Complete Summary

GUIDELINE TITLE

Breast cancer treatment.

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Breast cancer treatment. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2004 Sep. 41 p. [77 references]

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
CONTRAINDICATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY

SCOPE

DISEASE/CONDITION(S)

Early stage breast cancer: ductal carcinoma in situ and invasive breast carcinoma, stage 0, I, II, and III

This guideline does not apply to lobular carcinoma in situ (lobular neoplasia), invasive breast carcinoma, Stage IV, or male breast cancer.

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Nursing
Oncology
Plastic Surgery
Radiation Oncology

Radiology
Surgical Pathology

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Health Plans
Hospitals
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To improve access to information regarding all appropriate local treatment options for patients with a diagnosis of breast cancer
- To standardize follow-up schedules for patients with breast cancer
- To increase the use of standardized education materials and psycho-social support for patients with breast cancer and their families
- To enhance awareness of the importance of clinical trials in breast cancer treatment

TARGET POPULATION

All female patients with a diagnosis of Stage 0 – Stage III (excluding lobular carcinoma in situ) breast cancer who are candidates for treatment

INTERVENTIONS AND PRACTICES CONSIDERED

1. Patient education
2. Lumpectomy
3. Mastectomy
4. Axillary staging: axillary dissection and sentinel lymph node biopsy
5. Hormonal therapy
6. Chemotherapy
7. Radiation therapy
8. Breast reconstruction
9. Follow-up (annual mammograms, clinical breast examination, chest x-rays, serum chemistries, bone scans, soluble tumor markers, eye exams, and annual pelvic exams)

MAJOR OUTCOMES CONSIDERED

- Rates of survival for patients receiving breast conservation treatment versus patients receiving mastectomy
- Incidence of breast cancer recurrence (relapse-free survival)
- Overall mortality rate
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system presented below, and are designated as positive, negative, or neutral to reflect the study quality.

Conclusion Grades:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results of different studies or because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results

from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

Study Quality Designations:

The quality of the primary research reports and systematic reviews are designated in the following ways on the conclusion grading worksheets:

Positive: indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis.

Negative: indicates that these issues (inclusion/exclusion, bias, generalizability, and data collection and analysis) have not been adequately addressed.

Neutral: indicates that the report or review is neither exceptionally strong nor exceptionally weak.

Not Applicable: indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

Classes of Research Reports:

A. Primary Reports of New Data Collection:

   Class A:

   - Randomized, controlled trial

   Class B:

   - Cohort study

   Class C:

   - Nonrandomized trial with concurrent or historical controls
   - Case-control study
   - Study of sensitivity and specificity of a diagnostic test
   - Population-based descriptive study

   Class D:

   - Cross-sectional study
   - Case series
   - Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

   Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Clinical Validation-Pilot Testing
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Institute Partners: System-Wide Review

The guideline annotation, discussion, and measurement specification documents undergo thorough review. Written comments are solicited from clinical, measurement, and management experts from within the member groups during an eight-week review period.

Each of the Institute's participating member groups determines its own process for distributing the guideline and obtaining feedback. Clinicians are asked to suggest modifications based on their understanding of the clinical literature coupled with their clinical expertise. Representatives from all departments involved in implementation and measurement review the guideline to determine its operational impact. Measurement specifications for selected measures are developed by the Institute for Clinical Systems Improvement (ICSI) in collaboration with participating member groups following implementation of the guideline. The specifications suggest approaches to operationalizing the measure.

Guideline Work Group

Following the completion of the review period, the guideline work group meets 1 to 2 times to review the input received. The original guideline is revised as necessary and a written response is prepared to address each of the responses received from member groups. Two members of the Committee on Evidence-Based Practice carefully review the input, the work group responses, and the revised draft of the guideline. They report to the entire committee their assessment of four questions: (1) Is there consensus among all ICSI member groups and hospitals on the content of the guideline document? (2) Has the drafting work group answered all criticisms reasonably from the member groups? (3) Within the knowledge of the appointed reviewer, is the evidence cited in the document current and not out-of-date? (4) Is the document sufficiently similar to the prior edition that a more thorough review (critical review) is not needed by the member group? The committee then either approves the guideline for release as submitted or negotiates changes with the work group representative present at the meeting.

Pilot Test

Member groups may introduce the guideline at pilot sites, providing training to the clinical staff and incorporating it into the organization's scheduling, computer, and other practice systems. Evaluation and assessment occur throughout the pilot test phase, which usually lasts for three-six months. At the end of the pilot test phase, ICSI staff and the leader of the work group conduct an interview with the member groups participating in the pilot test phase to review their experience and gather comments, suggestions, and implementation tools.

The guideline work group meets to review the pilot sites' experiences and makes the necessary revisions to the guideline, and the Committee on Evidence-Based Practice reviews the revised guideline and approves it for release.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The recommendations for the treatment of breast cancer are presented in the form of four algorithms, accompanied by detailed annotations. The Main Treatment algorithm has 16 components, while the Stage 0 Post-Surgical Treatment algorithm and the Stage I Post-Surgical Treatment algorithm each have five components and the Stage II or III Post-Surgical Treatment algorithm

has six components. Clinical highlights and selected annotations (numbered to correspond with the algorithms) follow.

Class of evidence (A-D, M, R, X) ratings and key conclusion grades (I-III, Not Assignable) are defined at the end of the "Major Recommendations" field.

Clinical Highlights

1. Breast cancer treatment involves a multidisciplinary approach including both primary and specialty care. From the first encounter with a patient and her family, mutual expectations and a trust relationship must be established. (See Annotation #2, Main Treatment algorithm)
2. Appropriate treatment modalities must be applied and may include:
    a. Surgery (Annotations # 6-11, Main Treatment Algorithm)
    b. Medical oncology (Annotation # 18 of the Stage 0 Algorithm, Annotation # 23 of the Stage I Algorithm, and Annotation #28 of the Stage II or Stage III Algorithm)
    c. Radiation oncology (Annotation # 20 of the Stage 0 Algorithm, Annotation #25 of the Stage I Algorithm, and Annotation #31 of the Stage II or Stage III Algorithm)

Main Treatment Algorithm Annotations

1. Breast Cancer Proven

   Refer to the National Guideline Clearinghouse summary of the Institute of Clinical Systems Improvement (ICSI) guideline Diagnosis of Breast Disease for information on evaluation of breast abnormalities.

2. Education Regarding Options

   Key Points:

   - All options for local therapy should be thoroughly discussed with the patient and her family.

   All potential options are reviewed with the patient and her significant other(s) when appropriate. It is important to include all possible treatment options (based on the biopsy results) at this visit. Breast conservation versus mastectomy as well as axillary staging options need to be discussed, including the rationale for the selection of the type of procedure. The anticipated cosmetic appearance should be discussed with the patient prior to choosing a surgical option.

   Reconstruction should be offered to women with Stage 0-III breast cancer who require or desire mastectomy.

   Consideration needs to be given to the resources that may be needed based on the type of surgery and/or degree of involvement. It is important to assist the patient and her significant other(s) to have a seamless system of care. The following is a suggestion of services that the practitioner should consider:

- Patient education
- General surgery
- Medical oncology
- Radiation oncology
- Reconstructive plastic surgery

Evidence supporting this recommendation is of class: R

3. Is Patient a Candidate for Breast Conserving Treatment?

Breast conserving therapy is defined as excision of the primary tumor and adjacent breast tissue, followed by radiation therapy (XRT) of the whole breast or the breast and regional lymph nodes. Options and potential side effects are reviewed with the patient. Partial breast irradiation is still experimental and has not been shown to be more beneficial than whole breast radiation therapy. At this time, no subgroups have been defined in which XRT can be omitted.

Exclusion criteria for conservation management (outside of clinical trials):

- Diffuse microcalcifications
- Gross multicentric disease or gross multifocal disease
- Lesions greater than 5 cm
- Inflammatory carcinoma
- Previous significant radiation treatment which included breast in the field
- Pregnancy is a relative contraindication.
- Collagen vascular diseases, including lupus and scleroderma, are relative contraindications.

Note that exclusion based on age, central lesions, or histologic subtype is not appropriate.

The anticipated cosmetic appearance should be discussed with the patient prior to choosing any surgical option.

Patients with biopsy-proven invasive breast cancer may be eligible for neoadjuvant (presurgical) systemic therapy. For selected patients, neoadjuvant chemotherapy may make breast conservation feasible. Neoadjuvant therapy has not been shown to improve survival.

Evidence supporting this recommendation is of classes: A, B, D, R

4. Does Patient Choose Breast-Conserving Treatment?

The period of decision making immediately following breast cancer diagnosis is often extremely stressful for women and their families. Multiple sources of information and influences exist which may lead to confusion and decisions based on misunderstandings. Women should be provided sufficient time to receive answers to their questions and make their decision, as well as be

provided access to reputable educational and support resources and materials.

Evidence supporting this recommendation is of classes: C, D

5. Does Patient Want Breast Reconstruction?

All patients should be advised about the possibility of breast reconstruction. If the patient is considering reconstruction, a referral to a reconstructive plastic surgeon is indicated. For more information, refer to Annotation # 8, "Mastectomy and Breast Reconstruction."

6. Mastectomy

If only cytologic diagnosis (e.g., fine needle aspiration specimen) of cancer has been obtained, a core-type biopsy to prove the diagnosis may be considered (if there is uncertainty based on cytology) before proceeding with mastectomy. If the diagnosis of cancer was made by open biopsy, a transverse or obliquely-oriented elliptical incision should be used, encompassing the biopsy skin incision whenever possible. Peripherally located biopsy sites may need to be excised separately. The nipple-areolar complex and all apparent breast tissue should be excised. Tumor involvement of the chest wall must be documented, widely excised and marked with clips to direct postoperative XRT.

See Annotation # 30 "Is Postmastectomy XRT Indicated?"

7. Lumpectomy

Key Points:

- Every attempt should be made to obtain negative microscopic margins.

The abnormality should be excised intact with a small margin of normal breast tissue and careful orientation for the pathologist. Except in rare and unusual circumstances, additional tissue should be removed so that negative microscopic margins are obtained. If additional tissue cannot be removed, patients with focally positive microscopic margins (defined as less than or equal to 3 low-powered fields) and without an extensive intraductal component can still be considered for breast conserving treatment. In instances of reexcision, a thin margin of skin surrounding the incision and the entire biopsy cavity [if the site of involved margin(s) is unknown] should be removed, orienting the specimen to allow the pathologist to define areas of involved resection margins precisely. Four to six metal clips at the base of the lumpectomy site will aid in directing the radiation therapy boost and not adversely affect radiologic follow-up.

Stage 0

Guidelines for lumpectomy for carcinoma in situ are similar to those for invasive cancers requiring all known disease to be removed by clinical, pathologic, and radiographic evaluation.

Stage I

With rare exceptions, all T1 tumors can be excised with grossly and microscopically clear margins and acceptable cosmesis if the patient desires lumpectomy. Subareolar tumors usually require excision of the nipple/areolar complex to achieve clear margins.

Stage II or III

Similarly, adequate tumor clearance and an acceptable cosmetic result can ordinarily be achieved following lumpectomy in patients with larger primary cancers. Neoadjuvant therapy may need to be considered in certain patients with locally advanced tumors.

Evidence supporting this recommendation is of classes: B, C, D

8. Mastectomy and Breast Reconstruction

Key Points:

- Oncologic surgical principles should not be compromised
- Skin-sparing mastectomies are generally appropriate

When immediate reconstruction is to be performed by a reconstructive plastic surgeon, the general surgeon should complete the extirpative procedure without compromising oncologic surgical principles. Skin-sparing mastectomies are appropriate as long as there is an adequate anterior margin around the tumor and the previous biopsy incision is excised with the specimen. Injuries to the neurovascular bundles or fascial planes of the chest wall that are to be utilized in reconstruction should be avoided.

Implants/expander placement or free tissue transfer procedures can be used for immediate reconstruction. Cosmesis will be less satisfactory in patients who will receive post-mastectomy chest wall irradiation.

Evidence supporting this recommendation is of classes: C, D

11. Axillary Staging

Key Points:

- Proven or highly suspicious axillary involvement should be treated with axillary lymph node dissection.
- Sentinel lymph node biopsy (SLNB) should be strongly considered for patients with a clinically negative axilla.

A. Axillary Dissection

When axillary dissection is performed as part of a breast conserving operation, the procedure should usually be undertaken through a separate incision, preferably a transverse curvilinear incision within the anterior and posterior axillary folds rather than a vertical incision. In select and unusual cases, a separate incision may not be required. In these cases, the location of the primary tumor permits it to be excised through an incision placed posterior to the anterior axillary line. This same incision can also be used for performing the axillary dissection.

In any axillary dissection, all grossly involved lymph nodes should be excised but the tissues surrounding the axillary vein anteriorly and posteriorly should be left intact to lessen the risk of lymphedema. All tissue caudad to the axillary vein and lateral to the medial border of the pectoralis minor should be excised. Injury or intentional transection of the medial pectoral, long thoracic, and thoracodorsal nerves for improved nodal clearance should be exceedingly rare. At completion of axillary dissection, a closed-system suction drainage catheter should be placed.

Axillary dissection includes Level I and Level II lymph node regions. The surgeon is advised to remove all grossly evident disease if possible. If lymph nodes are fixed to one another or other structures, it should be noted in the operative report.

Stage 0

Axillary dissection is not usually necessary for intraductal carcinoma in situ (DCIS). However, in large (greater than 2.5 cm) noninvasive carcinoma, especially those with comedocarcinoma features or palpable lesions, invasive foci may be present. Consideration of axillary nodal sampling or partial axillary dissection should be given in these instances.

Stage I

Axillary sampling or dissection is routinely performed for clinical Stage I cancers primarily for staging purposes. In rare instances of small low grade cancers (i.e., tubular carcinoma less than 1 cm), particularly in elderly or debilitated patients with a benign axillary exam, axillary dissection may be omitted.

Stage II or III

Axillary sampling or dissection is routinely performed for Stage II or III breast cancers for staging the disease and regional control of tumor.

B. Sentinel Lymph Node Biopsy (SLNB)

In sentinel lymph node biopsy (SLNB), blue dye and/or a radioactive isotope is injected into the area of the tumor. The first draining lymph nodes are identified and evaluated for the presence of metastases. If

the sentinel nodes are free of cancer, additional lymph node removal may be avoided.

This approach requires a multidisciplinary team including surgeons, radiologists, pathologists, and oncologists with the experience and resources to perform the procedure and interpret results appropriately.

Numerous prospective validation studies confirm the accuracy of sentinel node biopsy in staging the axilla. Long-term survival data are not yet available.

Traditionally, axillary dissection has been the standard of practice. However, given the increasing experience and awareness of SLNB, with adequate experience and documentation of results it has become more widely accepted in medical practice. SLNB is appropriate for patients with a clinically negative axilla.

For more information about SLNB, please refer to Institute for Clinical Systems Improvement Technology Assessment #45 "Lymphatic Mapping with Sentinel Lymph Node Biopsy for Breast Cancer" (available from the Institute for Clinical Systems Improvement Web site).

Evidence supporting this recommendation is of classes: A, C

12. Is Staging Evaluation Complete?

Refer to the original guideline document for detailed recommendations for pathologic reporting.

Stage 0 Post-Surgical Treatment Algorithm Annotations

(Excludes lobular carcinoma in situ.)

18. Oncology Visit
    - Review predicted risk of recurrence.
    - Adjuvant chemotherapy is not advised for Stage 0.
    - Consider tamoxifen to reduce the incidence of ipsilateral recurrence and contralateral breast cancer.
    - Encourage clinical trial participation.

Evidence supporting this recommendation is of classes: A, M

20. Radiation Therapy Visit

Key Points:

- Radiation therapy (XRT) improves local control

Breast XRT following breast conserving surgery has been shown by randomized prospective data to improve local control in all subgroups

identified. However, no difference in survival has been observed. Randomized, prospective studies addressing the possible omission of XRT after lumpectomy in patients with intraductal cancer are in progress. If the patient is on a protocol, then follow the protocol specifics as to the delivery of radiotherapy. Otherwise the following recommendations are made:

- Breast XRT should be started in a timely fashion after conservative surgery is performed (usually within 2 to 4 weeks). XRT may be delayed if significant seroma is present, if a cellulitis is present, if arm range of motion is still limited, or if incisions are not healed.
- Megavoltage XRT is recommended to the whole breast using tangential fields (without bolus) treating to a dose of 4500 to 5000 cGy (180 to 200 cGy per fraction) over a 4 1/2 to 5 1/2 week period. This is usually followed by a boost of XRT to the area of the excisional biopsy for an additional 1000 to 2000 cGy. Omission of the boost may be associated with an increased risk of local recurrence, even in patients with negative margins.
- Placement of surgical clips within the excisional biopsy site is encouraged in order to aid in improving XRT portal localization.
- Although breast XRT is recommended for stage 0 disease, regional XRT (to lymph node areas) is not.
- Partial breast irradiation is still experimental and has not been shown to be more beneficial than whole breast irradiation therapy.

Evidence supporting this recommendation is of classes: A, C, D, R

21. Follow-up Protocol

Key Points:

- The guideline for follow-up refers only to the asymptomatic patient.
- New or persistent symptoms must be evaluated using whatever diagnostic studies are appropriate.
- Routine radiologic (other than mammogram) and laboratory studies have not been proven to be beneficial
- Use of chest x-rays, serum chemistries, bone scans, and soluble markers are not indicated for routine follow-up.
- Patients should be followed with yearly mammography.
- Clinical breast examination should be performed every 4 to 6 months for 5 years and then annually.

Patients taking tamoxifen should have annual eye exams due to increased risk of cataracts and annual pelvic exams in patients with a uterus due to risk of endometrial carcinoma. The routine use of transvaginal ultrasound or endometrial biopsy in the absence of symptoms is not supported by data.

[Conclusion Grade I: See Conclusion Grading Worksheet -- Appendix A -- Annotation # 21 (Stage 0) in the original guideline document.]

Evidence supporting this recommendation is of classes: A, B, R

Stage I Post-Surgical Treatment Algorithm Annotations

23. Oncology Visit

Key Points:

- All appropriate post-surgical treatment options should be discussed with the patient and her family.
- The patient should have the opportunity to be actively involved in making treatment decisions.

- Review predicted risk of recurrence.
  - Consider using web-based decision making tools, such as Adjuvant or the Mayo Clinic tool (www.adjuvantonline.com or www.mayoclinic.com/calcs)
- Encourage clinical trial participation.
- Determine need for adjuvant therapy on individual case basis.
  - Characteristics to consider:
    - Pathologic prognostic factors predictive of less favorable outcome such as tumor size, high histologic grade, high nuclear grade, presence of lymphatic or vascular invasion, HER2 overexpression
    - Overall health status
    - Menopausal status
    - Patient preferences
    - Receptor status
- Coordinate all therapeutic plans with radiation therapy for patients electing breast-conserving surgery.
- Educate patient about risks and benefits of adjuvant chemotherapy and hormonal therapy
- Treatment options:

  Estrogen receptor positive or progesterone receptor positive: Hormonal therapy* and Chemotherapy**

  Estrogen receptor negative and progesterone receptor negative: Chemotherapy** or observation

  *Hormonal therapy may include tamoxifen or an aromatase inhibitor or tamoxifen followed by an aromatase inhibitor. Aromatase inhibitors are only appropriate for postmenopausal women. Oophorectomy may be considered in premenopausal patients.

  **NOTE: Chemotherapy may be advised as a treatment option for women of any age depending upon their overall health status and life expectancy, although minimal data are available on its advantages for women over age 70. Risk may be sufficiently low in some patients that chemotherapy would not be of benefit.

  Chemotherapy should be administered using established protocols by physicians and/or personnel experienced in the use of chemotherapy and the management of associated toxicities.

Currently accepted chemotherapeutic regimens in node-negative breast cancer include:

- Doxorubicin/cyclophosphamide x 4 cycles
- Cyclophosphamide/doxorubicin/5 fluorouracil x 6 cycles
- Cyclophosphamide/methotrexate/5 fluorouracil x 6 cycles
- Doxorubicin/cyclophosphamide x 4 cycles, followed by 4 cycles of paclitaxel or docetaxel

Evidence supporting this recommendation is of classes: A, M, R

25. Radiation Therapy Visit

Key Points:

- Randomized, prospective studies addressing the possible omission of XRT after lumpectomy in patients with invasive breast cancer that is less than 1 centimeter in dimension are in progress
- Radiation therapy (XRT) improves local control

At this time, no subgroups have been defined in which XRT can be omitted following breast conserving surgery. If the patient is on a protocol, then follow the protocol specifics as to the delivery of radiotherapy. Otherwise the following recommendations are made:

- If chemotherapy is not to be given, XRT should be started in a timely fashion after conservative surgery is performed (usually within 2 to 4 weeks). XRT may be delayed if significant seroma is present, if a cellulitis is present, if arm range of motion is still limited, or if incisions are not healed. Data suggest that a delay of up to 8 weeks between the last breast surgery and the start of XRT is not associated with an increased risk of recurrence. The best way to integrate XRT and chemotherapy in patients who are to receive both is not yet well defined. The two modalities have been given concurrently, sequentially, or in a sandwich fashion (i.e., chemotherapy both prior to and after XRT). Often all or a portion of chemotherapy is given prior to XRT.
- Megavoltage XRT is recommended to the whole breast using tangential fields (without bolus) treating to a dose of 4500 to 5000 cGy (180 to 200 cGy per fraction) over a 4 1/2 to 5 1/2 week period. This is usually followed by a boost of XRT to the area of the excisional biopsy for an additional 1000 to 2000 cGy. Omission of the boost has been shown to increase the risk of local recurrence, even in patients with negative margins.
- Placement of surgical clips within the excisional biopsy site is encouraged in order to aid in improving XRT portal localization.
- Regional (lymph node) radiotherapy is not recommended for Stage I patients after conservative surgery including a Level I/Level II axillary lymph node dissection or a sentinel lymph node biopsy (SLNB).
- Supraclavicular area ± axillary area XRT is controversial in patients with more limited axillary dissection (i.e., if less than 6 lymph nodes were removed from the axilla without the aid of SLNB). If regional XRT

is given to the supraclavicular area ± axillary, a dose of 4500 to 5000 cGy over a 4 1/2 to 5 1/2 week period is recommended. Special care must be taken in matching the supraclavicular field with the tangential breast fields.
- Partial breast irradiation is still experimental and has not been shown to be more beneficial than whole breast radiation therapy.

Evidence supporting this recommendation is of classes: A, C, D, M, R

26. Follow-up Protocol

Key Points:

- The guideline for follow-up refers only to the asymptomatic patient.
- New or persistent symptoms must be evaluated using whatever diagnostic studies are appropriate.
- Routine radiologic (other than mammogram) and laboratory studies have not been proved to be beneficial.
- The use of chest x-rays, serum chemistries, bone scans, and soluble tumor markers are not indicated for the routine follow-up outside of clinical trials.
- Patients should be followed with yearly mammography.
- Clinical breast examination should be performed every 4 to 6 months for 5 years, and then at least annually.

[Conclusion Grade I: See , Conclusion Grading Worksheet - Appendix A - Annotation # 26 (Stage I)]

Patients taking tamoxifen should have annual eye exams due to increased risk of cataracts and annual pelvic exams in patients with a uterus due to increased risk of endometrial carcinoma. The routine use of transvaginal ultrasound or endometrial biopsy in the absence of symptoms is not supported by data. A baseline bone density should be considered for patients taking aromatase inhibitors and thereafter as indicated due to an increased risk of osteoporosis.

Evidence supporting this recommendation is of classes: A, B, R

Stage II or III Post-Surgical Treatment Algorithm Annotations

27. Stage II or Stage III

Key Points:

- This algorithm applies only to Stage II or Stage III patients whose initial treatment was surgery.

28. Oncology Visit

Key Points:

    - All appropriate post-surgical treatment options should be discussed with the patient and her family.
    - The patient should have the opportunity to be actively involved in making treatment decisions.
- Review predicted risk of recurrence.
    - Consider using web-based decision making tools, such as Adjuvant or the Mayo Clinic tool (www.adjuvantonline.com or www.mayoclinic.com/calcs)
- Encourage clinical trial participation.
- High dose chemotherapy with autologous stem cell or bone marrow support should not be used as part of the treatment of Stage II or Stage III breast cancer outside participation in a randomized clinical trial.
- Coordinate all therapeutic plans with radiation therapy for patients following breast conserving therapy, as well as for those patients for whom post-mastectomy XRT needs to be considered.
- Educate patient about risks and benefits of chemotherapy and hormonal therapy
- Treatment options:

  Estrogen receptor positive or progesterone receptor positive: Hormonal therapy** and Chemotherapy*

  Estrogen receptor negative and progesterone receptor negative: Chemotherapy* or observation

  *NOTE: Chemotherapy may be advised as a treatment option for women of any age depending upon their overall health status and life expectancy, although minimal data are available on its advantages for women over age 70.

  Chemotherapy should be administered using established protocols by physicians and/or personnel experienced in the use of chemotherapy and the management of associated toxicities.

  **Hormonal therapy may include tamoxifen or aromatase inhibitor or tamoxifen followed by aromatase inhibitor. Aromatase inhibitors are only appropriate for postmenopausal women. Oophorectomy may be considered in premenopausal patients.

  Currently accepted chemotherapeutic regimens outside of clinical trials include:

    - Cyclophosphamide/methotrexate/5 fluorouracil x 6 cycles
    - Cyclophosphamide/doxorubicin/5 fluorouracil x 6 cycles
    - Doxorubicin/cyclophosphamide x 4 cycles
    - Doxorubicin x 4 cycles followed by cyclophosphamide/methotrexate/5 fluorouracil x 8 cycles
    - Doxorubicin/cyclophosphamide x 4 cycles, followed by 4 cycles of paclitaxel or docetaxel
    - Cyclophosphamide/epirubicin/5 fluorouracil x 6 cycles

- Dose dense* doxorubicin/cyclophosphamide x 4 cycles, followed by paclitaxel x 4 cycles
- Dose dense* doxorubicin x 4 cycles, followed by paclitaxel x 4 cycles, followed by cyclophosphamide x 4 cycles
- Paclitaxel/doxorubicin/cyclophosphamide x 4 cycles

* Dose dense regimens administer standard doses of chemotherapy every other week with growth factor support.

Evidence supporting this recommendation is of classes: A, M, R

30. Is Post-mastectomy Radiation Therapy (XRT) Indicated?

Key Points:

- Post-mastectomy radiation therapy (XRT) improves local control and survival

Literature indicates a role for post-mastectomy XRT in improving locoregional control and survival for certain early stage patients with high-risk features and for patients with Stage III disease. These high-risk features include positive axillary lymph nodes especially when 4 or more positive lymph nodes are present, pectoralis fascia involvement, primary tumor size 5 cm or more in maximal diameter, estrogen receptor negativity (when present in conjunction with other high-risk features), and positive surgical margins. Patients with extranodal disease extension, a positive high axillary lymph node, or a large axillary lymph node have been considered for post-mastectomy XRT, although data to support this are lacking.

Evidence supporting this recommendation is of classes: A, B, C, D

31. Radiation Therapy Visit

Key points:

- Post-lumpectomy radiation therapy improves local control

At this time, no subgroups have been defined in which XRT can be omitted following breast-conserving therapy. If the patient is on a protocol, then follow the protocol specifics as to the delivery of radiotherapy. Otherwise the following recommendations are made.

- If chemotherapy is not to be given, XRT should be started in a timely fashion after conservative surgery is performed (usually within 2 to 4 weeks). XRT may be delayed if significant seroma is present, if a cellulitis is present, if arm range of motion is still limited, or if incisions are not healed. Data suggest that a delay of up to 8 weeks between the last breast surgery and the start of XRT is not associated with an increased risk of recurrence. The best way to integrate XRT and chemotherapy in patients who are to receive both is not yet well defined. The two modalities have been given concurrently,

sequentially, or in a sandwich fashion (i.e., chemotherapy both prior to and after XRT). Often all or a portion of chemotherapy is given initially.

- Megavoltage XRT is recommended to the whole breast using tangential fields (without bolus) treating to a dose of 4500 to 5000 cGy (180 to 200 cGy per fraction) over a 4 1/2 to 5 1/2 week period. This is usually followed by a boost of XRT to the area of the excisional biopsy for an additional 1000 to 2000 cGy. Omission of the boost has been shown to increase the risk of local recurrence, even in patients with negative margins.
- Placement of surgical clips within the excisional biopsy site is encouraged in order to aid in improving XRT portal localization.
- Regional (lymph node) radiotherapy is sometimes performed after breast conserving surgery including a level I/level II axillary lymph node dissection. Regional radiotherapy is controversial but frequently considered for patients with advanced primary disease, positive axillary lymph nodes, a positive high axillary lymph node, extranodal disease extension, or a large axillary lymph node, or if fewer than 6 lymph nodes were removed from the axilla without the aid of SLNB. When done, regional XRT may include the supraclavicular, axillary, and internal mammary area. If regional radiotherapy is given to the supraclavicular, axillary or internal mammary areas, a dose of 4500 to 5000 cGy over a 4-1/2 to 5-1/2 week period is recommended. Special care must be taken where these fields abut one another and the tangential breast fields. In the instance where a separate internal mammary field is used, a portion of the course should be given with an electron beam. When using deep tangential fields to treat the breast and internal mammary area, care must be taken to limit the amount of heart and lung within the fields.
- Partial breast irradiation is still experimental and has not been shown to be more beneficial than whole breast radiation therapy.

Post-Mastectomy Radiation Therapy

If a patient is on a protocol which requires post-mastectomy XRT, the XRT should be delivered according to the protocol specifics. Otherwise the following recommendations are made.

- Concerning the integration of post-mastectomy XRT and chemotherapy, a specific sequencing recommendation cannot be made. The two modalities have been combined in a number of ways, although often all or a portion of chemotherapy is given initially.
- Megavoltage XRT with a tangential field setup or an electron beam technique is recommended for treatment of the chest wall region itself to a total dose of 4500 to 5000 cGy (180 to 200 cGy per fraction) over a 4-1/2 to 5-1/2 week period. A boost of 1000 to 1500 cGy to the area of the primary site and/or chest wall scar region is also often performed. XRT should be delivered so as to minimize areas of dose nonuniformity within the treatment volume (e.g., use of appropriate energies, wedges, compensators, and tissue bolus) and the volume of lung and heart receiving a significant dose of radiation.
- In addition to chest wall, XRT to the supraclavicular area is usually performed. Consideration must also be given to the need for axillary

and internal mammary XRT. The total dose delivered to the regional lymph node areas is approximately 4500 to 5000 cGy over a 4-1/2 to 5-1/2 week period. Special care must be taken in matching the supraclavicular field with the tangential or electron beam chest wall fields. The internal mammary field should be given with at least a portion using an electron beam. In addition, if using deep tangential fields to treat the chest wall and internal mammary area, care must be taken to limit the amount of heart and lung within the fields.

Evidence supporting this recommendation is of classes: A, B, C, D, M, R

32. Follow-up Protocol

Key Points:

- This guideline for follow-up refers only to the asymptomatic patient.
- New or persistent symptoms must be evaluated using whatever diagnostic studies are appropriate.
- Routine radiologic (other than mammogram) and laboratory studies have not been proven to be beneficial.

- Use of chest x-rays, serum chemistries, bone scans, and soluble tumor markers are not indicated for the routine follow-up.
- Patients should be followed with yearly mammography.
- Clinical breast examination should be performed every 4 to 6 months for 5 years and then annually.

[Conclusion Grade I: See Conclusion Grading Worksheet – Appendix A--Annotation #32 (Stage II)]

Patients taking tamoxifen should have annual eye exams due to increased risk of cataracts and annual pelvic exams in patients with a uterus due to increased risk of endometrial and carcinoma. The routine use of transvaginal ultrasound or endometrial biopsy in the absence of symptoms is not supported by data. A baseline bone density should be considered for patients taking aromatase inhibitors and thereafter as indicated, due to an increased risk of osteoporosis.

Evidence supporting this recommendation is of classes: A, B, R

Definitions:

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Nonrandomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

Conclusion Grades:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results of different studies or because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

CLINICAL ALGORITHM(S)

Detailed and annotated clinical algorithms are provided for:

- Main Treatment Algorithm
- Stage 0 Post-Surgical Treatment Algorithm
- Stage I Post-Surgical Treatment Algorithm
- Stage II or III Post-Surgical Treatment Algorithm

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The guideline contains an annotated bibliography and discussion of the evidence supporting each recommendation. The type of supporting evidence is classified for selected recommendations (see "Major Recommendations").

In addition, key conclusions contained in the Work Group's algorithm are supported by a grading worksheet that summarizes the important studies pertaining to the conclusion. The type and quality of the evidence supporting these key recommendations (i.e., choice among alternative therapeutic approaches) is graded for each study.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Guideline implementation will help clinicians provide the best possible evaluation and treatment of patients with the diagnosis of breast cancer (ductal carcinoma in situ, stage 0, I, II or III invasive breast carcinoma).
- Breast conservation therapy is an appropriate method of primary therapy for the majority of women with stage I, II, or III breast cancer and is preferable because it provides survival equivalent to total mastectomy and axillary dissection while preserving the breast.

POTENTIAL HARMS

- Patients taking tamoxifen should have annual eye exams due to increased risk of cataracts and annual pelvic exams in patients with a uterus due to risk of endometrial carcinoma.
- A baseline bone density should be considered for patients taking aromatase inhibitors and thereafter as indicated due to an increased risk of osteoporosis.

CONTRAINDICATIONS

CONTRAINDICATIONS

Pregnancy and collagen vascular diseases, including lupus and scleroderma, are relative contraindications to Breast Conserving Treatment

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- These clinical guidelines are designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and are not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem.
- This clinical guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients are urged to consult a health care professional regarding their own situation and any specific medical questions they may have.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Once a guideline is approved for release, a member group can choose to concentrate on the implementation of that guideline. When four or more groups choose the same guideline to implement and they wish to collaborate with others, they form an action group.

In the action groups, each medical group sets specific goals they plan to achieve in improving patient care based on the particular guideline(s). Each medical group shares its experiences and supporting measurement results within the action group. This sharing facilitates a collaborative learning environment. Action group learnings are also documented and shared with interested medical groups within the collaborative.

Currently action groups may focus on one guideline or a set of guidelines such as hypertension, lipid treatment, and tobacco cessation.

Detailed measurement strategies are presented in the original guideline document to help close the gap between clinical practice and the guideline recommendations. Summaries of the measures are provided in the National Quality Measures Clearinghouse (NQMC).

IMPLEMENTATION TOOLS

Clinical Algorithm
Pocket Guide/Reference Cards
Quality Measures

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

RELATED NQMC MEASURES

- Breast cancer treatment: percentage of patients with Stage 0, I, II, or III breast cancer with documentation in their medical record that the option of a clinical trial has been discussed with them.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Breast cancer treatment. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2004 Sep. 41 p. [77 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1996 Sep (revised 2004 Sep)

GUIDELINE DEVELOPER(S)

Institute for Clinical Systems Improvement - Private Nonprofit Organization

GUIDELINE DEVELOPER COMMENT

Organizations participating in the Institute for Clinical Systems Improvement (ICSI): Affiliated Community Medical Centers, Allina Medical Clinic, Altru Health System, Aspen Medical Group, Avera Health, CentraCare, Columbia Park Medical Group, Community-University Health Care Center, Dakota Clinic, ENT Specialty Care, Fairview Health Services, Family HealthServices Minnesota, Family Practice Medical Center, Gateway Family Health Clinic, Gillette Children's Specialty Healthcare, Grand Itasca Clinic and Hospital, HealthEast Care System, HealthPartners Central Minnesota Clinics, HealthPartners Medical Group and Clinics, Hutchinson Area Health Care, Hutchinson Medical Center, Lakeview Clinic, Mayo Clinic, Mercy Hospital and Health Care Center, MeritCare, Mille Lacs Health System, Minnesota Gastroenterology, Montevideo Clinic, North Clinic, North Memorial Care System, North Suburban Family Physicians, Northwest Family Physicians, Olmsted Medical Center, Park Nicollet Health Services, Pilot City Health Center, Quello Clinic, Ridgeview Medical Center, River Falls Medical Clinic, Saint Mary's/Duluth Clinic Health System, St. Paul Heart Clinic, Sioux Valley Hospitals and Health System, Southside Community Health Services, Stillwater Medical Group, SuperiorHealth Medical Group, University of Minnesota Physicians, Winona Clinic, Ltd., Winona Health

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GUIDELINE COMMITTEE

Committee on Evidence-Based Practice

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

In the interest of full disclosure, Institute for Clinical Systems Improvement (ICSI) has adopted the policy of revealing relationships work group members have with companies that sell products or services that are relevant to this guideline topic. The reader should not assume that these financial interests will have an adverse impact on the content of the guideline, but they are noted here to fully inform readers. Readers of the guideline may assume that only work group members listed below have potential conflicts of interest to disclose.

No work group members have potential conflicts of interest to disclose.

ICSI's conflict of interest policy and procedures are available for review on ICSI's website at www.icsi.org.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Institute for Clinical Systems Improvement (ICSI). Breast cancer treatment. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2003 Jan. 45 p.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- ICSI pocket guidelines. April 2004 edition. Bloomington (MN): Institute for Clinical Systems Improvement, 2004. 404 p.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on July 10, 2000. The information was verified by the guideline developer on April 25, 2001. This summary was updated

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