis requiring treatment with corticosteroids occurred in only one of 164 irradiated patients in the British Columbia trial, in which chemotherapy and PMRT were given sequentially.\textsuperscript{10} However, high pneumonitis rates have been reported in other studies using sequential chemotherapy and PMRT.\textsuperscript{185}

The details of chemotherapy also seem to influence the risk of radiation pneumonitis developing. In a series from the University of Pennsylvania, there was only a 5\% incidence (three of 63) of radiation pneumonitis among patients treated with concurrent cyclophosphamide and fluorouracil (no methotrexate) and PMRT.\textsuperscript{186} In another study, cyclophosphamide and doxorubicin administered immediately after a course of radiotherapy was associated with a much higher incidence of developing pulmonary fibrosis on chest x-ray, compared with receiving CMF.\textsuperscript{187} Patients treated with radiotherapy after high-dose chemotherapy may also develop radiation pneumonitis more frequently than patients treated with lower-dose regimens.\textsuperscript{94} There are no systematic data yet on how the use of paclitaxel affects the risk of radiation pneumonitis, although there is one case report of an episode of pneumonitis apparently precipitated by the use of paclitaxel after irradiation.\textsuperscript{188}

The impact of tamoxifen on the risk of developing clinical radiation pneumonitis or on the development of pulmonary fibrosis is not clear. In a series from Philadelphia, there was no difference in the risk of clinical radiation pneumonitis when tamoxifen was given (0.2\%) than when it was not (0.3\%).\textsuperscript{189} In a Danish trial in which patients underwent routine chest radiography, tamoxifen use increased the risk of apical fibrosis developing after irradiation, but no clinical correlations (ie, whether patients developed symptoms) were reported.\textsuperscript{190}

Thus, careful treatment planning to limit the volume of treated lung is warranted. When this is done, the risk of pneumonitis is low and should not restrict the use of PMRT.

**RIB FRACTURES**

Rib fracture is an uncommon occurrence after radiation therapy to chest wall. In a series a 1,624 women treated with breast-conserving therapy at the JCRT, rib fractures occurred in 2\% of patients at a median time of 12 months after treatment.\textsuperscript{178} In a recent study of PMRT in which the median chest wall dose was 50 Gy, the risk of rib fracture was also 2\% (four of 221).\textsuperscript{88} The rate of rib fracture in the JCRT study was related to total radiation therapy dose and use of chemotherapy, as well as the energy of the photon beam used. Women who had a radiation doses greater than 50 Gy who also received chemotherapy had a rib fracture rate of 7\%.\textsuperscript{178}

Hence, since rib fractures heal without intervention, and the rate of rib fractures developing after chest wall irradiation is low, the possibility of their occurrence should not limit the use of PMRT.
CARDIAC COMPLICATIONS

Acute and subacute complications caused by PMRT, such as pericarditis and cardiac failure, have been reported infrequently. Long-term complications, notably an increase in cardiac-related mortality, has been reported more commonly. Registry-based studies also have demonstrated an increase in cardiac mortality for patients treated with left-sided breast cancers. This increase in cardiac deaths has been attributed primarily to ischemic heart disease. This was most clearly demonstrated by a meta-analysis of 10 randomized trials of PMRT initiated before 1975. The standard mortality ratio for heart disease was 1.62 times higher for irradiated patients than for the unirradiated patients (P < .01). These findings were confirmed in the larger Oxford overview of radiotherapy trials, which included patients treated with breast-conserving surgery as well.

Assessing the risk of long-term cardiac toxicity due to PMRT is complex, due to the long latency for such side effects and the possible contribution of patient-related factors, as well as treatment factors. Perhaps the most important treatment factor is the volume of heart irradiated. Many techniques used to irradiate the internal mammary nodes (such as the pure photon “hockey-stick” field) included large cardiac volumes, regardless of whether the tumor was left- or right-sided. In the Stockholm randomized study of pre- or postmastectomy radiation therapy versus observation, treatment technique clearly had an impact on the risk of cardiac events. With a median follow-up time of 20 years, patients who received radiation therapy to one internal mammary chain using techniques that exposed a “low” or “intermediate” dose-volume of the heart did not experience an increased risk of cardiac mortality, whereas patients treated to a “high” dose-volume had an increased risk.

Recent studies have demonstrated that doses to the heart from PMRT are considerably smaller when megavoltage energies and modern planning techniques are used. The Danish trials used electrons for treating the internal mammary nodes in an attempt to limit cardiac irradiation. No increase in cardiac morbidity or mortality was observed in the irradiated patients in those trials, with a median follow-up time of 122 months. Similarly, there was no difference in the incidence of cardiac events in the JCRT breast conservation series between patients with right- and left-sided lesions who had a potential follow-up time of at least 12 years, despite the fact that (during this period) the internal mammary nodes were commonly included in deep tangent fields. The volume of heart irradiated is further decreased when no specific attempt is made to treat the internal mammary lymph nodes. The Karolinska Hospital group in Stockholm found no evidence of increased rates of myocardial infarction in patients treated to the breast only with tangential fields, with a median follow-up of 9 years, as compared with patients treated with mastectomy or between patients with right- and left-sided lesions.

However, even when fields are limited to the breast or chest wall without deliberate attempts made to include the internal mammary nodes, there still may be a risk of cardiac toxicity when large daily fraction sizes are used. In a recent study of patients treated with breast-conserving therapy in Ontario, Canada, the relative risk of fatal myocardial infarction for patients with left-sided lesions, compared with patients with right-sided lesions, when treated with fraction sizes larger than 2 Gy (usually 2.5 Gy given four times weekly) was 2.60 (95% confidence interval, 1.14 to 5.91). The relative risk for such events in patients treated for left-sided lesions with fraction sizes of 2 Gy or smaller was 1.27 (95% confidence interval, 0.46 to 3.51). Of note, many trials of radiotherapy included in the Oxford Overviews used such large fraction sizes.

The impact of patient age or other patient-related factors on the risk of cardiac sequelae of PMRT is not clear. The Oxford Overview analysis found that there was a substantially higher excess of non–breast cancer deaths among patients over 60 years old (15.3% among irradiated patients, compared with 11.1% among unirradiated ones); however, the excesses were much smaller in patients aged 50 to 59 years (6.1% vs 4.5%, respectively) and patients younger than 50 (2.5% vs 2.0%, respectively). In the Ontario breast conservation study, the increased risk of cardiac mortality was confined to patients age 60 and older (P = .01), with no difference seen between left- and right-sided groups in patients younger than 60 years old (P = .68). However, in the Danish trials, the risk of death due to ischemic heart disease or acute myocardial infarction among irradiated and unirradiated postmenopausal patients was not different (2.5% and 3.1%), respectively. Finally, one registry study showed an increased risk of fatal myocardial infarction for women younger than 60 years treated to the left side, as compared with the right side, but there was no increased risk for women age 60 or older.

There remains concern that patients treated with chemotherapy (particularly with doxorubicin-containing regimens) might have an increased risk of developing cardiac complications. Such an effect was seen in short-term follow-up of patients treated in Milan, Italy. In a recent study in patients randomized to treatment with 10 cycles of cyclophosphamide (500 mg/m²) and doxorubicin (45 mg/m²) administered every 21 days, the incidence of cardiac toxicity (cardiac failure and ischemic heart disease) was signif-
icantly increased for patients who received radiation to a moderate or large portion of the heart, compared with patients not receiving radiotherapy.\textsuperscript{204} However, there was no such increase in irradiated patients randomized to five cycles of chemotherapy, compared with unirradiated patients. Hence, the total dose of doxorubicin delivered may be important to the risk of PMRT contributing to cardiac toxicity.

In summary, the safe dose or volume of heart that can be radiated is unknown. The impact of improvements in radiation therapy technique in the last decade and of new agents, such as the taxanes or trastuzumab (Herceptin), or of high-dose chemotherapy programs on the long-term cardiotoxicity of PMRT are as yet unknown. There are conflicting data on the effect of patient age on the risk of cardiac complications developing from PMRT. The panel recommends that in patients treated with radiation after mastectomy and systemic therapy, the volume and dose to the heart should be kept as low as possible. When this is done, the risk of serious cardiac disease should not prevent the use of PMRT when indicated.

**RADIATION CARCINOGENESIS**

The carcinogenic effects of radiotherapy used for the treatment of breast cancer patients have recently been reviewed elsewhere in detail.\textsuperscript{205} Second malignancies develop in the radiation field in a small number of cases.\textsuperscript{206–208} The two types of potentially lethal malignancy that appear in the radiation field most often are soft tissue and bone sarcomas and lung cancer.

Sarcomas develop an average of 10 years after irradiation. Therefore, the frequency of sarcomas developing in the radiation fields is especially difficult to ascertain for patients treated with current radiotherapy techniques and equipment. The best estimates come from patients treated with breast-conserving therapy. At the Marseilles Cancer Institute, two of 2,850 patients developed soft tissue sarcomas at 5 and 5.5 years after treatment, or nine cases per 100,000 patient-years observation.\textsuperscript{209} In a series from the Institut Gustav-Roussy near Paris, France, nine of 7,620 patients developed a sarcoma, or an estimated excess of 9.9 per 100,000 person-years observation.\textsuperscript{210} The 10-year actuarial incidence was 0.2%, the 20-year incidence was 0.43%, and the 30-year incidence was 0.78%. Two Swedish registry studies have suggested that an increase in the “integral dose” (a combination of radiation dose and treatment volume) increases the risk of sarcoma development.\textsuperscript{211,212}

Existing data on the risk of lung cancer due to PMRT are available only from studies in which the volume of lung included in radiation fields was higher than with current treatment techniques. Two case-control studies (using data from the Connecticut Tumor Registry) of patients treated predominantly with orthovoltage equipment have shown a modest elevation in the risk of ipsilateral lung cancer appearing more than 10 years after treatment (relative risks, 2.0 and 2.8, respectively).\textsuperscript{213,214} Contralateral lung cancers were not increased, however. In an earlier report, the use of such radiotherapy was associated with an estimated excess of seven to eight lung cancer cases per 10,000 women who survived more than 10 years after diagnosis.\textsuperscript{215} There seemed to be a substantially increased risk of lung cancer in irradiated patients who smoked, compared with patients with neither exposure (relative risk, 32.7); however, this estimate rested on only 89 cases.\textsuperscript{214} Thus, lung cancer in the treated field is likely to occur in fewer than 0.1% of patients treated with PMRT. Such cases may be nearly entirely limited to smokers.

A recent report using registry data from the Surveillance, Epidemiology, and End Results (SEER) program in patients treated from 1973 to 1993 found an increased relative risk of developing squamous cell esophageal cancer more than 10 years after treatment in irradiated breast cancer patients (5.42; 95% confidence interval, 2.33 to 10.68), compared with unirradiated patients; the absolute excess risk in this group was about 2.1 cases per 10,000 patient-years observation.\textsuperscript{216} However, the details of irradiation were not known, and hence these results may not be applicable to patients treated with current techniques, in which the dose to the esophagus should be much lower.

Leukemia may be a rare complication of PMRT in patients not receiving chemotherapy. In the NSABP B-04 trial, only five cases of leukemia were seen among 1,116 irradiated patients, compared with two among 2,068 in the nonirradiated groups.\textsuperscript{217} Similar results were found in a trial conducted in Denmark.\textsuperscript{218} One case-control study did not show a statistically significant increase in leukemia rates in patients treated with radiotherapy alone.\textsuperscript{219} In another study based on cancer registries, the risk of developing leukemia was strongly related to the volume of bone marrow treated.\textsuperscript{220}

There are few data yet on whether the risk of acute leukemia is increased when PMRT is combined with multiagent chemotherapy regimens containing alkylating agents used for relatively brief periods (eg, 6 months). There were no such events in the Piedmont Oncology Association trial at a median follow-up of 11 years, but the trial contained a total of only 158 patients.\textsuperscript{221} No cases of myelodysplasia or acute myelogenous leukemia occurred among the 569 patients treated in the Oncofrance trial using doxorubicin, vincristine, cyclophosphamide, and fluorouracil for six or 12 cycles, at a median follow-up of 13 years.\textsuperscript{222} In this study, 54% of patients underwent local-regional radiotherapy. In a study of 2,465 patients from Milan, Italy, treated with CMF-based regimens, the 15-year actuarial risk of
acute leukemia in 455 women receiving breast irradiation was 0.25%, compared with 0.17% in the rest of the study group. A case-control study using the Manitoba, Canada, Cancer Registry also found no increased risk of leukemia in patients treated with both chemotherapy and radiotherapy compared with chemotherapy alone. However, in a study from the M.D. Anderson Cancer Center, Houston, TX, with a median follow-up time of 97 months, the 10-year leukemia rate was 2.5% for 810 patients treated with fluorouracil, doxorubicin, and cyclophosphamide–based regimens plus radiotherapy, compared with 0.5% for 664 patients receiving fluorouracil, doxorubicin, and cyclophosphamide alone ($P = .01$).

Women with breast cancer are at a 0.3% to 1% per year risk of developing a contralateral breast cancer. The risk of contralateral breast cancer in several cancer registry case-control studies was increased slightly in women treated with radiation probably a result of the small dose of “scatter” radiation to the opposite breast. This increased risk seems confined to patients younger than 40 to 45 years old at treatment. In an analysis of data from the Connecticut Tumor Registry, patients age 45 or younger at exposure had an increased relative risk of 1.59 (95% confidence interval, 1.07 to 2.36); at an average dose of 1 Gy delivered to the contralateral breast, the estimated relative risk was 1.21.

Thus, the risk for most patients of developing a subsequent malignancy secondary to PMRT is very small. For younger patients, the risk of developing a contralateral breast cancer likely is increased after PMRT, but these are much more likely to be curable than lung cancers, sarcomas, or leukemias. The risk of carcinogenesis should therefore not limit the use of PMRT when it is indicated.

Toxicity Considerations for Special Patient Subgroups

**Guideline:** There is insufficient evidence to make recommendations or suggestions that PMRT should not be used for some subgroups of patients because of increased rates of toxicity (such as radiation carcinogenesis) compared with the rest of the population.

**Level of Evidence:** IV.

**Grade of Recommendation:** D.

It has been suggested that some patients, such as those with preexisting genetic predispositions to develop breast cancer due to mutations in the *BRCA1, BRCA2*, or the ataxia-telangiectasia (*ATM*) genes may be at markedly elevated risk of radiation-induced contralateral breast cancers. (The relationship of the *ATM* gene to the risk of developing breast cancer without exposure to irradiation has been controversial.) However, at present there are no data supporting such concerns. None of 57 patients who developed a contralateral breast cancer after breast-conserving therapy performed at the JCRT had a germline truncating mutation for *ATM*. Since the carrier rate for such mutations in the healthy population has been estimated to be 1%, it therefore seems highly unlikely that therapeutic irradiation increases their risk of developing contralateral breast cancer.

Limited information suggests that individuals likely to be *ATM* heterozygotes are not at markedly higher risk than normal for developing radiotherapy-related toxicities. There were also no unusual acute or long-term toxicities in a retrospective analysis of 21 patients in Utah with *BRCA1* or *BRCA2* mutations undergoing irradiation for breast cancer (14 with PMRT and seven after breast-conserving surgery). A recent multicenter retrospective case-control study of 73 patients with known *BRCA1* or *BRCA2* mutations also found no difference in acute or chronic morbidity rates (or LRF, disease-free survival, or overall survival rates) compared with unaffected patients.

There has been controversy as to whether rheumatologic or collagen-vascular diseases are contraindications to the use of radiotherapy for patients undergoing breast-conserving therapy. Only one of the available reports describes a patients who had PMRT. A patient with discoid lupus developed moist desquamation in all fields after receiving 40 Gy in 20 fractions using cobalt-60 and had to stop therapy. She developed slight arm edema and tingling on the treated side which stabilized after a year. No further complications were reported. The interpretation of these and other reports on this subject is complicated by the heterogeneity of the treatment techniques used and the patients’ illnesses; also, there was no formal comparison of the risk of complications in a matched “normal” population in three of these four studies.

Thus, there is insufficient evidence at present to show whether certain subgroups of patients should not receive PMRT because of increased rates of toxicity compared with the rest of the population. However, there are very few long-term data available, particularly with regard to issues of carcinogenesis for patients with genetic defects predisposing them to develop breast cancer.

**CONCLUSION**

PMRT reduces the risk of LRF and increases the long-term survival rate for a substantial proportion of women with positive axillary nodes treated with systemic therapy. However, many questions about PMRT cannot yet be answered. This means that the individual patient and her physicians must often make a decision about whether to use PMRT or not based on inadequate information. The panel believes that it would be helpful to perform further meta-analyses restricted to the trials of PMRT that included...
routine systemic therapy. More data on specific subgroups (defined by combinations of patient and tumor factors) and models to estimate the risk-benefit ratio for PMRT for them are needed. Further information is needed with regard to the optimal technical parameters of treatment, particularly the integration of PMRT with systemic therapy and reconstructive surgery. Few data are yet available regarding the long-term toxicities of PMRT when combined with systemic therapy and its impact on quality of life. Further research on these topics, including randomized trials, is necessary. The panel encourages physicians and patients alike to participate in such efforts.

ACKNOWLEDGMENT

The Expert Panel wishes to express its gratitude to Drs Allen S. Lichter, Monica Morrow, Thomas C. Hall, Beryl McCormick, Bruce G. Haffty, Nicholas J. Robert, S. Eva Singletary, Jeanne A. Petrek, and Patrick I. Borgen for their thoughtful reviews of earlier versions of the guideline.

APPENDIX

Postmastectomy Radiotherapy Expert Panel

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