

CLINICAL THERAPEUTICS

Radiation Therapy for Early-Stage Breast Cancer after Breast-Conserving Surgery

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This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.

A 45-year-old woman with a family history of postmenopausal breast cancer (in a maternal aunt) discovers a mass in the upper outer quadrant of her left breast. A mammogram reveals a spiculated density considered suspicious for cancer, and a core biopsy of the lesion reveals a high-grade infiltrating ductal carcinoma that is negative for estrogen and progesterone receptors and for HER2/neu. A lumpectomy and dissection of the sentinel lymph nodes are performed. Pathological evaluation reveals a 1.5-cm infiltrating ductal carcinoma with 3-mm disease-free surgical margins and two negative sentinel lymph nodes. After undergoing 6 months of adjuvant chemotherapy, the patient is referred to a radiation oncologist, who recommends irradiation of the left breast.

THE CLINICAL PROBLEM

Breast cancer remains the most common nondermatologic cancer among women in the United States. In 2008, more than 250,000 new cases were expected to be diagnosed, including 184,000 cases of invasive disease and 68,000 cases of in situ (non-invasive) disease.^{1,2} Risk factors for breast cancer include female sex, increasing age, a family history of the disease, inherited germ-line mutations in tumor-suppressor genes (e.g., *BRCA1*, *BRCA2*, and *p53*), nulliparity or late age at first pregnancy, regular alcohol use, and use of hormone-replacement therapy.^{1,3-8}

Although breast cancer remains the second most common cause of cancer-related death among women, the annual rate of death from breast cancer has decreased steadily since 1990.^{1,2} This decrease is thought to have resulted from improvements in treatment and increased use of screening, resulting in early detection. Most women in whom breast cancer is diagnosed in the United States will be cured. The National Cancer Institute estimated that in 2004, approximately 2.4 million women with a history of breast cancer were alive.^{1,9} The number was probably even higher in 2008.

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

Most breast cancers originate in ductal or lobular epithelial cells and are a consequence of a series of genetic events that result in aberrant regulation of cell cycling, inhibition of normal apoptotic responses, and development of the ability to invade surrounding tissues and to form a blood supply (angiogenesis).¹⁰ Several genes and signaling pathways have been implicated in the development of breast cancer, among them germ-line or somatic mutations in tumor-suppressor genes (e.g., *BRCA1*, *BRCA2*, *p53*, and *PTEN*), disruptions in estrogen receptor-related signaling pathways, and amplification or overexpression of proto-oncogenes such as *HER2/neu*.¹¹

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Histologically, invasive breast cancer is defined by the infiltration of malignant cells through the ductal or lobular basement membrane (Fig. 1). The infiltrative nature of the disease and the complex, three-dimensional structure of the breast ductal system often preclude accurate assessment of the extent of the malignant process. Breast cancer can also be multifocal, appearing in different noncon-

tiguous regions of the breast.^{12,13} Consequently, 30 to 40% of women who undergo successful surgical resection of the gross tumor mass, with surgical margins negative for disease, will still have residual microscopic disease that if left untreated can develop into recurrent disease.^{14,15}

Radiation therapy has been shown to minimize the risk of local recurrence after lumpectomy. Ra-

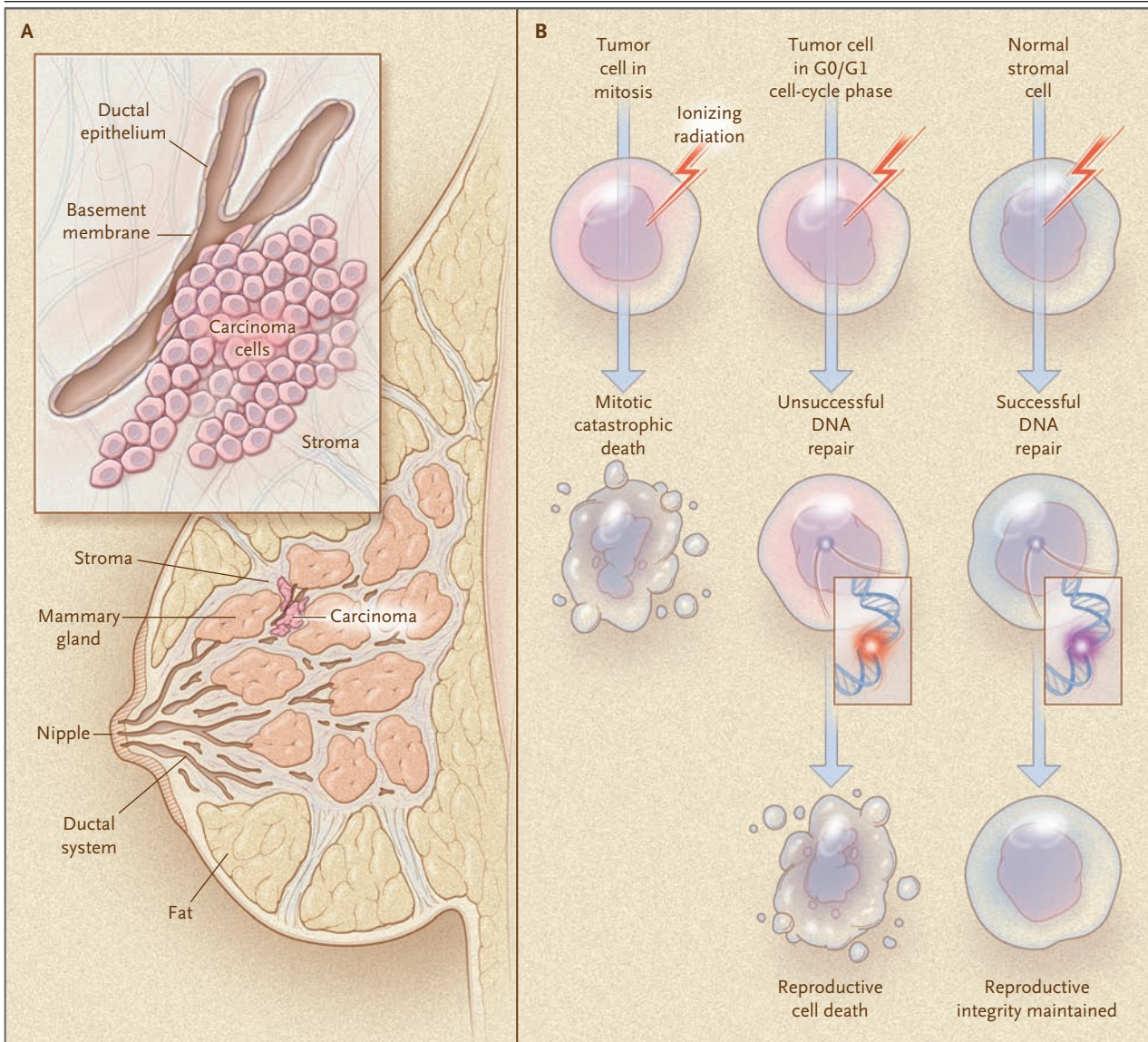


Figure 1. Infiltrating Ductal Carcinoma and Biologic Effects of Radiation Therapy.

Panel A shows a cancer in the upper outer quadrant of the left breast. The carcinoma cells originated in the ductal epithelium and invaded through the basement membrane into the breast stroma. Panel B shows biologic effects of ionizing radiation on the tumor cells and on a normal stromal cell. Radiation damages double-strand DNA, resulting in catastrophic cell death for the tumor cell in mitosis. The tumor cell in a G0/G1 cell-cycle phase does not immediately die, but the lack of successful repair of the DNA injury and aberrant cell-cycle checkpoints eventually lead to reproductive cell death. The normal cell is able to arrest the cell cycle and successfully repair the DNA injury, thus maintaining its reproductive integrity.

diation kills cells largely through the generation of free radicals, which deposit large amounts of energy that cause single- and double-strand breaks in the cell's DNA. The biologic goal of radiation treatment is to kill tumor cells selectively, without injuring normal tissue in the field. As a general rule, tumors are less able to repair DNA damage than are normal tissues and more frequently are in radiosensitive cell-cycle phases, such as mitosis. Division of the radiation dose into a number of treatment fractions provides two important biologic advantages: it allows DNA repair to take place within the normal tissues and allows proliferating tumor cells to redistribute through the cell cycle and move into the more radiosensitive phases (Fig. 1).

CLINICAL EVIDENCE

One of the first randomized studies conducted in the United States to evaluate breast irradiation after lumpectomy for early-stage invasive breast cancer began in the 1970s. The 20-year rate of local recurrence was reduced from 39% without radiation therapy to 14% with radiation therapy.¹⁴ The next generation of trials investigated whether radiation therapy could safely be omitted for selected patients with specific favorable treatment and disease characteristics. Unfortunately, most of these trials were unsuccessful in that radiation therapy continued to provide a significant benefit, both statistically and clinically.^{14,16-21}

A meta-analysis that was conducted by the Early Breast Cancer Trialists' Collaborative Group investigating data from 7300 women enrolled in breast-conservation trials again confirmed that breast irradiation substantially reduced the rates of local recurrence.¹⁵ This analysis also demonstrated that the use of radiation therapy decreased the 15-year risk of dying from breast cancer from 31% to 26% for patients with negative lymph nodes and from 55% to 48% for patients with positive lymph nodes. This group also analyzed findings from trials comparing breast-conserving therapy with mastectomy and found that the two approaches provided equivalent disease-free and overall survival.¹⁵

The outcome for patients who are treated with breast-conserving surgery has continued to improve, and the risk of local recurrence is now less than that reported in the initial clinical studies. For example, the probability of local recurrence for patients with lymph node–negative breast cancer

who received locoregional and systemic treatments has decreased to a rate of 0.5% per year.²²⁻²⁴

CLINICAL USE

Breast-conserving surgery was initially undertaken to minimize the physical and psychological consequences associated with removal of a breast. Efforts to combine breast-conserving surgery and breast irradiation evolved to address the concern that a less extensive surgical procedure would increase the risk of local recurrence. The efficacy of this approach was confirmed in the above-mentioned trials, and the combination of breast-conserving surgery and irradiation is now accepted as a locoregional treatment alternative to mastectomy for women with early-stage breast cancer.

Treatment of breast cancer ideally requires a multidisciplinary approach. For most patients with invasive breast cancer, the recommended treatment is surgical resection of the primary tumor with assessment of axillary lymph nodes; adjuvant systemic treatment with chemotherapy, hormonal therapy, or both; and adjuvant radiation therapy. Sequential treatment with these approaches typically requires 9 months. The goal is to offer the highest probability of disease eradication and cure while simultaneously allowing a return to a normal quality of life.

Breast irradiation is indicated for most patients who undergo breast-conserving surgery for invasive disease (Table 1). The one subgroup of patients for whom breast-conserving surgery without radiation can be considered an appropriate option is women who are at least 70 years of age who are treated with surgery and hormonal therapy for estrogen receptor–positive stage I breast cancer. In this cohort, the risk of local recurrence without radiation therapy is less than 10%.^{19,25,26}

Since some diseases, such as scleroderma and systemic lupus erythematosus, may increase the risk of irradiation injury in normal tissue, patients with these diseases are not ideal candidates for breast irradiation.²⁷ Radiation therapy should also be avoided in patients who are pregnant, particularly during the first trimester, when significant teratogenic effects from radiation are possible.²⁸ Finally, breast irradiation should be avoided in patients with previous cancer histories who received radiation therapy that included a portion of the affected breast. For example, many survivors of Hodgkin's disease underwent breast irradiation during treatment of mediastinal and axillary lymph

Table 1. Indications for Radiation Therapy and Treatment Volume after Breast-Conserving Surgery, According to Disease Stage.

Disease Stage	Indications for Radiation Therapy and Treatment Volume
Noninvasive breast cancer	
Lobular carcinoma in situ	Radiation therapy is not indicated.
Ductal carcinoma in situ	Irradiation of the ipsilateral breast is indicated for all patients treated with breast-conserving surgery (lumpectomy), with the possible exception of those with small foci of low-grade disease resected with wide disease-free surgical margins.
Early-stage (T1–T2) invasive disease	
Lymph-node–negative	Irradiation of the ipsilateral breast is indicated for all patients treated with breast-conserving surgery, with the possible exception of patients 70 years of age or older who also receive adjuvant hormonal therapy.
Lymph-node–positive	Irradiation of the ipsilateral breast is indicated for all patients treated with breast-conserving surgery. Irradiation of regional undissected lymph nodes is indicated for all patients with four or more positive lymph nodes and for selected patients with one to three positive lymph nodes.

nodes. These considerations may influence the decision to have breast-conserving surgery and should be taken into account during planning of the initial surgical therapy.

Radiation therapy typically begins 4 to 6 weeks after surgery or the completion of chemotherapy. For patients undergoing breast-conserving surgery, the most common targeted volume is the entire ipsilateral breast. Radiation therapy is also effective for treating regional lymph nodes that may contain microscopic disease; such treatment is typically reserved for patients with lymph node–positive cancer.

The planning of radiation treatment begins with a simulation session. A custom-molded immobilization cradle is created for each patient, with the goal of ensuring consistent positioning during the treatment sessions. Most commonly, patients are supine with their torso angled up 10 to 15 degrees and the ipsilateral arm abducted 100 to 120 degrees and the shoulder externally rotated (Fig. 2). Radioopaque wires are taped to the skin to delineate the anatomic boundaries of the breast and the lumpectomy scar, and computed tomographic (CT) simulation scans are obtained. The radiation oncologist then identifies an isocenter, which is a point in the treatment field that serves as the center of the axis of rotation of the treatment machine. This point and other setup indicators are then marked on the patient's breast with ink.

The treatment fields are then designed on the CT-simulation data set with the aid of virtual reality-type techniques. The goal of field design is

to include the targeted regions while avoiding normal structures, such as the heart and lungs. The width, length, and depth of the treatment fields are determined, and the optimal beam entrance angles are verified in the axial, coronal, and parasagittal planes. Optimal beam arrangements for breast treatment typically consist of two opposing beams that tangentially cross the ipsilateral anterior thorax and minimize the volume of lung in the field (Fig. 2).

Once the beam angles are determined, radiation oncologists, dosimetrists, and physicists work together to optimize the distribution of the radiation dose within the three-dimensional treatment volume. The anatomic shape of the breast and variations in tissue density within the field result in some areas within the breast receiving more than the prescribed dose (“hot spots”) and others less than the intended dose (“cold spots”). Treatment machines now allow for the modulation of beam intensity, which selectively blocks hot spots and supplements the dose to cold spots, resulting in more homogeneous radiation-dose distributions. Randomized trials have shown that these advances improve the homogeneity of dose distributions and minimize side effects and injury to normal tissue.^{29–31}

Once the treatment-planning process is completed (1 to 3 days after the simulation session), the daily treatments begin. Each day, the patient is positioned in the cradle, the field measurements are set, and positioning is checked with measurement tools, external marking of the field borders on the skin, and weekly film verification. Patients

are typically in the radiation-therapy room 15 minutes each day, during which the beam is on for 3 to 5 minutes. Treatments are given Monday through Friday, with weekends and holidays off. The first 25 to 28 daily sessions treat the ipsilateral breast to a dose of 45 to 50 Gy, after which the treatment volume is reduced to the tumor-bed region and treatments are continued for an additional 10 to 16 Gy delivered over 1 week.

During the course of treatment, the patient sees the radiation oncologist in clinic every week. These brief visits allow the radiation oncologist to monitor side effects, perform quality-assurance checks, and answer questions. It is very uncommon for patients to have an interruption in their radiation therapy because of side effects. Breaks in the treatment schedule should be avoided whenever possible, because delays can adversely affect efficacy.

Radiation oncologists typically see patients in follow-up 3 to 6 months after the completion of therapy to ensure that any side effects have resolved. After the resolution of short-term effects of treatment, long-term follow-up by a member of the multidisciplinary breast-cancer team is indicated to monitor for development of local recurrence or a new primary tumor in the breast.

The sophisticated techniques that are associated with optimal radiation therapy make such treatments expensive. The costs associated with a 6-week course of treatment can range from \$25,000 to \$50,000, depending on the specifics of the case.

ADVERSE EFFECTS

During radiation therapy, most patients have some degree of treatment-related fatigue, which varies in severity among patients. Many patients can continue to work full-time during their course of radiation therapy, whereas treatment-associated fatigue requires others to scale back their work schedule.

The other common short-term reaction involves the skin within the irradiated volume, which typically becomes dry and erythematous. This often leads to symptoms of pruritus and tenderness. A temporary breakdown of the skin in the inframammary sulcus or axilla develops by the end of treatment in 25 to 30% of patients.³⁰ When this occurs, new skin forms over the area of desquamation within 5 to 10 days. Topical therapies have not been shown to decrease the duration or severity of desquamation.³² The breast remains ten-

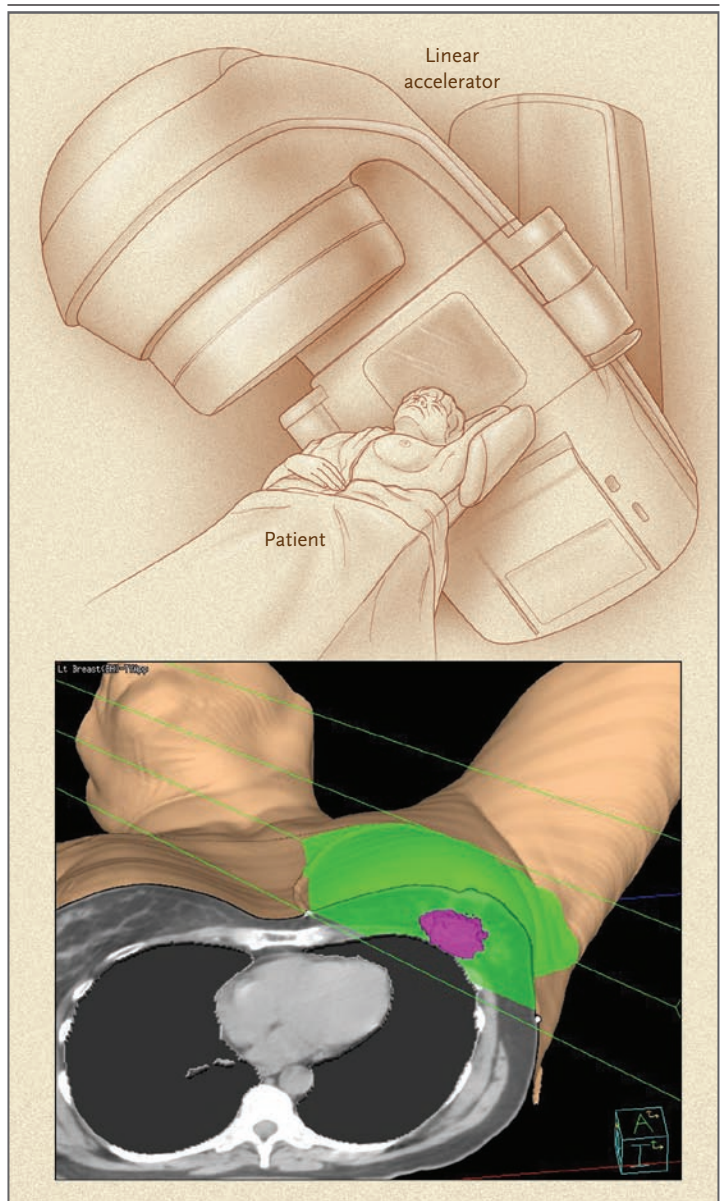


Figure 2. Radiation Treatment of Cancer in the Left Breast.

Radiation treatments are given from linear accelerators and typically use medial and lateral opposed tangential fields that obliquely cross the anterior or chest wall. Computed tomographic planning of treatment ensures that the heart is outside the radiation field and the included lung volume is minimal. Each treatment plan is customized for the individual patient.

der to palpation and the skin remains hyperpigmented for 6 to 9 months after treatment but then returns to normal.

The most common permanent effects on normal tissue are minor changes in the aesthetic appearance of the breast resulting from volume loss, fibrosis, or retraction at the tumor-bed site. Approximately 20 to 30% of patients who undergo

breast-conserving surgery and radiation therapy have less than a good or excellent aesthetic result as a consequence of locoregional therapy.³³⁻³⁵

The most serious potential late complications of radiation therapy are injury to the lungs and heart and the risk of inducing secondary cancers, such as sarcoma, lung cancer, and contralateral breast cancer. Early studies of radiation therapy in patients with breast cancer demonstrated that inclusion of the left ventricle in the high-dose region increased the long-term risk of death from cardiovascular disease.¹⁵ For example, in one study, for patients who had undergone breast-conserving surgery and radiation therapy, the risk of death from cardiovascular disease during 10 to 20 years of follow-up was 6.4% for those treated for a cancer in the left breast, as compared with 3.6% for those treated for a cancer in the right breast.³⁶

Improvements in radiation equipment and techniques have helped reduce these risks.³⁷ One way to avoid cardiac injury is to keep the heart outside the treatment field, which can be done with CT treatment planning. When the tumor bed is in the lower quadrants of the left breast and thus near the heart, therapy can be gated so that radiation is delivered only during periods of deep inspiration, when the diaphragm moves the heart in a medial and caudal direction relative to the left breast. Given the very low incidence of cardiac or pulmonary complications after treatment with current techniques, routine monitoring for toxic effects is not recommended.

Current techniques also minimize the small carcinogenic risks associated with radiation therapy by reducing the volume of normal tissue within the treatment fields and reducing the dose from scatter radiation to the contralateral breast.³⁸ The overall risk of a radiation-induced second cancer is approximately 1 to 2%.¹⁵

AREAS OF UNCERTAINTY

The protracted course of radiation therapy is inconvenient for patients, particularly for those who have to travel a substantial distance for daily treatment. To address this concern, investigators in the United Kingdom and Canada have conducted clinical trials comparing treatment over 3 weeks rather than 5 weeks. Initial results of these trials, which included mostly elderly patients with stage I disease, have been promising.^{35,39}

A second strategy to shorten the therapy course is to treat only the tumor-bed region of the af-

ected breast. Theoretically, treatment of a smaller volume of normal breast tissue should allow a larger dose of radiation to be given with each fraction without risking a higher rate of complications in normal tissue. In the United States, this technique, called accelerated partial-breast irradiation, has been delivered with double-plane or balloon-based radioactive implants and through conformal three-dimensional external-beam treatment. The most common treatment schedule involves 10 treatment sessions given over a 5-day period. Some treatment centers are investigating another approach that delivers the entire radiation dose intraoperatively, during the surgical resection of the primary tumor.

Thousands of patients with early-stage breast cancer have received accelerated partial-breast irradiation as a component of breast-conserving therapy. However, this technique remains investigational until information on its long-term efficacy and safety becomes available from clinical trials. In the United States, a large phase 3, randomized trial comparing accelerated partial-breast irradiation with conventional whole-breast radiation is ongoing. A number of other trials comparing various partial-breast irradiation strategies with whole-breast irradiation are being conducted in other areas of the world.⁴⁰

GUIDELINES

Guidelines concerning the use of radiation therapy for breast cancer have been established by the National Comprehensive Cancer Network and the American College of Radiology. Evidence from phase 3 trials has led both organizations to recommend breast-conserving therapy with whole-breast irradiation as an appropriate treatment option for patients with early-stage disease.^{41,42} The one subgroup of patients who can be offered breast-conserving therapy without irradiation as the standard of care are those who are at least 70 years of age who have stage I, estrogen receptor-positive disease treated with adjuvant hormonal therapy.

RECOMMENDATIONS

The patient described in the vignette is an excellent candidate for breast-conserving therapy, and I agree with the surgical choice of lumpectomy and dissection of the sentinel lymph nodes. Approximately 30% of patients with breast cancer have a

family history of the disease, and having such a family history does not usually adversely affect the outcome of breast-conserving therapy.^{43,44} The patient also has a biologically aggressive breast-cancer phenotype that lacks expression of the estrogen and progesterone receptors and HER2/neu ("triple negative" disease). However, patients with triple negative disease can still have an excellent outcome with breast-conserving surgery and whole-breast irradiation.^{45,46}

During the lumpectomy, the surgeon should orient the specimen for pathological examination and have the pathologist mark the specimen with ink for a final assessment of the surgical margins. Ideally, the surgery would also include the placement of radioopaque clips to mark the tumor bed to facilitate subsequent planning of radiation therapy. I also agree with the use of adjuvant chemotherapy, because evidence from clinical trials indicates that such therapy reduces the risk of distant metastasis.⁴⁷

After the patient completes systemic therapy, I would recommend that she undergo whole-breast irradiation to a total dose of 50 Gy, delivered in 25 fractions over 5 weeks, followed by a "boost" dose to the tumor bed of 10 to 16 Gy, delivered in 5 to 8 fractions over 1 week. Particular care should be taken to keep the heart completely outside the radiation fields to minimize the risk of long-term cardiovascular effects. Dose homogeneity within the treatment field should be optimized by modulating the intensity of the radiation beams to minimize skin reactions and optimize the cosmetic outcome. With this therapeutic approach, the patient has an excellent long-term prognosis and should be expected to return quickly to her normal quality of life after completing the treatment.

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