Original Study

Hypofractionated Breast Radiation: Shorter Scheme, Lower Toxicity

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Abstract

The standard radiation treatment times for breast cancer range from 5 to 7 weeks. However, a shorter treatment scheme is both safe and equally beneficial, allowing, among other advantages, for fewer treatment delays. Our study included a large sample of patients and a long follow-up period, allowing us to properly evaluate the incidence of late toxicities and cosmetic outcomes. Our data show excellent results.

Background: We analyzed the toxicity and cosmetic outcomes for patients who had undergone 3-dimensional conformal radiotherapy with a hypofractionated schedule and identified the risk factors associated with such a schedule. **Materials and Methods:** A total of 143 patients were treated for breast cancer (stage 0-III) with a hypofractionated radiation schedule after breast-conserving surgery from 2006 to 2011. Most patients received 42.4 Gy in 16 daily fractions, 2.65 Gy per fraction to the whole breast plus an additional simultaneous integrated or sequential boost to the tumor bed. **Results:** The median follow-up period was 36 months. Mild acute skin toxicity was observed in 62%; 7% of the patients developed moderate skin toxicity, but no grade 4 toxicity was observed. The prevalence of fibrosis within the boost area was 5%, but no grade ≥ 2 was observed. The prevalence of fibrosis of any grade was greater in the nonboost (23%) than in the boost area. Of all the patients, 91% had good or excellent cosmetic outcomes. From the multivariate analysis, the incidence of epithelitis correlated with the patient's treated volume ($P = .044$). The incidence of acute toxicity correlated with the boost type to the tumor bed and the total treatment dose ($P = .012$ and $P = .002$, respectively). Also, a poor to fair cosmetic outcome was significantly associated statistically with the surgery type ($P = .05$), boost type ($P = .004$), and total dose ($P = .001$). **Conclusion:** Delivering whole-breast irradiation with a hypofractionated schedule of 42.4 Gy plus a simultaneous integrated boost to the tumor bed appears to be a safe and effective technique, with good cosmetic results and lower toxicity.

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Introduction

Radiotherapy (RT) after breast-conserving surgery (BCS) in early-stage breast cancer has been demonstrated to be equivalent in terms of overall survival, local control, and disease-free survival rates compared with mastectomy.[1-10] The Early Breast Cancer Trialists' Collaborative Group meta-analysis has confirmed that breast irradiation after BCS substantially reduces the 5-year local recurrence rate from 26% to 7%.[1]

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The usually recommended radiation dose is 50 Gy to the whole breast in 25 daily fractions of 2 Gy over 5 weeks, with a boost of 10 to 16 Gy to the tumor bed.[1-9] This long RT schedule has many disadvantages, including delays in treatment initiation, increased total treatment costs from the larger number of fractions, and increased patient discomfort and inconvenience because of the greater number of hospital visits to complete treatment. All these problems have resulted in many centers developing a hypofractionated schedule to optimize resources. Thus, clinical and theoretical evidence has shown that a small increase in the dose per fraction, together with a decrease in the total administered dose, will be as effective as a traditional scheme. This is in agreement with the hypothesis regarding the potential benefit of hypofractionation in tumors with a low α/β ratio.[10-12]

The schedules used in studies of hypofractionated breast RT have ranged from 40 to 44 Gy in 15 to 16 fractions during a 3-week period, with daily fractions of 2.5 to 2.7 Gy.[11,13-16] The results

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from these studies showed low recurrence rates and good cosmesis.[17-19] Four large recent randomized trials have confirmed the equivalence between hypofractionated RT and conventional RT in terms of local recurrence and cosmetic outcomes.[10,11,20,21]

A 3-dimensional conformal RT with a simultaneous integrated boost (3D-CRT-SIB) technique can be applied as a part of breast-conserving therapy. In 3D-CRT-SIB, the breast and boost beams are combined into 1 integrated treatment plan and given simultaneously. The advantages of 3D-CRT-SIB, compared with the conventional sequential boost technique, are an increase in dose homogeneity (with less unintended excessive dose outside the boost area) and a higher dose per fraction to the tumor bed, resulting in a shorter overall treatment time.[22]

The aims of the present study were to evaluate the incidence of acute and late toxicity and the cosmetic outcomes in a series of patients with breast cancer who underwent hypofractionated RT. We also analyzed the correlation with the clinical outcomes.

Materials and Methods

The present study included 143 women who underwent RT after BCS. All patients underwent RT at the radiation oncology department of the Virgen de las Nieves University Hospital from January 1, 2006 to December 31, 2011. The inclusion criteria were BCS for stage pT1-T3, pN0-N3, M0, age $\geq$ 50 years, invasive or ductal carcinoma in situ, tumor margin $\geq$ 1 mm, no immediate reconstruction, and neoadjuvant or adjuvant chemotherapy required. Patients with a history of connective tissue disease previously treated with RT or who had undergone mastectomy were excluded.

We used a standard follow-up program after RT, with examinations every 3 months for the first 2 years, every 6 months from 2 to 5 years, and annually thereafter. The tumor, toxicity, and cosmetic results were prospectively collected, with last follow-up examination on June 31, 2014. Acute and late toxicities were assessed clinically using the Common Terminology Criteria for Adverse Event, version 4.[23] Late toxicity was defined as toxicity from 6 months after the end of RT and thereafter.

Cosmesis was evaluated using a 4-point scale, ranging from a poor to excellent global cosmetic result, comparing the treated and untreated breast.[24] The variables for cosmesis were skin toxicity, hyper- and hypopigmentation, grade of fibrosis in the nonboost area, grade of fibrosis in the boost area, grade of telangiectasia, grade of breast edema, and the cosmetic outcome using the 4-point scale. The independent variables in the analysis were the tumor size, breast size, repeat resection rate, axillary clearance rate, chemotherapy use, regional RT, radiation dose to the whole breast, and boost dose to the tumor bed.

We studied the relationships among the different parameters. For the cosmetic outcomes (classified into 2 groups: good to excellent and poor to fair), toxicity (yes or no), and epithelitis (grade $<$ 3 vs. $\geq$ 3), we analyzed the influence of surgery (lumpectomy vs. quadrantectomy), axillary dissection (yes, sentinel node only, no dissection), breast size (normotrophic or hypotrophic vs. hypertrophic), RT boost type (simultaneous integrated, nonconcomitant, or none), radiation dose (42.4 Gy vs. other treatment schedules), RT volume (breast only vs. breast plus regional lymph nodes), systemic treatment (chemotherapy, hormonal therapy, or combined systemic treatment), and chemotherapy (neoadjuvant, adjuvant, or none).

Surgery

The patients were treated with tumorectomy or quadrantectomy. In the case of more than focally involved resection margins, repeat resection was performed. Axillary staging was assessed using sentinel lymph node biopsy (SLNB). Axillary clearance was performed if the SLNB results were positive or the cytology results in clinically node-positive axillary lymph nodes were positive.

RT Protocol

RT was delivered using 3D-CRT to the whole breast with a boost dose to the tumor bed area. All patients were treated with opposing tangential fields in the supine position, arm above the head. Two opposing tangential beams were directed to the whole breast, prescribed to the isocenter or the appropriate isodose line. A hypofractionated SIB or sequential boost were given to most patients. The main fractionation scheme used was 16 daily fractions at 2.65 Gy per fraction, with a total dose of 42.4 Gy to the whole breast. For negative lumpectomy margins, we added a SIB of 0.48 Gy per fraction (7.7 Gy), for a total dose of 50.1 Gy to the tumor bed. If the margins were positive, we used a SIB of 0.75 Gy per fraction (12 Gy), for a total dose of 54.4 Gy to the tumor bed. In cases in which the sequential boost was used, corresponding doses of 10 Gy and 16 Gy at 2 Gy per fraction to the tumor bed were used. The boost dose was administered by 1 or 2 direct fields, depending on the size and location of the tumor bed. In high-risk patients, higher doses to the whole breast were administered.

Regional RT, including RT to the axillary and supraclavicular nodal areas, was performed for patients with $>$ 1 positive axillary lymph node or a single positive apical lymph node. A dose of 42.4 Gy at 2.65 Gy per fraction to the lymph node areas was administered using a combination of anteroposterior and posteroanterior fields and a monoisocentric split-field technique to protect both the spinal cord and the esophagus.

Systemic Therapy

Neoadjuvant systemic therapy was indicated for patients with large tumors to reduce the tumor size and perform BCS. Adjuvant systemic therapy was indicated for patients with node-positive disease and high-risk node-negative tumors. Patients were considered high risk according to the tumor size, tumor grade, hormonal receptor status, and age. The chemotherapy regimen was epirubicin and cyclophosphamide (EC), and, in patients with node-positive disease, EC was combined with taxane chemotherapy. Hormonal therapy, tamoxifen, or aromatase inhibitors, depending on menopausal status, were indicated for all patients with hormonal receptor-positive status. Trastuzumab was indicated for tumors overexpressing human epidermal growth factor receptor 2.

Ethical Approval

The provincial Biomedical Research Ethics Committee approved the study, which was been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All patients gave their informed consent before inclusion in the present study. Any details that might disclose the identity of the subjects included in the study have been omitted.