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GYNECOLOGIC ONCOLOGY

Adherence to guidelines and benefit of adjuvant radiotherapy in patients with invasive breast cancer: results from a large population-based cohort study of a cancer registry

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Abstract

Purpose According to German S3 guidelines, radiotherapy (RT) is indicated in patients with invasive breast cancer after breast-conserving therapy (BCT). The aim of this analysis was to assess adherence to guidelines, long-term survival, recurrence rates, and recurrence-free survival after adjuvant RT in patients with BCT in daily clinical practice.

Methods This retrospective cohort study comprised data from the population-based clinical cancer registry of the Tumor Centre Regensburg (Bavaria, Germany). 6370 patients with non-metastatic invasive breast cancer and UICC tumor stages I, II, and III who were treated in certified breast cancer centers by BCT and diagnosed between 2003 and 2013 were included in the study.

Results 6184 (97.1%) breast cancer patients received guideline concordant RT and showed a 3-year overall survival (OAS) of 96.8% in contrast to 90.9% in patients without RT (5-year OAS of 93.1% vs. 79.0%, $p<0.001$). In multivariable Cox regression models, better overall survival was confirmed for the RT group (HR 0.64, 95% CI 0.46–0.88, $p=0.007$). The 5-year local recurrence-free survival rate (RFS) in the irradiated patients was 92.1% vs. 62.0% in the comparison group ($p<0.001$). The 10-year RFS was 80.5% vs. 36.0% ($p<0.001$). This difference persisted after adjusting in multivariable analysis (HR 0.20, 95% CI 0.16–0.26, $p<0.001$).

Conclusions This population-based analysis showed that the implementation of German guidelines in clinical routine was successful and guideline concordant adjuvant radiotherapy after BCT leads to better overall and recurrence-free survival and lower local recurrence rates.

Keywords Radiotherapy · Breast cancer · Overall survival · Recurrence-free survival · Cancer registry

Abbreviations

RT	Radiotherapy
BCT	Breast-conserving therapy
OAS	Overall survival
HR	Hazard ratio
APBI	Accelerated partial breast irradiation
SD	Standard deviation
CI	Confidence interval

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RFS Recurrence-free survival
DKG German Cancer Society, "Deutsche Krebsgesellschaft"
ER Estrogen receptor

Introduction

Breast cancer still remains both the most common cancer and the most common cause of cancer death in women in Germany and worldwide [1]. In 2014, about 69,220 women and 650 men were initially diagnosed with breast cancer. In contrast to other forms of cancer, about 30% of the patients suffering from breast cancer are younger than 55 years [1]. The first Interdisciplinary S3 guideline for diagnosis, treatment and follow-up care of breast cancer was implemented in 2004 to standardize and improve cancer care in Germany [2].

Due to continuous research findings, these guidelines are updated regularly according to the evidence-based medicine. The last update of the Interdisciplinary S3 guideline for diagnosis, treatment and follow-up care of breast cancer was published in 12/2017 [3]. These guidelines strongly recommend RT after BCT in invasive breast cancer. The omission of RT could be discussed in subgroups with special histopathological parameters.

Large randomized controlled trials showed that breast-conserving therapy (BCT) as a less radical operation technique followed by RT is equivalent in local recurrence rate and overall survival compared to mastectomy [4]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 convincingly affirmed the role of adjuvant radiotherapy in BCT lowering the ratio of death. BCT became the standard operation technique and is associated with better quality of life compared to mastectomy [5].

Thus, the vast majority of patients with early-stage breast cancer receives BCT for macroscopic tumor removal. Nevertheless, microscopic tumor deposits can remain in the conserved breast and require a subsequent RT. Various radiation techniques can be offered to patients with breast-conserving therapy. Most patients receive standard whole-breast radiation therapy after BCT with boost to the tumor bed. A meta-analysis of 10,000 patients with breast-conserving therapy demonstrated the long-term benefit of radiation with a reduction of recurrence rate at 10 years of 35% vs. 19% and reduction in cancer mortality at 15 years of 21% vs. 25% [6]. Furthermore, accelerated partial breast irradiation (APBI) can be offered to patients older than 45 years with small, node-negative R0 tumors. APBI shortens treatment duration using higher doses per fraction [3]. Furthermore, RT of regional lymph nodes is recommended according to the current S3 guidelines depending on tumor localization, number of positive lymph nodes, hormone receptor status and menopause status [3]. A meta-analysis of three population-based randomized studies showed a significant improvement of overall survival in patients treated with RT due to the reduction of distant metastasis [7].

Compared to other adjuvant treatments such as chemotherapy or endocrine therapy, the side effect profile of RT is better [8]. Local skin reactions can occur as short-term reaction. Severe long-term consequences including lung or heart injuries or second cancers are rare due to improved radiation techniques [8]. By irradiating non-target volumes with an acceptable dose, the risk of side effects was significantly reduced [9].

Several studies showed the impact of RT on survival. RT leads to better survival and lower local recurrence rates. The aim of this analysis was to assess adherence to guidelines, long-term recurrence, and survival rates after adjuvant RT in BCT patients in daily clinical practice in a large cohort of 6370 patient based on the data of a population-based clinical regional cancer registry in Bavaria.

Materials and methods

Database

The following study analyzed data from the Tumor Centre Regensburg (Bavaria, Germany). Established in 1991, this high-quality population-based regional cancer registry comprises data from more than 2.3 million cancer inhabitants of Upper Palatinate and Lower Bavaria. Following a stringent protocol, it accomplishes a follow-up documentation of all breast cancer patients in the catchment area. The University Hospital Regensburg, 53 regional hospitals and more than 1500 practicing doctors cooperate by transmitting patients' data to the Tumor Centre. These population-based data originate from medical reports, pathology, and follow-up records. Documented parameters comprise diagnosis, therapies, course of disease and long-term follow-up including locoregional or distant recurrence, and death. Mortality data are received from regional registry offices and death certificates.

Certified breast cancer center

The following analysis focused on breast cancer patients who received treatment from a certified breast cancer center. After certification by German Cancer Society (DKG), these institutions are obliged to apply German S3 guidelines for breast cancer and their quality indicators. Annual benchmarks and the process of (re-)audits and re-certification guarantee a comparable quality of treatment which is transparent for the general public. In this study, patient data

originate from eight certified breast cancer centers in Lower Bavaria and Upper Palatinate.

Inclusion and exclusion criteria (patient selection)

Overall, 23,960 cases of malignant neoplasm of breast are recorded in Lower Bavaria and Upper Palatinate in the period from January 2003 to December 2013 (11 years). Patients were followed up until August 2016. General exclusion criteria were primary metastatic breast cancer, histopathological criteria (such as metastasis in breast from another primary tumor or Paget's disease) and patients from institutions that were not certified as breast cancer centers. We restricted the analysis on patients from certified breast cancer centers to assure a high quality and standardized procedure in therapy indication and decision-making process. The proportion of patients treated in certified breast centers increased from 50.0% in 2004 to 75.3% in 2013 in our cohort. Furthermore, patients with ductal carcinoma in situ, not specified tumor stage or UICC stage 0 and IV as well as patients with mastectomy, no tumor operation and insufficient follow-up were excluded. In 8.1% (562 cases), there was no information available about RT. These patients were excluded from further analyses. Scheme of data extraction for the following study is presented in Fig. 1.

Overall, 6370 patients with invasive non-metastatic breast cancer of tumor stage I, II, and III and BCT were included for subsequent statistical analysis. In this cohort, 6184 (97.1%) patients were treated with RT after BCT and 186 (2.9%) patients did not receive RT.

The reasons for non-performance of RT were mainly refusal by the patients or contraindications for RT in elderly people.

Statistical analysis

Statistical analysis and calculations were conducted using software packages IBM SPSS 24 (Chicago, EUA). Continuous data were depicted in means and standard deviation (SD), whereas categorical data are expressed as frequency counts and percentages. Comparison of means was performed by *t* test in case of normally distributed continuous variables, otherwise by Mann–Whitney *U* test. Pearson's Chi-square test was applied for categorical variables to compare the baseline characteristics of patients.

The method of Kaplan–Meier was used to estimate overall survival (OAS), local recurrence-free survival (RFS), and cumulative local recurrence rates. OAS was defined as the period of time in years from the date of cancer diagnosis to death from any cause. RFS additionally included local recurrences as an event. Patients, who were alive, were right censored at the last follow-up date or general cutoff date (1/4/2016). Mean follow-up was 6.3 years (median 6.1).

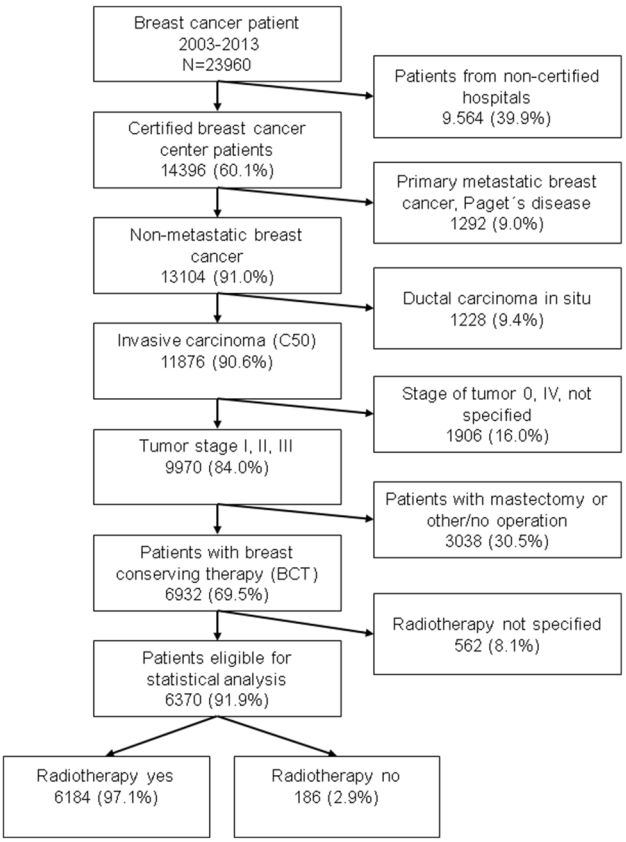

Fig. 1 Scheme of data extraction

A multivariable Cox regression analysis was performed to figure out the influence of RT on OAS, adjusted for the confounding variables: age at diagnosis, grading, tumor size, nodal status, stage of tumor, HER2 status, hormone receptor status, lymphatic/venous invasion, endocrine therapy, immunotherapy, and chemotherapy. In Cox regressions, hazard ratios (HR) and corresponding 95% confidence intervals (CI) were estimated and regarded as statistically significant if CI excluded 1.0. A log-rank test was employed to evaluate the difference between the patients treated with RT versus those who did not receive RT. Listed *p* values from log-rank tests were two-sided and statistical results were regarded as significant at a p value < 0.05.

Results

Patients' characteristics

In total, 97.1% ($n = 6184$) of the 6370 patients for whom RT was recommended received this therapy, whereas 2.9% ($n = 186$) had surgery only. The proportion of patients with RT remained stable over 10 years. The annual number of

patients treated in breast cancer centers increased from 476 in 2003 to 741 in 2013 (Table 1).

The mean age in this cohort was 59.5 years (median 59.8 years, range 21.7–95.3 years). Age is significantly lower in patients with RT (Chi-square $p < 0.001$). Small tumor sizes were treated more often with RT than larger tumors (T1 97.5%, T4 89.8%, $p = 0.001$). Regarding nodal status, there were no differences in treatment. Concerning grading, hormone and HER2 receptor status, lymphatic, and venous invasion, no differences between patients with and without RT were observed in the evaluated cohort. Detailed distributions of conducted RT according to the patients' characteristics are shown in Table 2.

Survival analysis

Patients receiving RT had a 3-year OAS rate of 96.8% compared to those without RT with a 3-year OAS rate of 90.9%. The 5-year OAS rates were 93.1% vs. 79.0%, and 10-year OAS rates were 83.0% with RT compared to 51.7% without RT. Patients receiving RT had statistically significantly higher overall survival rates than patients without RT ($p < 0.001$) (Fig. 2, Table 3).

In a multivariable Cox regression model adjusted for all influential variables (age at diagnosis, grading, tumor size, nodal status, stage of tumor, HER2 status, hormone receptor status, lymphatic/venous invasion, endocrine therapy, immunotherapy, and chemotherapy), superior overall survival persisted in the radiotherapy group (HR 0.64, 95% CI 0.46–0.88, $p = 0.007$, Table 4). Among all variables, age, grading, tumor size and nodal status proved to be independent factors for overall survival.

Local recurrence rate and local recurrence-free survival

For further statistical investigation of local recurrence rates and recurrence-free survival, we only included patients with R0 resection of the tumor ($n = 6227$, 97.8%). Among 6227 patients with R0 resection, 97.3% ($n = 6057$) were treated with RT. 154 (2.5%) of the 6057 patients treated with RT and 45 (26.5%) of 170 patients without RT suffered from a local relapse.

Kaplan–Meier curves (Fig. 3) depict the lower cumulative local recurrence rates in the cohort with guideline concordant RT. Patients obtaining RT showed a cumulative local recurrence rate of 1.3% after 3 years, whereas 16.6% of the group without radiation suffered from a local recurrence within 3 years after cancer diagnosis. The trend continued 5 years after diagnosis (2.0% local recurrence rate in RT-treated patients vs. 27.4% in patients without RT). The difference in cumulative local recurrence rate was highly significant (log rank $p < 0.001$). Using a multivariable Cox regression model, it is confirmed that patients treated with RT showed significantly lower local recurrence rates (HR 0.07, 95% CI 0.05–0.10, $p < 0.001$, Table 4).

Consequently, a remarkable difference in RFS between patients with and without RT can be found (Fig. 4). The 3-year local RFS was 96.0% for patients treated with RT compared to 78.0% of those who did not receive RT. Similarly, the 5-year RFS was 92.1% with RT vs. 62.0% without therapy. The lowest RFS rates were found in patients without RT with a 10-year rate of 36.0% ($p < 0.001$) (Table 3). After adjusting for all influencing variables, there is still a statistically significant difference concerning local RFS between treated patients and those who did not receive RT (HR 0.20, 95% CI 0.16–0.26, $p < 0.001$), which is even stronger than for OAS (Table 4).

Analyzing RFS rates of older patients ≥ 70 years ($N = 1253$), the 3-year RFS rate within those with RT was

Table 1 Development of conducted radiotherapy over 10 years

Year of diagnosis	Radiotherapy					
	Radiotherapy yes		Radiotherapy no		Total	
2004	469	98.5%	7	1.5%	476	100%
2005	427	98.8%	5	1.2%	432	100%
2006	511	94.3%	31	5.7%	542	100%
2007	563	98.6%	8	1.4%	571	100%
2008	576	98.1%	11	1.9%	587	100%
2009	757	97.2%	22	2.8%	779	100%
2010	751	96.9%	24	3.1%	775	100%
2011	709	97.3%	20	2.7%	729	100%
2012	704	95.4%	34	4.6%	738	100%
2013	717	96.8%	24	3.2%	741	100%
Total	6184	97.1%	186	2.9%	6370	100%

Table 2 Associations between conducted radiotherapy and clinical and histopathological characteristics

Parameter	Radiotherapy					*p* value[c]
	Radiotherapy yes		Radiotherapy no		Total	
Age at diagnosis (years)						
< 50	1406	97.6%	34	2.4%	1440	< 0.001
50–69	3569	98.2%	65	1.8%	3634	
≥ 70	1209	93.3%	87	6.7%	1296	
Grading						
G1	1153	97.1%	35	2.9%	1188	0.630
G2	3596	97.2%	102	2.8%	3698	
G3/4	1419	96.7%	49	3.3%	1468	
Unknown	16	100.0%	0	0.0%	16	
Tumor size						
T1	4223	97.5%	110	2.5%	4333	0.001
T2	1847	96.5%	67	3.5%	1914	
T3	61	95.3%	3	4.7%	64	
T4	53	89.8%	6	10.2%	59	
Nodal status						
N0	4382	97.1%	132	2.9%	4514	0.127
N1	1275	97.0%	39	3.0%	1314	
N2	351	98.6%	5	1.4%	356	
N3	173	94.5%	10	5.5%	183	
Unknown	3	100.0%	0	0.0%	3	
Stage of tumor						
I	3363	97.3%	92	2.7%	3455	0.315
II	2245	96.9%	72	3.1%	2317	
III	576	96.3%	22	3.7%	598	
Hormone receptor status[a]						
Negative	721	95.8%	32	4.2%	753	0.137
Positive	5454	97.3%	153	2.7%	5607	
n.s.	9	90.0%	1	10.0%	10	
HER2/neu status						
Negative	4500	97.4%	120	2.6%	4620	0.027
Positive	796	97.1%	24	2.9%	820	
n.s.	888	95.5%	42	4.5%	930	
Lymphatic invasion						
L0	3630	97.3%	102	2.7%	3732	0.570
L1	1595	96.8%	53	3.2%	1648	
L n.s.	959	96.9%	31	3.1%	990	
Venous invasion						
V0	4808	97.2%	141	2.8%	4949	0.480
V1	175	95.6%	8	4.4%	183	
V n.s.	1201	97.0%	37	3.0%	1238	
Total	6184	97.1%	186	2.9%	6370	

n.s. not specified

[a]Estrogen and/or progesterone receptor

[b]Pearson's Chi-square

92.6% compared to 79.6% without RT (Fig. 5). The 5-year rate was 84.0% with RT and 56.9% without therapy. 10-year RFS rate was 60.7% in patients with RT, whereas in the untreated group all patients had died or relapsed in the period (log rank $p < 0.001$).

Patients with small tumors [N (T1) = 4251] showed a 3-year RFS rate of 97.0% with RT and 79.5% without RT

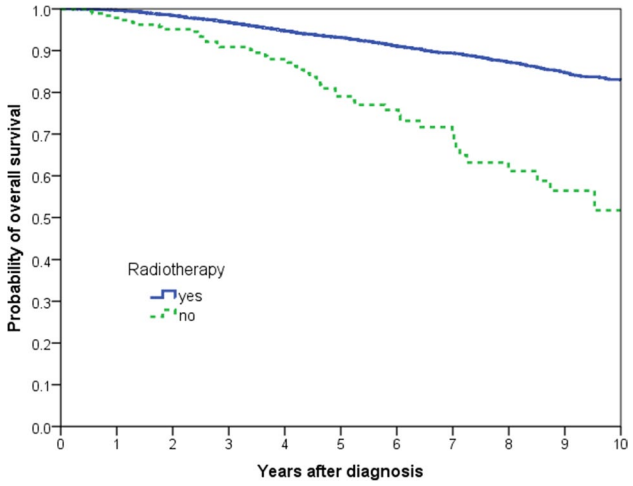

Fig. 2 Kaplan–Meier plot of overall survival

(Fig. 6). The 5-year RFS was higher in irradiated patients (94.4% with RT vs. 67.3% without RT). The difference in 10-year RFS is even higher (84.3% compared to 34.6%) ($p < 0.001$).

Discussion

National and international oncological guidelines for breast cancer were implemented to standardize and improve cancer treatment. Recommendations in guidelines worldwide are similar, only the quality of treatment differs within each country [10]. Most of the German breast cancer patients receive treatment in a certified breast cancer center (in 2016, an estimated percentage of 82% [11]). After certification by DKG, these institutions are obliged to apply German S3 guidelines for diagnosis and treatment. Thus, high-quality standards in cancer treatment can be ensured. Guidelines recommend RT to all patients with invasive breast cancer after BCT [3, 12]. The following study analyzed guideline concordance and long-term effects based on the data from a high-quality population-based regional cancer registry.

Even at the beginning of the establishment of certified breast centers in 2003/2004, 98.5% of the operated patients received RT. Remaining were stable over the next 10 years (on average 97.1% over the follow-up period of 10 years); Table 1 shows the good implementation of guidelines in clinical routine. However, an average of 2.9% of them were not treated with RT. Furthermore, the increasing number of patients per year in this observation period is noticeable. In the course of this study, up to eight breast cancer centers were certified, leading to an increasing number of patients in the cohort.

Further statistical investigation showed the correlation between conducted radiotherapy, and clinical and histopathological characteristics. In this cohort guideline, concordant radiotherapy was significantly higher in younger patients and patients with small tumor sizes, but not statistically significantly higher in nodal disease (Table 2). After BCT, microscopic tumor deposits can remain in the conserved breast

Table 3 Kaplan–Meier estimates of overall survival rate, local recurrence-free survival rate and cumulative local recurrence rate 3, 5 and 10 years after diagnosis

Outcome	Radiotherapy	Time after diagnosis (years)			Log rank *p*
		3 years (%)	5 years (%)	10 years (%)	
Overall survival rate	Yes	96.8	93.1	83.0	< 0.001
	No	90.9	79.0	51.7	
Local recurrence-free survival rate	Yes	96.0	92.1	80.5	< 0.001
	No	78.0	62.0	36.0	
Cumulative local recurrence rate	Yes	1.3	2.0	4.6	< 0.001
	No	16.6	27.4	39.6	

Table 4 Results from multivariable Cox regression analyses for overall survival, local recurrence-free survival and cumulative local recurrence, adjusted for confounding variables age at diagnosis, grading, tumor size, nodal status, stage of tumor, HER2 status, hormone receptor status, lymphatic/venous invasion

Outcome	Radiotherapy	Hazard ratio	Lower 95% CI	Upper 95% CI	Log rank *p*
Overall survival	Yes	0.64	0.46	0.88	< 0.007
	No (reference)	1.00			
Local recurrence-free survival	Yes	0.20	0.16	0.26	< 0.001
	No (reference)	1.00			
Cumulative local recurrence	Yes	0.07	0.05	0.10	< 0.001
	No (reference)	1.00			

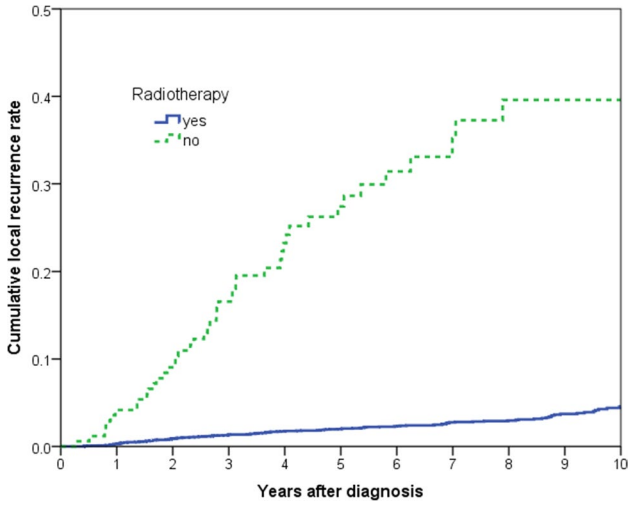

Fig. 3 Kaplan–Meier plot of cumulative local recurrence rate

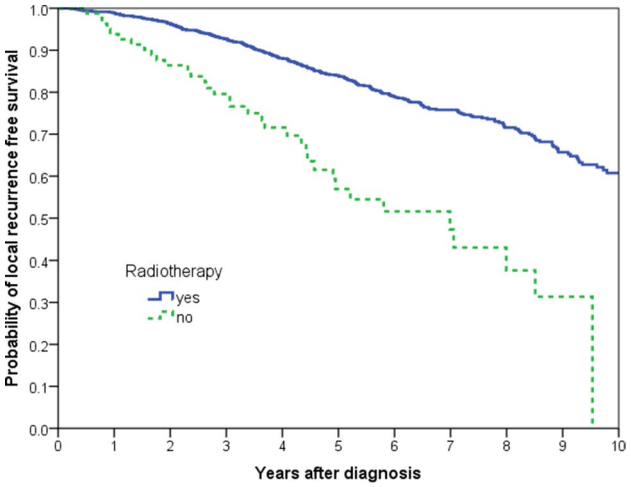

Fig. 5 Kaplan–Meier plot of local recurrence-free survival in patients ≥ 70 years

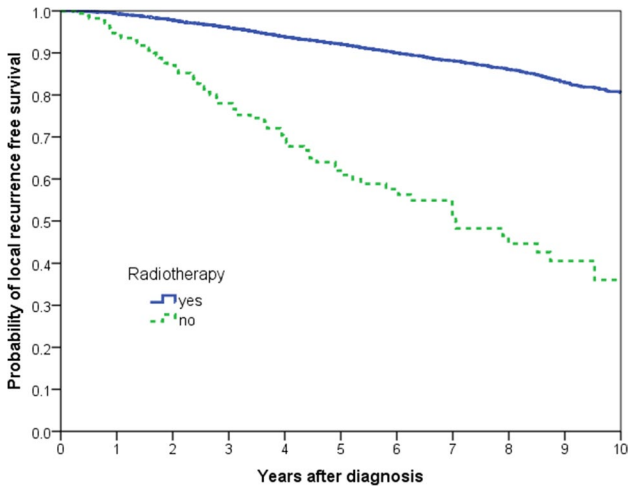

Fig. 4 Kaplan–Meier plot of local recurrence-free survival

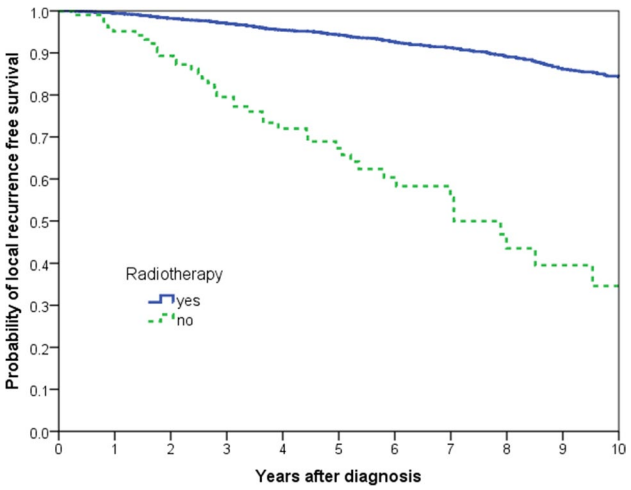

Fig. 6 Kaplan–Meier plot of local recurrence-free survival in patients with tumor size T1

and require a subsequent radiation to decrease local recurrence risk. Veronesi and colleagues determined that young age and peritumoral invasion favor local recurrence, whereas tumor size and nodal status correlate with distant but not local recurrence [13–15]. Consequently, guideline adherence matters most in young patients < 50 years to reduce the risk of local relapse. A main cause for non-adherence to guideline recommendations may be patient's refusal and advanced age as reported in records.

The study confirms the benefit of RT on overall and recurrence-free survival. Both 3-year and 5-year OAS were significantly higher in patients treated with RT, and the 5-year OAS rates were 93.1% in patients with RT compared to 79.0% with surgery only (Fig. 1). Even after adjustment for further influential variables, better overall survival persisted in the RT group (HR 0.64, 95% CI 0.46–0.88, $p = 0.007$). In this cohort, 10-year OAS was 83.0% with RT and 51.7% with surgery alone. This finding is comparable to the data from Corradini et al. [16]. The shown survival advantage emphasizes the importance of guideline concordant RT and is in accordance with a meta-analysis of 17 randomized trials [17].

Based on the hypothesis, that cancer cells react with a higher degree of sensitivity to radiation than normal cells, adjuvant RT is used to remove tumor deposits after surgical therapy [8]. Hence, the effect of radiation on local recurrence risk can also be seen in this analysis. 5 years after diagnosis, RT-treated patients showed 2.0% local recurrence rate vs. 27.4% in non-RT-treated patients (HR 0.07, 95% CI 0.05–0.10, $p < 0.001$). This finding is comparable to the meta-analysis of Early Breast Cancer Trialists' Collaborative

Group (EBCTCG): in this cohort, the 5-year risk of local recurrence was 26% of patients without RT [18].

Consequently, the difference in RFS between treated and untreated patients is even stronger than for survival (HR 0.20, 95% CI 0.16–0.26, $p < 0.001$). Thus, 10-year recurrence-free survival amounts 80.5% in patients who received RT compared to 36.0% in patients without RT. A comparable retrospective register-based study reported a 10-year RFS of 42.0% in patients treated in RT facilities cohort who only received surgery. The cause of this difference in recurrence-free survival is not to be found in a worse treatment quality. In this study, patients who were not treated with RT represent a collective with an unfavorable prognosis due to severe comorbidities or advanced age. Such confounders can lead to lower 10-year RFS rates [16].

Since these data derive from a regional clinical cancer registry, it might not be a representative for international comparisons. Furthermore, risk adjustment was possible for the most important factors, though not for comorbidities. There might have been concurrent life shortening health issues for example, that lead to refusal of RT. Furthermore, non-compliance to RT might implicate non-compliance to other therapies as well. It cannot be ruled out that to some extent survival is worse in those without RT for this reason. Patients were followed up over an extensive period of time concerning vital and relapse status. Any lack of information on RT was criteria for exclusion of the study. However, these data derive from a large population-based and multicentric cohort followed up in a real life health care situation. Consequently, it can be used to analyze the structures of patient-centered, guideline adherence and efficacy of recommended therapies in real life situation.

In recent years, the question arises whether RT can be withheld for a certain low-risk subgroup of breast cancer patients. According to the 15th St. Gallen International Breast Cancer Conference in 2017, older women > 65–70 years, with ER +, low-stage tumors, and no lymph node involvement have a low risk of local recurrence [19]. In this study, older patients ≥ 70 years show a worse local RFS, whether they received RT or not. Nevertheless, elderly patients benefit statistically significant from RT as well. 3 years after cancer diagnosis, local RFS is higher within irradiated patients. Patients with small tumors (T1) generally boast a better RFS, though there is still a statistically significant difference between T1 patients with and without RT.

In the last decade, several clinical analyses tried to evaluate the omission of adjuvant radiotherapy in patients with above mentioned good prognostic factors. A prospective, multicenter study was launched in Italy to investigate local recurrence and OAS when irradiation is omitted. One treatment arm received BCS and whole-breast irradiation (WBI) and the second arm received only BCS. After a medium follow-up of 108 months, there was no statistically significant difference regarding local recurrence and death in the two treatment groups [20]. Nevertheless, the Milan Cancer Center required long-term follow-up studies. Moreover, a few studies compared local relapse and survival in patients treated with endocrine therapy and RT versus endocrine therapy alone [21–24]. Local recurrence rates were significantly higher in patients without irradiation but neither hormone treatment nor RT showed a clinically relevant survival benefit. Due to side effects of endocrine therapy such as cardiovascular disease or complication through osteoporosis and bone fracture, the estimated 5-year adherence of tamoxifen differs from 35 to 60% [25]. Consequently, this observation should be considered in the multidisciplinary decision-making process of omitting RT in favor of other adjuvant therapies.

Regarding the current discussion, Poortmans et al. suggest a more personalized treatment to avoid overradiation [26]. Now, physicians take classical risk factors as age, margins, lymph node involvement, tumor size, hormone receptor status and HER2 expression in decision-making process into account. Nevertheless, future studies have to investigate the role of molecular subtypes for local recurrence risk. Although subgroups exhibit low risk for local relapse, they also benefit from RT due to local tumor control [27]. This finding could be also demonstrated in the following study. It has been shown, that luminal A tumors exhibit enhanced radiosensitivity, whereas HER2-positive also triple-negative tumors are more radioresistant [28, 29].

Meanwhile, the burden of whole-breast RT was reduced over the last years through hypofractionated schedules, reduction of target volume and dose. In addition, constantly increasing costs in public health and aging society (rising incidence of breast cancer in elderly people) require more adequate treatment and the avoidance of overtreatment. According to the current German S3 guideline for diagnosis, treatment and follow-up care of breast cancer, limited life expectancy (< 10 years), small tumor size (pT1), negative nodal status (pN0), cell-free margins and HER2-negative patients with endocrine therapies could be an exception for the conduction of RT at the risk of higher local recurrence rates [3]. Nevertheless, long-term studies of omitting RT in subgroups and other systemic adjuvant therapies are still missing.

Conclusion

In conclusion, this population-based study demonstrates that guideline adherent RT is accomplished from the beginning, remaining stable over 10 years. The implementation of German S3 guidelines leads to a statistically significant better OAS and RFS. We conclude that these positive effects of

guideline adherent RT could be confirmed on the basis of registry data in real life situation. Consequently, it is now of great importance to evaluate the omission of RT in patients with good prognostic factors to avoid overradiation.

Author contribution TW: project development, data collection, data analysis, and manuscript writing. OO: project development and manuscript editing. MG: project development, data collection, data analysis, and manuscript editing. MK: project development and manuscript editing. OK: manuscript editing. ECI: project development and manuscript editing.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this retrospective type of study formal consent is not required.

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human and/or animal participants This article is a retrospective study and does not contain any studies with human participants or animals performed by any of the authors.

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