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The impact of adjuvant radiotherapy on the survival of primary breast cancer patients: a retrospective multicenter cohort study of 8935 subjects†

A. Wöckel[1,‡], R. Wolters[2,†], T. Wiegel[3], I. Novopashenny[2], W. Janni[1], R. Kreienberg[1], M. Wischnewsky[2], L. Schwentner[1*] & for the BRENDA study group

[1]*Department of Gynecology and Obstetrics, University Ulm, Ulm;* [2]*Department of Mathematics and Computer Science, University Bremen, Bremen;* [3]*Department of Radiotherapy and Radiooncology, University Ulm, Ulm, Germany*

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Background: Radiotherapy (RT) is proven to be an important backbone for adjuvant therapy in randomized, controlled trials, but it is unclear if these effects are provable in a daily routine cohort of breast cancer patients. This study sought to answer the following questions in a daily routine cohort of breast cancer patients:
1. Does guideline-adherent RT improve primary breast cancer patient survival?
2. Is breast-conserving surgery (BCS) followed by RT equal to a mastectomy (MA) with regard to outcome parameters?
3. Does adjuvant RT compensate for an incomplete tumor resection (R1)?

Patients and methods: In this retrospective, multicenter cohort study, we investigated data from 8935 primary breast cancer patients recruited from 17 participating certified breast cancer centers in Germany between 1992 and 2008. Guideline adherence based on internationally validated guidelines.

Results: The patients who received guideline-adherent RT for primary breast cancer were associated with significantly improved survival parameters [recurrence-free survival (RFS): $P < 0.001$; overall survival (OS): $P < 0.001$] compared with patients who did not receive guideline-adherent adjuvant RT. Furthermore, the results demonstrated that there were no significant differences in RFS and OS between BCS followed by RT and MA [RFS: $P = 0.293$; OS: $P = 0.104$]. Adjuvant RT did not improve the outcome of patients receiving nonguideline-adherent incomplete tumor resection via BCS (R1); these patients showed a significantly impaired RFS [$P < 0.001$] and OS [$P < 0.001$] compared with patients who underwent guideline-adherent complete tumor resection via BCS (R0). In addition, non-guideline-adherent RT after MA (over-therapy) did not significantly influence survival [RFS: $P = 0.838$; OS: $P = 0.613$].

Conclusion: Our study confirms the importance of guideline-adherent adjuvant RT. It shows highly significant associations between RFS or OS and guideline adherent RT. Nevertheless, inadequate (R1-) surgical resection in a daily routine cohort of patients increases the risk of local recurrence and appears not to be compensated by the following RT.

Key words: radiotherapy, breast cancer, guideline adherence, survival, cohort

*Correspondence to: Dr Lukas Schwentner, Tel: +49-731-500-58589; Fax: +49-731-500-58502; E-mail: lukas.schwentner@yahoo.de

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‡These authors contributed equally to this work.

introduction

Breast cancer continues to be the most common malignancy in women, with an annual frequency of ~70 000 new cases in Germany alone [1]. Annually, ~25% of breast cancer patients die of the consequences associated with this malignancy. Despite continuing efforts to improve therapy, particularly systemic adjuvant therapies, this disease remains a therapeutic problem with major relevance to economics and health care policies.

In recent decades, the therapeutic patterns have changed dramatically, improving morbidity and outcome in breast cancer patients. Patients diagnosed with primary breast cancer typically undergo standardized adjuvant treatment according to internationally validated guidelines. These guidelines recommend adjuvant radiotherapy (RT) after breast-conserving surgery (BCS) and, for patients with certain risk factors (i.e. T3/T4 or multicentricity), after mastectomy (MA). Wolters et al. [2] demonstrated that internationally validated guidelines do not significantly differ in their recommendations regarding adjuvant RT for breast cancer. This analysis included the most important international validated evidence-based guidelines. These RT recommendations are mainly based on the idea of locoregional tumor control, which might positively influence breast cancer patient mortality and morbidity. Breast cancer patients with large primary tumors (T3/T4), incomplete tumor resection (R1), multicentric tumors, lymphatic or vascular invasion (L1/V1), or more than three involved axillary lymph nodes are at a higher risk for locoregional recurrence [3–7]. These risk factors are restricted to patients undergoing MA as the primary surgical intervention; however, Fisher et al. [8] and Veronesi et al. [9] were the first to demonstrate that BCS followed by adjuvant RT is an equivalent alternative to MA, and these initial data were confirmed by several other trials [10]. Therefore, the current internationally validated evidence-based guidelines have implemented RT following BCS as the standard of care for breast cancer patients.

However, in our daily routine, patient- and physician-related factors occasionally detain patients with primary breast cancer from obtaining guideline-adherent RT after surgery. Two typical situations include patients with small tumors undergoing MA to prevent the need for RT after BCS and patients declining or abandoning adjuvant RT. Therefore, the aim of this study was to analyze the association between guideline-adherent RT and survival outcome in an observational retrospective multicenter study referred to as BRENDA (quality of breast cancer care under evidence-based guidelines).

patients and methods

In this retrospective clinical cohort study, we analyzed patients with primary breast cancer who were diagnosed or treated at the Department of Gynecology and Obstetrics at the University of Ulm and 16 partner clinics (all certified breast cancer centers) in Baden-Württemberg (Germany) between 1992 and 2008. For this purpose, a new documentation system called BRENDA was designed and used. This system includes a retrospective chart to review the abstract TNM (including R-status) stage (current valid TNM at first diagnosis), histological subtype, grading, lymphatic and vascular invasion, estrogen/progesterone/erbB-2-expression, date of diagnosis, and all adjuvant therapies. The data regarding therapy, including surgery (date of surgery, BCS, MA, sentinel-node-biopsy, axillary lymph node dissection), adjuvant systemic chemotherapy, and adjuvant RT, were recorded. At follow-up, data on first recurrences, secondary primary tumors, and date and cause of death were collected. Questionnaires were sent to the physicians involved in follow-up care, to the local death registries, and to the patients to determine their recurrence and survival status. As measures of comorbidity, the physical status parameter developed by the American Society of Anesthesiologists and the cardiac score developed by the New York Heart Association (NYHA) at the time of surgery were collected for all patients. Furthermore, data on the occurrence of myocardial infarction, stroke, and malignant diseases were documented. Documentation was carried out by a team of medical recorders who were all specially trained for the BRENDA documentation system. Owing to thorough registrar training and computerized consistency checks, the quality of these data is considered high [11].

Written and informed consent was obtained from all patients included in this clinical study. The inclusion criterion was histologically confirmed invasive breast cancer. The exclusion criteria consisted of carcinoma in situ, M1 status, bilateral breast cancer, primary occult disease, and incomplete follow-up.

The definition of evidence-based, guideline-adherent adjuvant treatment was based on internationally validated guidelines [2]. Therefore, we decided to base the definition of guideline-adherent adjuvant treatment on the German national consensus guideline (S3 guideline) for the decision regarding locoregional treatment (surgery, RT), chemotherapy, and endocrine therapy [12]. Omission of any suggested adjuvant treatment or the abandonment of any adjuvant treatment was classified as noncompliance with the suggested adjuvant therapy (see supplementary Table S1, available at *Annals of Oncology* online).

statistical analysis

The primary end points were recurrence-free survival (RFS) and overall survival (OS), which were assessed by a standard survival analysis using the Kaplan–Meier approach. The log-rank test was used to provide a formal statistical assessment of the differences between treatment arms with respect to RFS, OS, etc. The Cox proportional hazards model was used to estimate the hazard ratio (HR) and confidence intervals (CI). Comparisons of categorical variables between the groups were carried out using χ^2 tests. Multivariate Cox proportional hazard regression models were used to adjust for differing risk factor distributions between the groups. The proportional hazard assumption was assessed by including the product of the individual terms with time in the models. The dataset was analyzed for selection bias, confounders, and inhomogeneities in the baseline status. The data were adjusted for all therapy types (surgery, RT, endocrine therapy, and chemotherapy), the Nottingham Prognostic Index, and comorbidities.

results

A total of 8935 patients with primary invasive breast cancer were evaluated for adherence to RT. Of these patients, 7790 patients (87.2%) were treated with guideline-adherent adjuvant RT [this included 1205 cases (13.5%) of guideline-adherent omission of RT], whereas 1145 patients (12.8%) did not receive guideline-adherent RT (this included cases of omission or abandonment of guideline-indicated RT and patients who received RT but not according to the guidelines; see supplementary Table S2, available at *Annals of Oncology* online). A total of 6585 patients (73.7%) received guideline-adherent adjuvant RT, and 390 patients (4.4%) received nonguideline-adherent (overtherapy) RT. Seven hundred fifty-five patients (8.4%) did not receive any adjuvant RT, although this treatment should have been recommended according

to the guidelines (nonguideline-adherent). The median age of patients with nonguideline adherent RT was 66 years and with guideline adherent RT 62 years ($P < 0.001$).

Patients with guideline-adherent adjuvant RT demonstrated a significant RFS advantage [$P < 0.001$; HR = 0.28 (95% CI 0.24–0.33)] and a significant OS advantage [$P < 0.001$; HR = 0.26 (95% CI 0.19–0.36)] compared with those with nonguideline-adherent RT. Guideline-adherent omission of RT also demonstrated a significant survival advantage compared with nonguideline-adherent omission of RT [RFS: $P < 0.001$; HR = 0.32 (95% CI 0.26–0.40); OS: $P < 0.001$; HR = 0.51 (95% CI 0.43–0.61)] (see supplementary Figure S1, available at *Annals of Oncology* online).

The 5-year RFS was 91.0% (95% CI 90.3% to 91.8%) for patients who received guideline-adherent RT, 89.7% (95% CI 87.7% to 91.7%) for patients who did not receive RT in accordance with the guideline and 72.7% (95% CI 69.0% to 76.3%) for patients who did not receive RT, although it was indicated (nonguideline-adherent).

Also after adjusting for age, Nottingham Prognostic Index, and guideline adherence for endocrine therapy and chemotherapy, patients with guideline-adherent RT demonstrated a significant survival advantage compared with patients with nonguideline-adherent RT [RFS: $P < 0.001$; HR = 0.23 (95% CI 0.15–0.34; OS: $P < 0.001$; HR = 0.23 (95% CI 0.20–0.26)]. The same is true for patients who did not receive RT in accordance with the guideline compared with patients who did not receive RT, although it was indicated [RFS: $P < 0.001$; HR = 0.34 (95% CI 0.27–0.43); OS: $P < 0.001$; HR = 0.55 (95% CI 0.46–0.65)]

Upon comparing the impact on survival of nonguideline adherence for other adjuvant treatment modalities (surgery, chemotherapy, and endocrine therapy) to the impact of nonguideline adherence on survival following RT, we were able to demonstrate that nonadherence concerning chemotherapy [$P < 0.001$, HR = 0.52 (95% CI 0.45–0.60] and RT [$P < 0.001$, HR = 0.57 (95% CI 0.48–0.68] had the most significant impact on survival (see supplementary Table S3, available at *Annals of Oncology* online).

Unfortunately, we are not able to present data on technical advantages in RT. However, when comparing RT over the time (1992–2000; 2001–2005; 2005–2008), we do see a statistical significant increase in guideline adherence (84%; 87.2%; 87.7%). The results presented remain statistically significant when stratifying for these time periods, but if we only compare patients receiving guideline adherent RT, we do observe a statistically significant improvement in survival parameters (2001–2005: $P < 0001$; 2005–2008: $P < 0.001$) (see supplementary Figure S2, available at *Annals of Oncology* online).

BCS followed by guideline-adherent RT versus mastectomy without RT (guideline-adherent)

Of the 6052 (67.7%) patients undergoing BCS, 5636 (93.1%) received guideline-adherent adjuvant RT, and 416 (6.9%) did not receive RT, although it was indicated (nonguideline-adherent). Of the 12.9% (1152) patients undergoing MA, 33.7% (388) received guideline-adherent adjuvant RT, 36.6% (422) did not receive RT because it was not indicated (guideline-adherent), 14.1% (163) received RT that was not indicated (nonguideline-adherent), and 15.5% (179) did not receive adjuvant RT, although it was indicated (nonguideline-adherent). There was no significant difference between the patients who received BCS followed by RT (guideline-adherent) versus patients who received MA without RT (guideline-adherent) [RFS: $P = 0.293$; HR = 1.20 (95% CI 0.85–1.70); OS: $P = 0.104$; HR = 1.31 (95% CI 0.95–1.81] (see supplementary Figure S3, available at *Annals of Oncology* online).

Next, we investigated patients who received BCS (T1/T2 and R0) and adjuvant RT (guideline-adherent) versus BCS with the omission of adjuvant RT (nonguideline-adherent). The patients with BCS who did not undergo adjuvant RT demonstrated a significantly inferior RFS [$P < 0.001$; HR = 3.93 (95% CI 3.12–4.94)] and OS [$P < 0.001$; HR = 4.15 (95% CI 3.37–5.10)]. The patients with BCS but without RT further demonstrated a significantly inferior RFS [$P < 0.001$; HR = 3.21 (95% CI 2.17–4.74)] and OS [$P < 0.001$; HR = 3.21 (95% CI 2.24–4.61)] compared with the patients who received MA without RT (not indicated after MA, guideline-adherent).

BCS with R1 resection followed by RT versus conforming BCT followed by RT

A total of 135 patients underwent BCS with incomplete tumor resection (R1) (nonguideline-adherent BCS) followed by RT. According to the guidelines, these patients should have received at least secondary MA after incomplete tumor resection via BCS. These patients receiving incomplete tumor resection (BCS R1) were associated with a significantly inferior RFS [$P < 0.001$; HR = 2.87 (95% CI 2.00–4.12)] and OS [$P < 0.001$; HR = 2.06 (95% CI 1.43–2.98)] when compared with patients who received a MA without RT (guideline-adherent; see supplementary Figure S4, available at *Annals of Oncology* online).

However, we also found patients within the BRENDA cohort who received BCS instead of guideline-adherent MA e.g. in cases of T3/4 carcinomas. In these cases, if R0 resection was achieved, after adjusting for tumor size, grade, and nodal status, we did not find a significant difference in RFS [$P = 0.514$; HR = 1.21 (95% CI 0.68–2.17)] or OS [$P = 0.388$; HR = 1.29 (95% CI 0.72–2.31)]. These data indicate that the outcome parameters of the patients who underwent nonguideline-adherent BCS (e.g., T3/4) with complete tumor resection (R0) followed by RT were not negatively influenced.

mastectomy followed by nonguideline-adherent RT (overtherapy)

To determine the possibility of overtherapy, we compared patients undergoing MA followed by nonguideline-adherent RT versus patients with MA without RT (only guideline-adherent without RT, excluding those patients with a recommendation for RT according to the guidelines). We found no significant difference concerning RFS [$P = 0.838$; HR = 1.07 (95% CI 0.57–1.98)] or OS [$P = 0.613$; HR = 1.18 (95% CI 0.63–2.20)] between these two groups. The 5-year RFS rate in the group with MA but without RT (guideline-adherent) was 91.4% (95% CI 88.3% to 94.6%), whereas the rate in the MA followed by RT group (nonguideline-adherent overtherapy) was 90.3% (95% CI 85.1% to 95.5%).

discussion

The influential 2005 meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) demonstrated how radiation after BCS and MA affects locoregional disease recurrence and long-term survival [13]. This study compared the outcome of patients with or without RT after BCS in 10 randomized clinical trials and the outcome of patients with or without RT after MA in 36 RCTs and included a total of 23 488 patients treated between 1976 and 1998 [13]. In 2011, an update was published on the effect of RT after BCS [10]. These two meta-analyses showed that radiation strongly affects locoregional disease recurrence, with HRs of 0.248 and 0.277 for 10-year locoregional disease recurrence after MA (node-positive patients only) and BCS, respectively. Radiation demonstrated a limited effect on long-term survival, with HRs of 0.919 and 0.900 for overall mortality after MA (node-positive patients only) and BCS, respectively [10]. Other recently published randomized, controlled trials (RCTs) confirmed the strong effects of RT on locoregional disease recurrence, but these results were inconclusive with regards to OS due to a short follow-up period at the time of publication or small numbers of observed deaths [14–16]. Meta-analyses that focused on the effects of RT after MA [17] on locoregional RT given in addition to systemic adjuvant therapy [18] and on optimal RT as well as two updates of the Danish trial, which was previously included in the EBCTCG meta-analysis [19, 20], confirmed the results of the EBCTCG meta-analysis.

RCTs are generally viewed as the gold standard for the evaluation of therapy regimens. However, empirical proof demonstrating that results from observational studies are inaccurate is rare. An observational study provides a useful tool for describing everyday clinical practice since, in these trials, the efficacy of a therapy in a nonselected group of patients from community practice is reported, providing evidence to support clinical trial findings. In particular, the results from RCTs may not be generalizable to everyday clinical practice because the patients, participating health care professionals, and treatments in RCTs may not be representative of those found in clinical practice. Because the settings of RCTs may deviate from those encountered in real-world settings, RT effects that physicians observe in everyday practice may deviate from the effects reported in RCTs, yet RCTs generally guide physicians' decisions on therapy schemes. The main advantage of the BRENDA cohort, which represents the daily routine of patients observed in clinical practice, is that it avoids any selection bias that occurs in clinical trials. Therefore, the BRENDA cohort is also associated with greater comorbidities, is older, and includes several patients who declined adjuvant treatment modalities [21]. The data obtained with this cohort clearly demonstrated the benefit of guideline-adherent adjuvant RT, especially in the case of BCS followed by guideline-adherent RT. Furthermore, our results demonstrate that RT following incomplete tumor resection via BCS cannot compensate for the impact of failed surgery on survival outcome. The results of this study are therefore consistent with the EBCTG analysis and validated the RFS and OS end points after the data were adjusted. Within the MA group, the results were consistent with the EBCTG analysis. In particular, the patients who were overtreated with MA (T1–T2) did not profit from adjuvant RT, and these results further underscore the results of Fisher et al. [9] and Veronesi et al. [10].

The methodological difficulty associated with retrospective data collection in all of these studies, including the present study, only allows us to draw associations between guideline-adherent treatment and favorable outcome parameters; drawing causal conclusions concerning survival parameters would only be appropriate if treatment allocations were randomized and prospective. However, randomization concerning guideline-adherent treatment was not possible because we could not randomly assign guideline-adherent and nonguideline-adherent therapeutic regimens to patients. The retrospective design of this trial represents another important methodological limitation. Adjuvant RT has changed dramatically over time (1992–2008), including the introduction of 3D planning or RT boost of the breast. Unfortunately, these technical aspects of adjuvant RT could not be sufficiently documented. However, several randomized trials have demonstrated that these technical advantages do impact local recurrence rates, DFS, and OS. Another point to consider is the evolution and improvement of adjuvant therapies concerning chemotherapy and endocrine therapy, which might confound the survival outcomes presented.

In this retrospective study, there were confounding factors affecting both treatment and outcome parameters. To reduce this problem, our analyses controlled for the most important prognostic factors (age, affected lymph nodes, grade, hormone receptor status, menopause status, year of diagnosis, treatment in a university hospital, tumor size, erbB-2-status, and comorbidities).

Within our cohort, age was the most important risk factor for not undergoing guideline-adherent adjuvant treatment. The BRENDA population investigated represents a nonselected collective of patients, which is the most important difference in comparison to the populations investigated in clinical trials. Comorbidities are likely one of the most important factors preventing patients from guideline-adherent treatment, which may substantially influence prognosis [22, 23]. In this specific cohort, all patients are treated in specialized and certified interdisciplinary breast cancer centers, in which an interdisciplinary tumor board is a requirement for certification. Of course, several other factors influence guideline-adherence in breast cancer, such as education, access to medical resources, health care services obtained, urban versus rural setting, etc. [24].

However, there may also be physician-related factors that prevent patients from obtaining guideline-adherent treatment, and it is possible that patients were deemed unsuitable for strict guideline-adherent treatment because of medical reasons or other reasons that were not recorded. In fact, there is an association between age, patient- and physician-related factors, and guideline-adherent treatment, which influences survival parameters and may explain why guideline adherence decreases rapidly with age [25] and why noncancer-related mortality is rising. Hebert-Croteau et al. [25] showed that compliance with guidelines is an independent significant predictor of survival in women with primary breast cancer [24]. Although there have only been a few health care research studies that have investigated the impact of guideline-adherent therapeutic regimens on clinical outcome [26–28], these studies have confirmed that, especially for several subtypes of breast cancer, there appears to be a strong association between guideline-adherent treatment and improved survival [29–31].

ethical approval

This study and the BRENDA project have been approved by the Ethics Committee of the University of Ulm.

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disclosure

All the authors declare that there are no potential conflicts of interest, including any financial, personal, or other relationship with other people or organizations that could inappropriately influence this work.

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