LUMPECTOMY PLUS TAMOXIFEN OR ANASTROZOLE WITH OR WITHOUT WHOLE BREAST IRRADIATION IN WOMEN WITH FAVORABLE EARLY BREAST CANCER

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Purpose: In women with favorable early breast cancer treated by lumpectomy plus tamoxifen or anastrozole, it remains unclear whether whole breast radiotherapy is beneficial.

Methods and Material: Between January 1996 and June 2004, the Austrian Breast and Colorectal Cancer Study Group (ABCSG) randomly assigned 869 women to receive breast radiotherapy (n = 414) or not (n = 417) after breast-conserving surgery (ABCSG Study 8A). Favorable early breast cancer was specified as tumor size <3 cm, Grading 1 or 2, negative lymph nodes, positive estrogen and/or progesterone receptor status, and manageable by breast-conserving surgery. Breast radiotherapy was performed after lumpectomy with 2 tangential opposed breast fields with mean 50 Gy, plus boost in 71% of patients with mean 10 Gy, in a median of 6 weeks. The primary endpoint was local relapse-free survival; further endpoints were contralateral breast cancer, distant metastases, and disease-free and overall survival. The median follow-up was 53.8 months.

Results: The mean age was 66 years. Overall, there were 21 local relapses, with 2 relapses in the radiotherapy group (5-y rate 0.4%) vs. 19 in the no-radiotherapy group (5.1%), respectively (p = 0.0001, hazard ratio 10.2). Overall relapses occurred in 30 patients, with 7 events in the radiotherapy group (5-y rate 2.1%) vs. 23 events in the no-radiotherapy group (6.1%) (p = 0.002, hazard ratio 3.5). No significant differences were found for distant metastases and overall survival.

Conclusion: Breast radiotherapy ± boost in women with favorable early breast cancer after lumpectomy combined with tamoxifen/anastrozole leads to a significant reduction in local and overall relapse. © 2007 Elsevier Inc.

Breast irradiation, Women with favorable early breast cancer, Lumpectomy plus hormone therapy with/without irradiation.

INTRODUCTION

In breast-conserving treatment, whole breast radiotherapy is in general recognized as being capable of significantly reducing local recurrence (1, 2) and is therefore considered a standard constituent of the interdisciplinary treatment regime for a vast majority of breast cancer patients. According to recent findings of the Early Breast Cancer Trialists’
Collaborative Group (EBCTCG), whole-breast radiotherapy applying modern techniques may even have an impact on long-term survival (3). However, because of logistic and economic burdens and adverse side effects associated with breast irradiation, there have been several attempts to identify a subgroup of patients who might not need radiotherapy to achieve an acceptable level of local control. Because adjuvant endocrine treatment not only improves disease-free survival but also provides local control, such a subgroup will most likely comprise endocrine-responsive disease. Selective estrogen receptor modulators, such as tamoxifen, have been proven to significantly reduce local breast recurrence (4, 5). More recently, third-generation aromatase inhibitors (e.g., anastrozole) have been tested against tamoxifen alone and have been shown to significantly reduce any disease recurrence and slightly improve overall survival (6–8).

In women with favorable early breast cancer (postmenopausal status, small-size tumors, lymph node-negative, Grade 1 and 2, hormone-responsive disease), it has been an issue of controversial debates whether patients benefit from additional whole-breast radiotherapy, in particular when adjuvant long-term hormonal treatment is applied.

More recently, randomized trials of women with favorable early breast cancer treated with tamoxifen for 5 y (20 mg/day) have demonstrated a significant effect on breast recurrence when whole-breast radiotherapy was applied (9), even in patients older than 70 years (10).

The role of switching from tamoxifen to anastrozole has been tested in a randomized trial conducted by the Austrian Breast and Colorectal Cancer Study Group (ABSG trial 8) and others (11), and the switch to anastrozole showed beneficial effects on event-free survival (6).

Within this trial of postmenopausal women treated with breast-conserving surgery and hormonal treatment including tamoxifen and anastrozole (50%), a favorable subgroup of patients with early disease was selected prospectively on the basis of a retrospective analysis of highly selected patients treated at Vienna General Hospital from 1983 to 1994 (12). This subgroup of patients with a very favorable risk profile was invited to participate in a randomized trial to evaluate whether whole-breast irradiation is still beneficial with regard to local relapse-free survival, disease-free survival, and overall survival.

METHODS AND MATERIALS

Patients

The ABSG trial 8A was a prospective, multicenter, randomized trial for a favorable subgroup of patients participating in ABSG-8 (6).

Between January 1996 and June 2004, 869 women were assigned to radiotherapy vs. no radiotherapy.

Eligible patients were postmenopausal women with histologically verified, locally radically treated invasive or minimally invasive breast cancer who had received no previous chemotherapy, hormone therapy, or radiotherapy.

Postmenopausal status was assumed for patients whose last menstruation took place at least 12 months before study entry, for those who had undergone bilateral ovariectomy, or those for whom follicle-stimulating hormone and luteinizing hormone concentrations indicated postmenopausal status. All patients had a tumor 3 cm or less in diameter, pathologic stage T1 or early T2, a G1 or G2 ductal carcinoma, or a Gx lobular tumor. Important inclusion criteria were the absence of both positive lymph nodes and organ metastases. All patients had endocrine-responsive tumors, with positive estrogen and/or positive progesterone receptors.

Thirty-eight women were ineligible (because of positive lymph nodes, tumor diameter >3 cm, nonbreast-conserving surgery, no preclusion of distant metastases, no R0 resection, proven existence of carcinoma before randomization, no informed consent, premenopausal status, or violation of other inclusion criteria).

The intention-to-treat analysis included 831 randomized patients.

Eligible patients were randomized into 2 groups (Table 1): the radiotherapy (RT) group (n = 414) receiving whole-breast radiotherapy ± boost to the tumor bed after surgery plus adjuvant hormone therapy, and the no-radiotherapy (no-RT) group (n = 417) given exclusively endocrine treatment post surgery. Seventeen women did not receive the treatment of the group into which they were randomized: 4 patients refused radiotherapy in the RT group and 13 patients received radiotherapy in the no-RT group.

All patients provided written informed consent. The study was approved by the relevant ethics committees in Austria.

Patient characteristics

Patients received a physical examination and were monitored for safety and tolerance. Monitoring took place at 3-monthly intervals throughout the first 3 years, at 6-monthly intervals in the fourth and fifth years, and yearly thereafter.

Gynecological examinations, chest wall radiographs, bone scintigraphy, and standard mammography were done as appropriate to identify the presence of disease recurrence.

Table 1. Trial profile

<table>
<thead>
<tr>
<th>Radiotherapy Group (RT) (n = 414)</th>
<th>No Radiotherapy Group (no RT) (n = 417)</th>
</tr>
</thead>
<tbody>
<tr>
<td>869 randomized women in ABSG trial 8A</td>
<td>38 ineligible</td>
</tr>
<tr>
<td>831 women included in Intention to treat analysis</td>
<td></td>
</tr>
<tr>
<td>Assigned to be treated with surgery, hormone therapy (tamoxifen/anastrozole) and radiotherapy</td>
<td>Assigned to be treated with surgery and hormone therapy (tamoxifen/anastrozole)</td>
</tr>
<tr>
<td>4 refused radiotherapy</td>
<td>13 received radiotherapy</td>
</tr>
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</table>

Abbreviation: ABSG = Austrian Breast and Colorectal Study Group.
Table 2. Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Radiotherapy group (414)</th>
<th>No Radiotherapy group (417)</th>
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</thead>
<tbody>
<tr>
<td>Age at diagnosis (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>9 (2)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>50–59</td>
<td>115 (28)</td>
<td>115 (28)</td>
</tr>
<tr>
<td>60–69</td>
<td>145 (35)</td>
<td>149 (36)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>145 (35)</td>
<td>148 (35)</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT1b</td>
<td>143 (35)</td>
<td>136 (33)</td>
</tr>
<tr>
<td>pT1c</td>
<td>228 (55)</td>
<td>246 (59)</td>
</tr>
<tr>
<td>pT2</td>
<td>43 (10)</td>
<td>35 (8)</td>
</tr>
<tr>
<td>Pathological grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>135 (33)</td>
<td>138 (33)</td>
</tr>
<tr>
<td>G2</td>
<td>257 (62)</td>
<td>259 (62)</td>
</tr>
<tr>
<td>Gx</td>
<td>22 (5)</td>
<td>20 (5)</td>
</tr>
<tr>
<td>Estrogen receptor status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+/+</td>
<td>252 (61)</td>
<td>278 (67)</td>
</tr>
<tr>
<td>++</td>
<td>156 (38)</td>
<td>134 (32)</td>
</tr>
<tr>
<td>Negative</td>
<td>6 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Progesterone receptor status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+/+</td>
<td>122 (29)</td>
<td>128 (31)</td>
</tr>
<tr>
<td>++</td>
<td>207 (50)</td>
<td>208 (50)</td>
</tr>
<tr>
<td>Negative</td>
<td>85 (21)</td>
<td>79 (19)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>2 (&lt;1)</td>
</tr>
</tbody>
</table>

The majority of women in both groups had a tumor stage pT1c and G2 disease (Table 2).

The treatment groups were well balanced in terms of age, tumor stage and grade, estrogen receptor and progesterone receptor status, and by the type of systemic therapy (RT/no-RT group: 50.5%/49.1% tamoxifen and 49.5%/50.9% anastrozole).

The mean age at the time of diagnosis was 65.7 years (RT group = 65.4, no-RT group = 66.1). The youngest patient was 46 years old, and the oldest was 80 years. All 831 eligible women were lymph node-negative.

Treatment

Surgery and hormone therapy. All women underwent breast-conserving surgery, lumpectomy or wide resection with appropriate margins (aim = 10 mm). Classical quadrantectomy was used only in occasional cases when R0 resection was not achievable otherwise.

Axillary lymph node dissection was performed, with a minimum of 10 lymph nodes removed as prerequisite for inclusion into the trial.

In 2001, an amendment of the study protocol was introduced, allowing for sentinel lymph node biopsy after extensive quality control in individual centers.

Invasive ductal carcinoma grade G1 or G2 and lobular tumors were the predominant pathohistological characteristics.

Surgery was followed by adjuvant hormone therapy for 5 years, which started within 6 weeks after surgery. After 2 years of adjuvant oral tamoxifen therapy (20 mg/day), the women who were randomly assigned (before the beginning of hormone therapy) switched to 1 mg anastrozole once daily for 3 years.

Radiotherapy. Radiotherapy to the whole breast was to be given within 6 weeks post surgery in the radiotherapy group. Three different options of irradiation were applied (Table 3): external beam whole-breast photon radiotherapy alone, external beam whole-breast photon radiotherapy plus electron, or the same plus iridium 192 boost. Whole-breast dose, boost dose, fractionation, and technique of radiotherapy were at the discretion of the participating center, which followed its traditional treatment schedule for adjuvant radiotherapy in this patient group.

The mean dose of whole-breast irradiation was 51 Gy (± 4 Gy), given in daily fractions to the breast and adjacent chest wall over a period of 39 days (±7 days). A parallel-opposed pair of tangential fields was treated daily, Monday to Friday, and photons or cobalt 60 gamma rays were used.

In 269 women, whole-breast radiotherapy was followed by an electron boost with a mean dose of 10 Gy (±2 Gy) to the tumor bed.

The target volume was determined on the basis of the preoperative mammogram, operative notes, clinical assessment and location of clips, if available.

Twenty women were treated with an iridium 192 boost of mean 9 Gy (±2 Gy) in high-dose-rate afterloading technique.

End points

The major end point was local relapse-free survival defined as time between randomization and occurrence of local relapse. Other points of interest were disease-free survival (defined as time between randomization and the first occurrence of local relapse or distant metastasis), overall survival (time between randomization and death of any cause), and incidence of contralateral breast cancer and distant metastasis, respectively.

Statistics

Randomization for the study was done centrally at the ABCSG randomization center in Vienna, Austria. Patients were allocated to the treatment groups according to the method of Pocock and Simon (13), stratifying for the following prognostic factors: age, tumor stage, tumor grade, treatment (tamoxifen or anastrozole), and participating centers grouped into federal states.

Analyses were by intention to treat. Additional sensitivity anal-

Table 3. Radiation dose, technique, and duration in RT group (n = 414)

<table>
<thead>
<tr>
<th></th>
<th>Mean dose</th>
<th>Mean overall treatment time</th>
</tr>
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<tbody>
<tr>
<td>Whole-breast radiotherapy alone (n = 118)</td>
<td>51 Gy (± 4 Gy)</td>
<td>39 d (± 7)</td>
</tr>
<tr>
<td>Whole-breast radiotherapy (plus boost) (n = 289)</td>
<td>50 Gy (± 2 Gy)</td>
<td>46 d (± 8)</td>
</tr>
<tr>
<td>Electron boost (n = 269)</td>
<td>10 Gy (± 2 Gy)</td>
<td>46 d (± 7)</td>
</tr>
<tr>
<td>Iridium 192 boost (HDR brachytherapy) (n = 20)</td>
<td>9 Gy (± 2 Gy)</td>
<td>43 d (± 9)</td>
</tr>
</tbody>
</table>

Abbreviations: HDR = high-dose-rate; RT = radiotherapy.
yses were performed by allocating patients to treatment groups (RT/no-RT) according to their actual treatment. Data are presented in absolute numbers, percentages, and Kaplan-Meier curves (14). Data were tested by log-rank tests (15, 16). Hazard ratios (HR) and their corresponding 95% confidence intervals (CI) were estimated by the proportional-hazards regression model of Cox (17).

All p values are two-sided, and a p value ≤ 0.05 was significant.

The ABCSG statistician analyzed all data using the statistical software package SAS (version 8.02; SAS Institute, Cary, NC).

Quality control: Because local relapse was the primary end point in this trial, the surgery and pathology reports of all patients suffering a local relapse were centrally reviewed by a pathologist and surgeon blinded for treatment allocation to assess the quality of primary treatment.

RESULTS

A total of 869 women were randomized in ABCSG trial 8A to either radiotherapy after lumpectomy and adjuvant hormone therapy or only lumpectomy and adjuvant hormone therapy.

The median follow-up was 53.8 months after randomization.

The results show a significant reduction in breast recurrence among the patients who received radiation. Two local relapses were observed in the RT group (414 women) compared with 19 in the no-RT group (417 women). One relapse in the RT group occurred after 104 months.

This corresponds to a hazard ration of 10.21 (95% CI, 2.38 – 43.84) with a p value of 0.0001 (Fig. 1).

Overall, 10 women presented with distant metastases, 5 in the RT group vs. 5 in the no-RT group.

With regard to disease-free survival, there were 7 events in the RT group vs. 23 events in the no-RT group (overall relapse). One woman presented with 2 events simultaneously, both local relapse and distant metastasis. The HR for disease-free survival is 3.48 (95%CI, 1.49 – 8.12) with a p value of 0.0021 (Fig. 2).

There were 2 women with contralateral breast cancer in the RT group vs. 5 in the no-RT group.

The 5-year survival rate (overall 96.2%) was slightly higher in patients who were treated with radiotherapy (97.9%) than in those who received lumpectomy and adjuvant hormone therapy alone (94.5%). There were 11 deaths in the RT group and 18 deaths in the no-RT group, respectively; the difference was not statistically significant (p = 0.18). In the RT and no-RT groups, 2 deaths occurred each after a preceding recurrence (total deaths = 4). There were 9 deaths in the RT group and 16 deaths in the no-RT group without preceding recurrence.

All results derived from the intention-to-treat analysis are robust with respect to patients who did not receive their randomized treatment. If such patients are allocated to treatment groups according to their actual treatment, results remain unchanged.

DISCUSSION

This trial demonstrates that the addition of radiotherapy to tamoxifen and/or anastrozole significantly reduces the rate of local relapse, even in this prognostically favorable group of women with early breast cancer characterized by postmenopausal status, hormone responsiveness, small tumor size, good differentiation, and negative lymph node
status. The estimated 5-year actuarial rate of 0.4%, after a median follow-up of 54 months, is to be considered as outcome of excellent local control and is significantly different from the rate of 5.1% for those without radiotherapy (Fig. 1). The trial thus failed to prospectively identify a subgroup of women with early breast cancer not benefiting from adjuvant radiotherapy.

Our overall results are comparable with 5-year actuarial local relapse rates as recently reported by Fyles et al. and Hughes et al., with 0.6% vs. 7.7% and 1% vs. 4% (9, 10). The patient selection criteria in both studies were comparable to our trial. However, there was a minimum age of 70 years in the trial reported by Hughes et al. (10).

Moreover, the large difference in local relapse rates translated into a significant difference in overall relapse rate at 5 years, with 2.1% vs. 6.1% in favor of the radiotherapy group (Fig. 2).

From the natural history of favorable breast cancer, a slow evolution of recurrent disease is well known (3). With longer follow-up, more recurrences will likely occur in both groups, with a somewhat higher probability for the group administered 5 years of hormonal treatment and then stopped (Fig. 1). Similar recurrence rates as observed during the first years of follow-up (1% vs. 0.1% per year) will probably occur during longer follow-up (3, 18). We do not yet know if the long-term difference (>5 years) will become larger, smaller, or will remain the same (compare Fig. 1). At present, our Kaplan-Meier estimates suggest that the difference in absolute numbers is growing with time: 0.4% vs. 9% at 6 years. This is in accordance with the estimates reported by Fyles et al. (3.5% vs. 17.6% at 8 years) (9), Hughes et al. (1% vs. 7% at 7 years) (10), and Fisher et al. (2.8% vs. 16.5% at 8 years) (5). Longer follow-up is needed before any solid conclusions can be drawn. It will be interesting to observe whether a “carry-over” effect of adjuvant therapy can be observed after the end of endocrine treatment.

On the other hand, subgroups may be defined with a very low rate of recurrence, even in the group of patients not receiving radiotherapy. At present, the additional key factors seem to be age and tumor size. However in clinical trial research, a prospective investigation requiring a very large number of patients in a very small subcohort of patients to detect a very small difference in local relapse rate may not prove feasible because it would call for an enormous number of participating centers over a very long time period.

The overall low risk of local relapse at 5 years (5.1%) in the surgery-alone group has to be discussed separately. First, it has to be stated that this local relapse rate is far lower than local relapse rates in historical randomized trials with 35% at 8 years (19) and 24% at 10 years (2). Selection of patients in these trials was less precise and hormonal status had not been included in the selection criteria. Furthermore, the results at 5 years in the surgery-alone group can be regarded as acceptable in terms of absolute numbers \((n = 19/417)\). It can be argued that the patients who have a local recurrence have a second chance to be cured because the majority can successfully be salvaged. These patients would then actually not have had major benefit from upfront radiotherapy, balancing advantages against disadvantages (e.g., logistics, side effects).

Clinical practice, reflecting everyday problems, may still be discussed as outweighing the advantages and drawbacks of radiotherapy on an individual basis. This is particularly
true for aging or frail patients. We were able to demonstrate that in the group without radiotherapy, 94.9% would not have had any benefit from radiotherapy at 5 years. However, for putting into practice such individual decision-based strategy on indication of radiotherapy, excellent surgical and histopathologic quality control is a precondition, which has to be integrated into an accurate assessment of the individual patient within multidisciplinary tumor boards.

Axillary recurrence was seen in 1 woman only (n = 1/417). Negative findings from axillary node dissection and sentinel-node biopsy, respectively (in recent years), were reported for all women. This underlines clearly that in this favorable group with proven negative findings in the axilla, there is no evident risk for recurrence, which was also reported by Hughes et al. (10).

There was no difference in distant metastases and no significant difference in overall survival. Such a difference can only be expected after long-term follow-up (e.g., at about 15 years), when local failure may then translate into overall failure as shown by the EBCTCG in their recent meta-analysis of breast-conserving treatment (3). However, this may also be questioned taking into account the low frequency of events observed until now and given that local relapse can be successfully salvaged and thus is frequently nonlethal.

In conclusion, for patients with favorable early breast cancer as addressed in this randomized trial, further evidence is provided to indicate that whole-breast radiotherapy remains the major integral part of adjuvant treatment in breast-conserving treatment, even if tamoxifen is replaced partly by aromatase inhibitors. It is a matter of future research, to investigate whether even more favorable subgroups can be prospectively defined, in whom radiotherapy is not beneficial, or whether whole-breast radiotherapy can be replaced by partial-breast irradiation, as currently investigated by different European and North American trial groups (20, 21).

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