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CLINICAL TRIAL

Comparing the outcome between multicentric and multifocal breast cancer: what is the impact on survival, and is there a role for guideline-adherent adjuvant therapy? A retrospective multicenter cohort study of 8,935 patients

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Abstract Multifocal (MF) and multicentric (MC) breast cancers have been comprehensively studied, and their outcomes have been compared with unifocal (UF) tumors. We attempted to answer the following questions: (1) Does MF/MC presentation influence the outcome concerning BC mortality?, (2) Is there an impact of guideline-adherent adjuvant treatment in these BC subtypes?, and (3)What is the influence of guideline violations concerning surgery (breast-conserving surgery versus mastectomy) on the survival of MF/MC BC patients? Between 1992 and 2008, we retrospectively analyzed 8,935 breast cancer patients from 17 participating breast cancer centers within the BRENDA study group. Of 8,935 breast cancer patients, 7,073 (79.2 %) had UF tumors, 1,398 (15.6 %) had MF tumors, and 464 (5.2 %) had MC tumors. RFS was significantly worse for MF/MC BC patients compared to patients with UF tumors (MF $p = 0.007$; MC $p = 0.019$). OAS was significantly worse for MC patients but not for MF patients compared to patients with UF tumors (MF $p = 0.321$; MC $p = 0.001$). Guideline adherence was significantly lower in patients with MF ($n = 580$; 41.5 %) and MC ($n = 204$; 44.0 %) compared to patients with UF ($n = 3{,}871$; 54.7 %) ($p < 0.001$) tumors. Guideline violations were associated with a highly significant deterioration in survival throughout all subgroups except for MC, with respect to RFS and OAS. For 100 %-guideline-adherent patients, we could not find any significant differences in RFS and OAS after adjusting by nodal status, grade, and tumor size. Furthermore, we could not find any significant differences in RFS and OAS in patients with MF or MC stratified by breast-conserving therapy (*BCT* lumpectomy and radiation therapy) and mastectomy. There is a strong association between improved RFS and OAS in patients with MF/MZ BC. There are no significant differences in RFS and OAS for patients with breast-conserving therapy or mastectomy.

Keywords Breast cancer · Multicentric · Multifocal · Guideline adherence · Survival · Cohort study

Introduction

Breast cancer (BC) comprises a complex and heterogeneous group of diseases at the clinical, morphologic, and molecular levels [1–4]. Aside from well-established factors for predicting the outcome of BC, the impact of multicentric (MC) and multifocal (MF) BC on survival is not well characterized. The incidence of MC and MF tumors in the literature ranges from 6 to 60 % [5–7]. Advances in preoperative breast imaging have especially increased the rates of MC and MF breast cancers [8–10]. MC and MF breast carcinomas have increased lymph node involvement compared to unifocal (UF) breast cancer, and available data suggest that MC/MF breast cancers carry worse overall outcomes than UF disease [11–16]. However, the literature is divided on whether there is a corresponding

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negative impact on survival. In other studies, multifocality itself does not appear to be a contributing factor for a worse outcome [17]. The outcome in breast cancer is also dependent on several other factors, such as hormone receptor expression or tumor size. In the current TNM-staging guidelines, the gold standard method to treat MC and MF breast cancers is based on the diameter of the largest tumor, without taking other foci of the disease into consideration [18, 19]. It is also generally accepted to investigate parameters such as hormone receptor expression, erbB-2 receptor expression, and ki-67 status on the largest tumor, although this might ignore individual foci, which may be different due to tumor heterogeneity [18, 19]. Recently, Lynch et al. [5] found MC/MF breast cancers to be associated with poor prognostic factors, but MC/MF were not independent predictors of worse survival outcomes.

In this large retrospective multicenter cohort study, we aim to investigate the impact of MC/MF breast cancer defined according to the TNM classification on survival, but we also aim to investigate if current internationally validated guidelines present effective treatment recommendations to improve outcomes in these subtypes of breast cancer.

Materials and methods

In this retrospective multicenter cohort study, we analyzed data from 8,935 patients with primary breast cancer 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 (*BRENDA* breast cancer care under evidence-based guidelines) was designed and used. This system included a retrospective chart review to extract TNM-stage, histologic subtype, grading, lymphatic and vascular invasion, estrogen/progesterone/erbB-2-expression, date of diagnosis, and all adjuvant therapies. Data on adjuvant therapies, including surgery (date of surgery, *BCT* breast-conserving surgery, mastectomy, sentinel-node-biopsy, and axillary lymph node dissection), adjuvant systemic chemotherapy, adjuvant endocrine therapy, and adjuvant radiotherapy, were collected. During the follow-up, data on the first recurrences, secondary primary tumors, and date as well as the cause of death were collected. Questionnaires were sent to physicians involved in follow-up care, to local death registers and to patients to determine the recurrence and survival status of patients. As measures of comorbidity, the American Society of Anesthesiologists Physical Status (ASA) and the New York Heart Association cardiac score (NYHA) were collected for all patients at the time of surgery. Furthermore, the occurrences of myocardial infarction, stroke, and malignant diseases were collected. A team of medical documentalists, who were all specially trained for the BRENDA documentation system, performed the documentation in the participating breast cancer centers and in the university department in Ulm. Owing to the thorough registrar training and computerized consistency checks, the quality of these data is considered high [20].

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 were carcinoma in situ, primary metastatic disease, bilateral breast cancer, primary occult disease, phyllodes tumor, and patients with incomplete follow-up.

The definition of multicentric and multifocal breast cancer is based on the internationally accepted definition, which defines multifocal breast cancer as being localized within the same quadrant. Multicentric breast cancer is defined as being localized in different quadrants of the breast. If patients showed both multicentric and multifocal breast cancer lesions, they were defined as being multicentric.

The definition of evidence-based guideline-adherent adjuvant treatment was based on internationally validated guidelines. Wolters et al. [21] demonstrated that treatment recommendations within national guidelines (all guidelines valid in 2011) are identical and only differ marginally in adjuvant endocrine therapy. We therefore decided to base the definition of guideline-adherent adjuvant treatment on the German national consensus guideline [S3-guideline, retrieved 2008 (not annually updated)] for the decision of loco-regional treatment (surgery, radiotherapy), for chemotherapy, and for endocrine therapy [22]. All applied therapy regimens were retrospectively evaluated concerning their adherence to the S3-guideline. The omission of any suggested adjuvant treatment or the abandonment of any adjuvant treatment was classified as noncompliance with the suggested adjuvant therapy. Therefore, the adjuvant therapy is divided into subgroups (operation on the breast, axillary lymph node dissection, chemotherapy, endocrine therapy, and radiotherapy) (see Table 1).

Statistical analysis

The primary endpoints are RFS and OAS. Nominally scaled variables were tabulated in contingency tables and tested for differences in frequency distribution. Variables for location and variance were calculated whenever ordinally or intervally scaled continuous variables were involved. The comparisons of categorical variables

Table 1 Inclusion criteria for guideline adherence based on the German national consensus guideline (S3-guideline) for the decision for loco-regional treatment (surgery, radiotherapy), chemotherapy, and endocrine therapy

Conform to guideline recommendations	Nonconform to guideline recommendations
Group A—surgical therapy	
Breast-conserving therapy (References: statements 7, 8)	
BCT in DCIS and LCIS <4 cm	BCT when tumor size >4 cm
BCT in R0	BCT in R1
	BCT in presence of multicentricity
	BCT in presence of inflammatory carcinoma
Mastectomy (References: Statement 9)	
Mastectomy for microcalcification of malignant type	No mastectomy in the presence of microcalcification of malignant type
Mastectomy for intraductal carcinoma and tumor size > 4 cm	No mastectomy in the presence of multicentricity
Mastectomy for multicentricity	Mastectomy for intraductal carcinoma with a tumor size <4 cm
Mastectomy for R1	No mastectomy for inflammatory breast cancer
Mastectomy for inflammatory breast cancer	
Axillary dissection (References: Statements 12, 13)	
Removal of invasive carcinoma + dissection for at least level I and II + removal of at least 10 lymph nodes	Lymph node removal in noninvasive carcinoma
	Invasive carcinoma + (only dissection for level I or removal of < 10 lymph nodes)
Group B—Radiotherapy	
Radiotherapy secondary to BCT (References: statements 23, 24)	
Radiotherapy secondary to BCT for invasive carcinoma	No radiotherapy secondary to BCT for invasive carcinoma
Postmastectomy strategy (References: Statements 25, 26)	
Radiotherapy secondary to mastectomy and R1/R2	Radiotherapy in mastectomy and R0
Radiotherapy secondary to mastectomy and nodes involved ≥4	Radiotherapy in mastectomy and T = T1 or T2
Radiotherapy T = T3 or T4	No radiotherapy in mastectomy and R1/R2
	No radiotherapy in mastectomy and nodes involved ≥4
	No radiotherapy in T = T3 or T4
Group C—Endocrine therapy	
Endocrine therapy (References: statements 33–37)	
Tamoxifen for invasive carcinoma in patients with positive hormone receptor status	Hormone therapy in receptor-negative patients
GnRH + Tamoxifen or GnRH in premenopausal patients with positive hormone receptor status	
Postmenopausal patient and positive hormone receptor status and tamoxifen or aromatase inhibitor	
Endocrine therapy after chemotherapy in positive receptor status	
Tamoxifen for DCIS	

Risk group	Chemotherapy	Guideline conformity
When ER (estrogen receptors) and PgR (progesterone receptors) are negative		
Low	CTx performed	Overtherapy
	No CTx performed	Guideline conformity
Moderate	CMF/EC/AC	Under-therapy
	FEC/T	Guideline conformity
	No CTx performed	Under-therapy
High	CMF/EC/AC	Under-therapy
	FEC/T	Guideline conformity
	No CTx performed	Under-therapy

Table 1 continued

Risk group	Chemotherapy	Guideline conformity
ER and PgR >0 and <6		
Low	CTx performed	Overtherapy
	No CTx performed	Guideline conformity
Moderate		
Premenopausal	CTx performed	Guideline conformity
	No CTx performed	Guideline conformity
Postmenopausal	CTx performed	Guideline conformity
	No CTx performed	Under-therapy
High	CMF/EC/AC	Under-therapy
	FEC/T	Guideline conformity
ER or Pgr ≥6		
Low	CTx performed	Overtherapy
	No CTx performed	Guideline conformity
Moderate	CTx performed	Guideline conformity
	No CTx performed	Guideline conformity
High	CMF/EC/AC	Undertherapy
	FEC/T	Guideline conformity
	No CTx performed	Undertherapy

DCIS ductal carcinoma in situ, *R1/2* microscopic incomplete tumor resection/macroscopic incomplete tumor resection, *CTx* Chemotherapy, *CMF* Cyclophosphamide, methotrexate, fluorouracil, *EC/AC* Epirubicin cyclophosphamide/Doxorubicin cyclophosphamide, *FEC* Fluorouracil, epirubicin, cyclophosphamide, *T* Taxanes

between groups were performed using $\chi 2$ tests. Standard survival analysis using a Kaplan–Meier approach was performed to assess RFS and OAS. The log-rank test was used to provide a formal statistical assessment of the differences between treatment arms with respect to RFS, OAS, etc. The Cox proportional hazards model was used to estimate the hazard ratio (HR) and confidence intervals (CIs). Multivariate Cox proportional hazard regression models were used to adjust for differing risk factor distributions between 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 baseline status. There is always a fundamental risk for selection bias by analyzing non-randomized data (meaning that the patients of several groups to be compared were not assigned to these groups with the same probability). Therefore, the results were adjusted by taking into account all measurable confounders and inhomogeneities in baseline status initially in the form of multivariate adjustment using the "Cox proportional hazard regression" method, and the data were further analyzed in tiers according to the basic risk factors. We calculated several Cox models. First, we generated a model in which each variable is represented by a single model term. Then, we included in the model all main effects, two-way interactions, three-way interactions, and four-way interactions, representing all possible interactions of our four main prognostic parameters.

Results

The clinical cohort consisted of 8,935 patients with histologically confirmed invasive breast cancer. In this cohort, 7,073 (79.2 %) patients had unifocal BC [median age: 62 years (range 18–98)], 1,398 (15.6 %) had multifocal BC [median age: 59 years (range 22–94)], and 464 (5.2 %) had multicentric BC [median age: 60 years (range 24–91)]. Of the patients, 21.8 % were premenopausal, and 74.3 % were postmenopausal. There was no significant difference ($p = 0.192$; independent samples median test) between the median observation times for unifocal BC (54 months), multifocal BC (55 months), and multicentric BC (50 months). Patients with MC or MF BC had a significantly (Pearson χ^2 $p < 0.001$) higher risk for Nottingham Prognostic Index (NPI) than patients with UF carcinomas (high risk MC 36.6 %; MF 22.9 %; UF 14.8 %). MC carcinomas were significantly (Pearson χ^2 $p < 0.001$) more often in locally advanced T3/T4-status than MF or UF carcinomas (T3/T4 MC 10.1 %; MF 4.4 %; UC 4.3 %). Additionally, in the case of lymph node metastasis, there were significantly (Pearson χ^2 $p < 0.001$) more patients with positive nodes in MC or MF breast cancers compared

to patients with UF tumors [$1 \leq n \leq 3$: MC (25.6 %), MF (26.0 %), UF (20.5 %); $3 < n \leq 10$: MC (18.1 %), MF (13.8 %), UF (8.6 %); $n > 10$: MC (17.7 %), MF (7.8 %), UF (4.1 %)]. The percentage of G1-patients decreases from UF to MC carcinomas [G1 UF (9.8 %), MF (6.2 %), MC (4.1 %)].

The rate of premenopausal women was significantly (Pearson χ^2 $p < 0.001$) higher in MC (24.8 %) and MF (26.6 %) than in UF (20.6 %) patients. The basic characteristics are shown in Table 2.

We initially attempted to identify the impact of multicentricity and multifocality on survival and therefore chose UF tumors as a reference group. Compared to UF breast cancer, RFS was significantly worse in MC [RFS $p = 0.019$; HR 1.38 (95 % CI 1.06–1.80)] and in MF [RFS $p = 0.007$; HR 1.25 (95 % CI 1.06–1.48)] breast cancer patients (see Fig. 1). Compared to UF breast cancer, OAS was significantly worse in MC breast cancer patients [OAS $p = 0.001$; HR 1.46 (95 % CI 1.16–1.83)]. In contrast, we could not find a significant difference in OAS by comparing MF to UF cancers [OAS $p = 0.321$; HR 0.92 (95 % CI 0.79–1.08)].

In our dataset, we were able to distinguish between the following tumor subtypes HR+/Her2−, HR+/Her2+,

Table 2 Baseline characteristics of the study group

	Total *n* (%)	Unifocal *n* (%)	Multifocal *n* (%)	Multicentric *n* (%)	Significance *p*
Number	8,935 (100)	7,073 (79.2)	1,398 (15.6)	464 (5.2)	
Age at the first diagnosis	61 ± 13	62 ± 13	59 ± 13	60 ± 14	<0.001
	Median 62	Median 63	Median 60	Median 61	
	Range 18–98	Range 18–98	Range 22–94	Range 24–91	
Menopausal status					
Unknown	45 (0.5)	36 (0.5)	8 (0.6)	1 (0.2)	<0.001
Premenopausal	1,944 (21.8)	1,457 (20.6)	372 (26.6)	115 (24.8)	
Perimenopausal	303 (3.4)	226 (3.2)	61 (4.4)	16 (3.4)	
Postmenopausal	6,643 (74.3)	5,354 (75.7)	957 (68.5)	332 (71.6)	
Grading					
1	802 (9.0)	696 (9.8)	87 (6.2)	19 (4.1)	<0.001
2	5,500 (61.6)	4,346 (61.4)	863 (61.7)	291 (62.7)	
3	2,606 (29.2)	2,013 (28.5)	442 (31.6)	151 (32.5)	
Unknown	27 (0.3)	18 (0.3)	6 (0.4)	3 (0.6)	
Receptor status					
Negative	1,299 (14.5)	1,049 (14.9)	193 (13.8)	57 (12.3)	0.294
Positive	7,626 (85.3)	6,017 (85.1)	1,202 (86.0)	407 (87.7)	
Unknown	10 (0.1)	7 (0.1)	3 (0.2)	0 (0.0)	
T-category					
T1	5,087 (56.9)	4,123 (58.3)	780 (55.8)	184 (39.7)	<0.001
T2	3,386 (37.9)	2,606 (36.8)	554 (39.6)	226 (48.7)	
T3	389 (4.4)	288 (4.1)	56 (4.0)	45 (9.7)	
T4	25 (0.3)	18 (0.3)	5 (0.4)	2 (0.4)	
TX	48 (0.5)	38 (0.5)	3 (0.2)	7 (1.5)	
Nodal status					
Nodal negative	5,531 (61.9)	4,628 (65.4)	724 (51.8)	179 (38.6)	<0.001
$1 \leq n \leq 3$	1,929 (21.6)	1,447 (20.5)	363 (26.0)	119 (25.6)	
$3 < n \leq 10$	882 (9.9)	605 (8.6)	193 (13.8)	84 (18.1)	
$n > 10$	484 (5.4)	293 (4.1)	109 (7.8)	82 (17.7)	
Unknown	109 (1.2)	100 (1.4)	9 (0.6)	0 (0.0)	
Guideline					
Adherent	4,655 (52.1)	3,871 (54.7)	580 (41.5)	204 (44.0)	<0.001
nonadherent	4,280 (47.9)	3,202 (45.3)	818 (58.5)	260 (56.0)	

The *p* values are based on differences between the reference groups using the χ^2 test

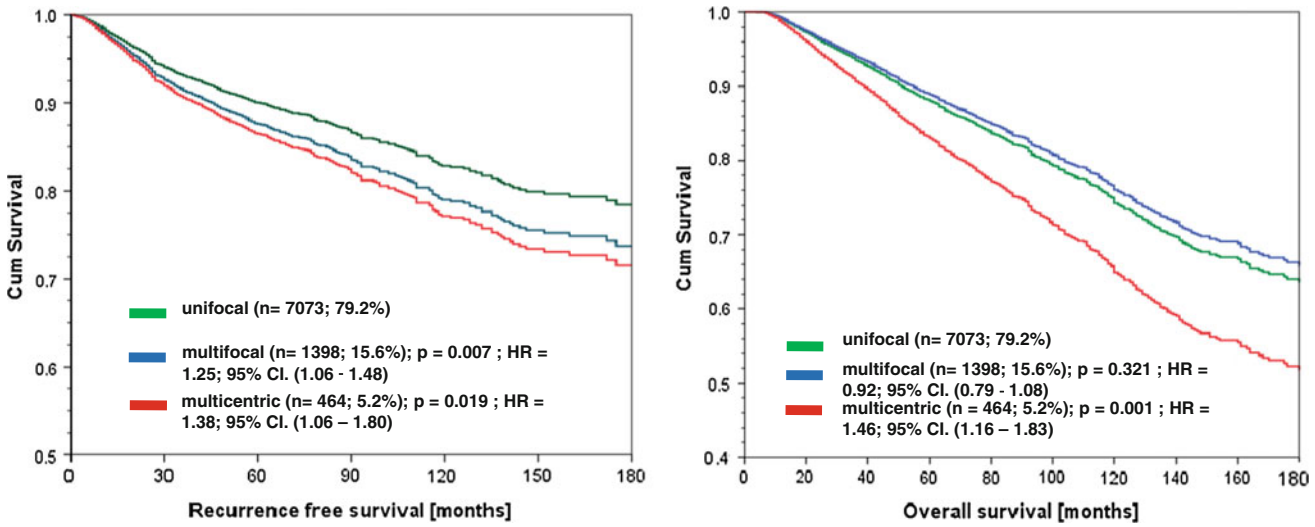

Fig. 1 Recurrence-free and overall survival stratified for unifocal, multifocal, and multicentric breast cancers

HR−/Her2+, and HR−/Her2−. When assessing the impact of these subtypes on survival parameters in MF and MC subtypes, we observe an analog to UF subtype that in both MF and MC HR−/Her2− subtypes demonstrates the most unfavorable outcome, followed by HR−/Her2+, HR+/Her2+, and HR+/Her2− subtypes.

Guideline adherence

54.7 % (3,871) of the UF subgroup, 41.5 % (580) of the MF subgroup, and 44.0 % (204) of the MC subgroup were treated in a 100 % guideline-adherent fashion in all adjuvant treatment modalities (Table 2). Compared to UF, there was a significantly reduced guideline adherence in MF and MC breast cancers (Pearson χ^2 $p < 0.001$). We then attempted to correlate ASA and NYHA score with guideline adherence in UF/MF/MC. We could observe a statistically significant increase in guideline violations for both ASA 3–4 and NYHA 3–4 in UF ($p < 0.001/p = 0.001$). Surprisingly, in MF and MZ, we could not demonstrate a significant influence of the rates of guideline adherence by ASA/NYHA 1–2 versus ASA/NYHA 3–4, indicating that comorbidities measured by ASA and NYHA scores do not influence guideline adherence in MF/MZ. As a next step, we compared the dependencies of RFS and OAS on guideline adherence in the three subgroups. UF and MF patients with nonguideline-adherent treatment had a significant decrease in RFS and OAS [UF: RFS $p < 0.001$; HR 2.65 (95 % CI 2.26–3.11); OAS $p < 0.001$; HR 3.74 (95 % CI 3.21–4.36)] and [MF: RFS $p = 0.001$; HR 1.77 (95 % CI 1.27–2.47); OAS $p < 0.001$; HR 2.97 (95 % CI 2.00–4.40)] compared to patients with 100 % guideline adherence. For MC patients with nonguideline-adherent treatment, we observed a significant decrease in OAS [OAS $p = 0.003$; HR 2.19 (95 % CI 1.32–3.65)] compared to patients with 100 % guideline adherence (Fig. 2) as well as a decrease in RFS [RFS $p = 0.077$; HR 1.64 (95 % CI 0.95–2.84)], but with a borderline p value of 0.077.

Next, we compared RFS and OAS for patients with 100 % guideline adherence throughout the three subgroups of UF, MF, and MC. As a result of the imbalance of prognostic factors in these subgroups, there should be a significant decrease at least in RFS and perhaps also in OAS for MF and MC patients compared to UF patients. Indeed, guideline-adherent MC patients had a significant decrease in RFS and OAS [MC: RFS $p = 0.013$; HR 1.81 (95 % CI 1.13–2.90); OAS $p = 0.003$; HR 2.03 (95 % CI 1.28–3.21)], and guideline-adherent MF patients also had a significant decrease in RFS [MF $p = 0.009$; HR 1.51 (95 % CI 1.11–2.07)] but no significant decrease in OAS [MF $p = 0.858$; HR 0.97 (95 % CI 0.66–1.42)] compared to guideline adherent UF patients (Fig. 3).

After adjusting for age, tumor size, grading, and nodal status, we could not find any significant difference in RFS and OAS between 100 %-guideline-adherent MF or MC patients in comparison to 100 %-guideline-adherent UF patients [MC: RFS $p = 0.356$; HR 0.88 (95 % CI 0.67–1.16); OAS $p = 0.542$; HR 1.08 (95 % CI 0.85–1.36)] and [MF: RFS $p = 0.597$; HR 1.05 (95 % CI 0.89–1.24); OAS $p = 0.282$; HR 0.92 (95 % CI 0.78–1.08)] (Fig. 4).

Guideline violations concerning BCT

As a further step, we investigated the impact of guideline violations concerning surgery on survival. In the case of

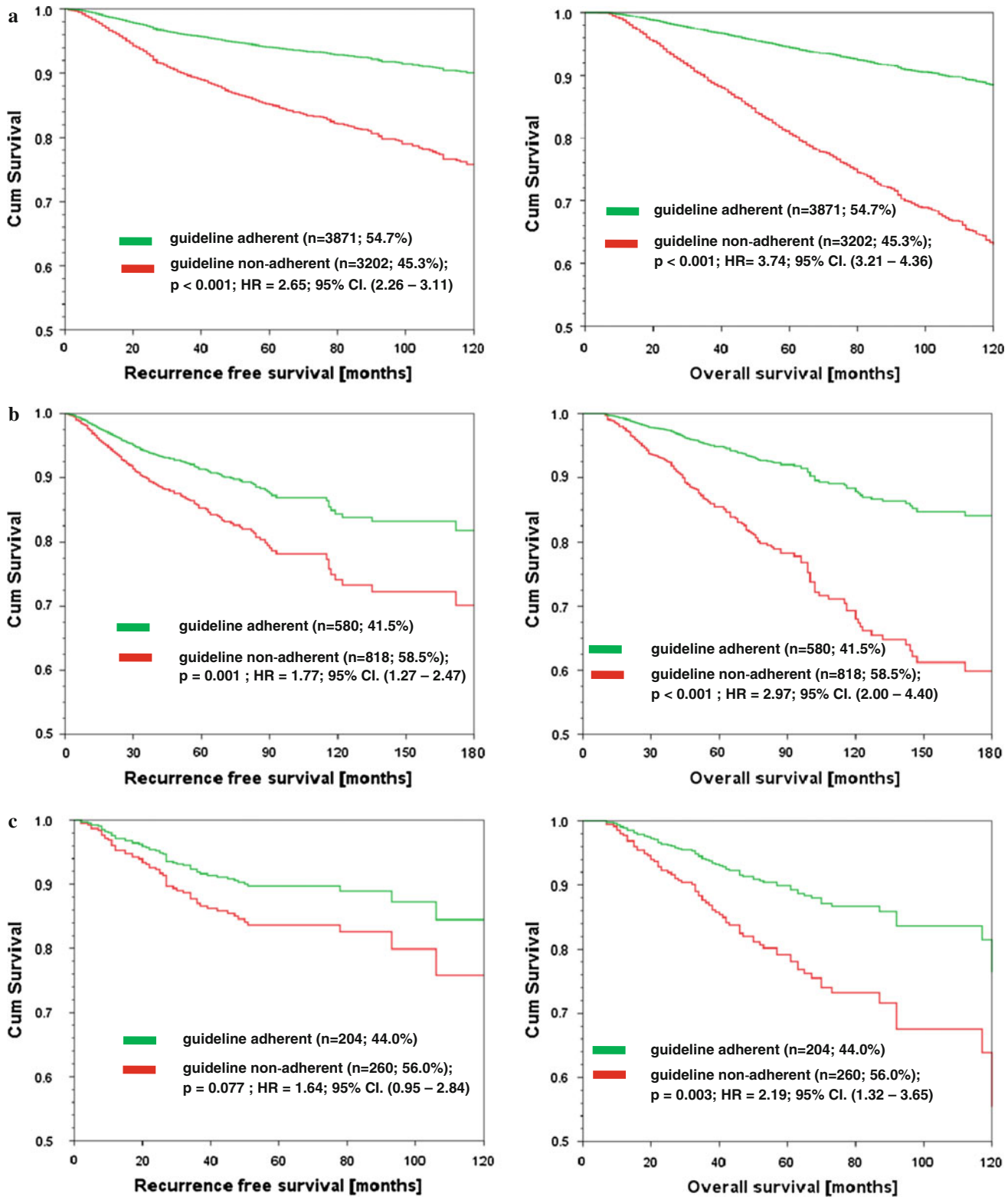

Fig. 2 Recurrence-free and overall survival stratified for 100 % guideline adherence in unifocal (**a**), multifocal (**b**), and multicentric breast cancers (**c**)

MF breast cancers (only T1/T2), both BCT followed by radiotherapy (RT) ($n = 623$, 47.6 %) and mastectomy ($n = 319$, 23.9 %) are guideline-adherent options. When comparing MF (only T1/T2 and 100 % guideline conformity in all other treatment modalities) patients receiving BCT followed by RT versus mastectomy, we could not find

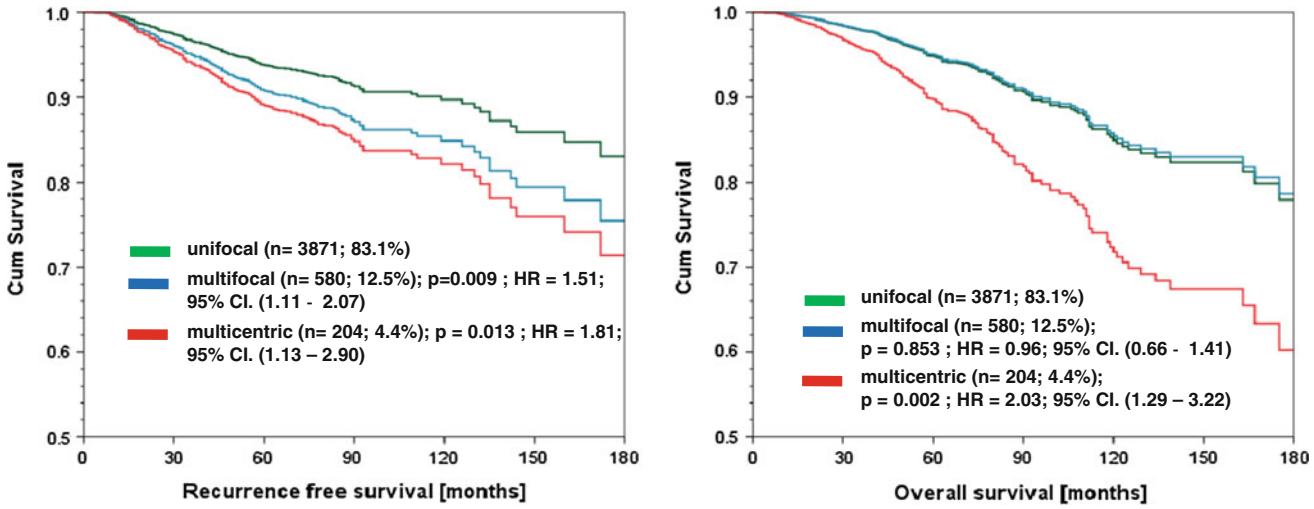

Fig. 3 Recurrence-free and overall survival of 100 %-guideline-adherent patients (not adjusted)

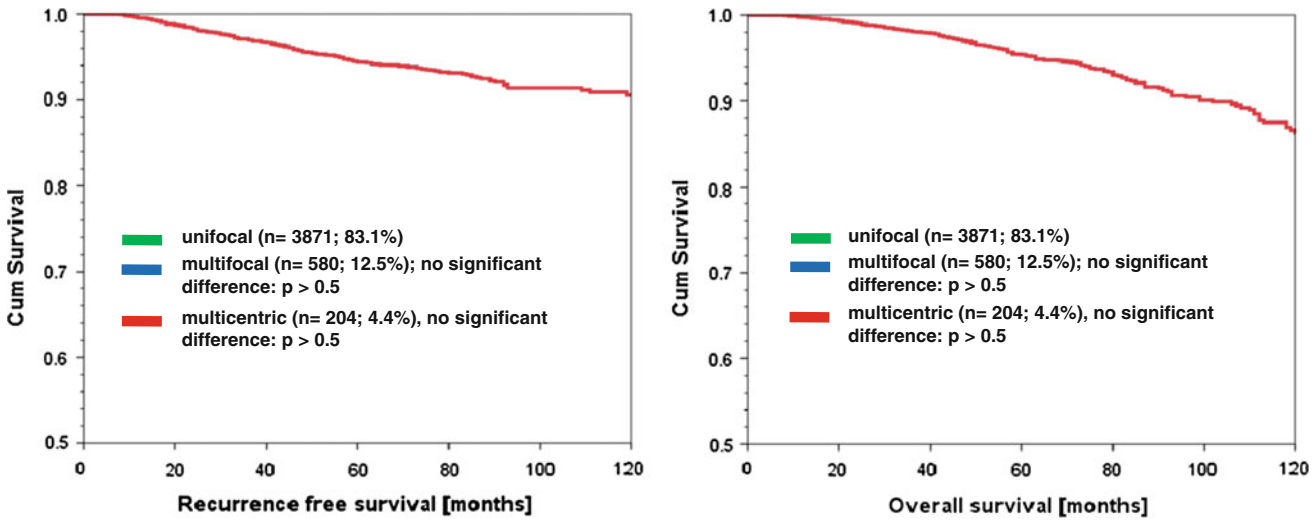

Fig. 4 Recurrence-free and overall survival of 100 %-guideline-adherent patients, adjusted for tumor size, nodal status, grading, and Nottingham prognostic index

a significant difference in RFS [$p = 0.284$; HR 1.25 (95 % CI 0.83–1.88)] (see Fig. 5).

In MC breast cancers, BCT followed by RT is not a guideline-adherent option. However, there is some evidence that small tumors in which complete tumor resection with appropriate cosmetic results can be achieved might be able to be treated via BCT. In our collective 60 patients, 13.0 % with MC breast cancer received BCT followed by RT. When comparing BCT followed by RT, mastectomy ($n = 184$, 39.9 %), and mastectomy followed by RT ($n = 217$, 47.1 %), we have to consider the impact of tumor size on survival. The impact of tumor size on survival is thereby highly significant in MC breast cancer (Fig. 6). We therefore had to adjust our data for tumor size. After adjusting, we could not find a significant difference between BCT followed by RT (only if R0 resection could be achieved), mastectomy ($p = 0.710$), and mastectomy followed by RT ($p = 0.648$) (see Fig. 6).

Discussion

Multifocal and MC breast cancers remain a challenge for clinical oncologists. One of the most important problems facing multicentricity and multifocality is the lack of standardized definitions. However, several authors have reported that MF and MC breast cancers are associated with poorer prognostic factors, and this study confirms

these prior results. In this study, MF and MC breast cancers showed significantly inferior survival parameters compared to UF carcinomas. Nevertheless, guideline-adherent adjuvant treatment is associated with an improvement in survival throughout all investigated subgroups (UF, MF, and MC). When comparing the outcome of all 100 %-guideline-adherent patients, the MF and MC subgroups remain inferior with respect to survival. After adjusting our data, we could not find a significant difference, which suggests that the associated poorer prognostic factors might be the reason for the inferior outcome in MF and MC. We also could not demonstrate any difference in BCT versus mastectomy in MF (only T1/T2) or after adjusting for tumor size in MC breast cancer.

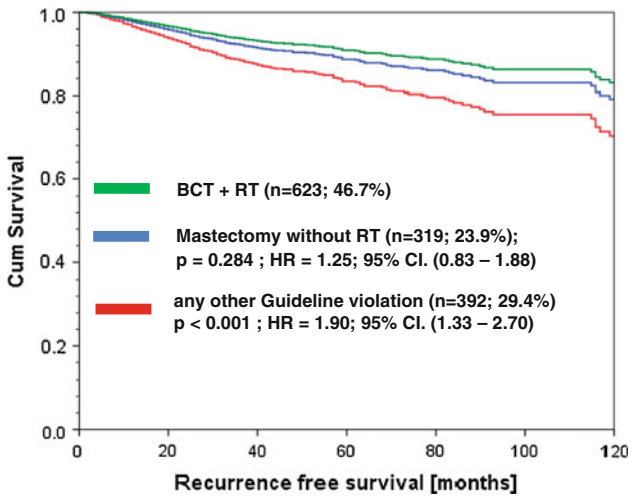

Fig. 5 Recurrence-free survival in multifocal (MF) breast cancer patients stratified for BCT followed radiotherapy and mastectomy versus patients (MF) with any other guideline violation

Although the literature provides conflicting results concerning the impact of MF and MC on survival, there are several studies that confirm the results of this trial [11–16]. We also already know from several studies that MF and MC breast cancers are associated with poorer prognostic factors, such as more frequent lymph node metastasis. Recently, Lynch et al. [5] hypothesized that the inferior outcome in these subgroups might be based on the poorer prognostic factors. They found multicentricity and multifocality not to be independent predictors of outcome. However, there is large variability of findings in the literature. Several authors describe survival differences based on a single tumor lesion size (<2 cm) [23]. With respect to the current evidence, we cannot sufficiently emphasize the need to conduct prospective studies addressing this question. Unfortunately, this retrospective trial is also unable to answer this question. We attempted to obtain retrospective data on tumor sizes and the histology variability of the different tumor foci, but based on the gold standard definition in the TNM system, it was not possible to obtain valid data on this question.

Internationally validated guidelines aim to improve outcome and medical service quality in breast cancer care. Based on the evidence gained primarily in prospective trials, several National and International breast cancer guidelines have been developed and are updated regularly. Nevertheless, the effect of guideline-adherent adjuvant treatment on the outcome in MF and MC breast cancer has, to the best of our knowledge, never been investigated. The most important difference between other clinical trials, which have already demonstrated survival benefits, and this

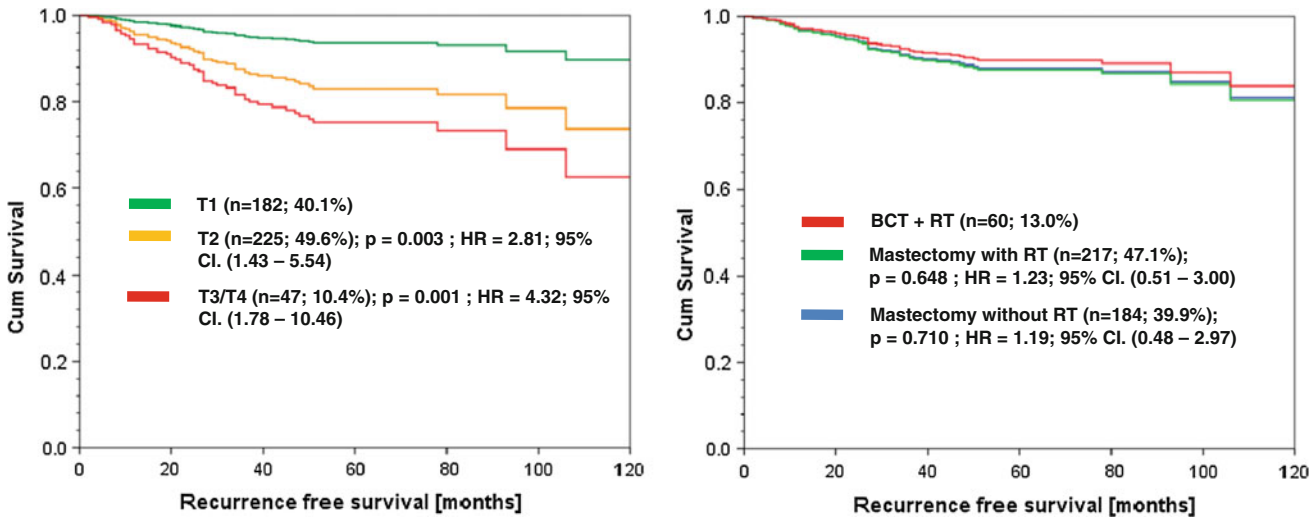

Fig. 6 Recurrence-free survival in multicentric breast (MC) breast cancer stratified for tumor size and recurrence-free survival stratified for BCT followed by RT, mastectomy, and mastectomy followed by RT and adjusted for tumor size

trial is the unselected collection of patients, which is associated with a higher incidence of patient- and physician-related factors that might prevent patients from effective guideline-adherent adjuvant treatments. In both the MF and MC subgroups, the percentage of guideline-adherent adjuvant treatment was significantly lower. Although patient-related and physician-related factors prevent patients from guideline-adherent treatment, comorbidities are most likely one of the most important factors preventing patients from guideline-adherent treatment, and this may substantially influence their prognosis [24, 25]. Unfortunately, this study cannot completely determine the importance of comorbidities for guideline adherence, because only NYHA and ASA scores were recorded. Recording Charlson scores, for example, might have been better, but this was not possible due to the retrospective design.

Several other confounding factors affecting both treatment and outcome in those patients were included in this study. To reduce this problem, we controlled for the most important prognostic factors (tumor size, grading, nodal status, and Nottingham prognostic index) in our analyses. There may be, however, physician-related factors that detain patients from guideline-adherent treatment. In fact, there is an association between age and patient-related, physician-related, and guideline-adherent treatments, which influences survival parameters. This might be an important factor in why guideline adherence decreases rapidly with age [26] and why both noncancer-related mortality is increasing and survival is impaired because of insufficient treatment. Hebert-Croteau et al. [26] even showed compliance with guidelines as an independent significant predictor of the survival of women with primary breast cancer [26]. There have only been a few health care research studies that have investigated the impact of guideline-adherent therapeutic regimens on clinical outcome [32–35]. These studies have confirmed that there appears to be a strong association between guideline-adherent treatment and improved survival, especially for several subtypes of breast cancer [27–30]. There are clearly methodological difficulties in all of these studies, including the present study's retrospective data collection. This design only allows us to draw associations between guideline-adherent treatment and survival parameters. Drawing causal conclusions concerning survival parameters would only be appropriate if treatment allocations were randomized and prospective. However, a randomization concerning guideline-adherent treatment is not viable, because we cannot randomly assign guideline-adherent and nonguideline-adherent therapeutic regimens to patients.

In the current internationally validated evidence-based guidelines, the recommendations concerning surgical treatment in MF and MC breast cancer are based on very limited evidence. It is therefore not clear if BCT could provide an opportunity demonstrating equal oncologic safety concerning survival parameters. This study also attempts to address the question of the adequate surgical approach in MF and MC breast cancer. In the MF subtype, both BCT and mastectomy would be appropriate guideline-adherent options for T1/2 tumors. In this case, we also could not demonstrate any significant difference in survival. In MC, tumor size has an important impact on survival [31], and after adjusting for tumor size, we could not demonstrate a significant difference in patients undergoing BCT or mastectomy. Recently, there has been some evidence that BCT can provide a feasible option in MF and MC breast cancer [32–34]. However, Chung et al. recently investigated a cohort of MF patients undergoing BCT and found that both RFS and OAS were significantly reduced in the group of MF carcinomas compared to UF breast cancer patients [35]. Further prospective and maybe randomized trials are needed to address the role of BCT in MF and MC.

To our knowledge, this is the first study demonstrating an association between guideline conformity in adjuvant treatment and survival in MF and MC breast cancers. We must ask why so many patients still cannot follow a guideline-adherent adjuvant treatment pathway. Unfortunately, this study cannot provide adequate answers to this question, because patient-related and physician-related circumstances could not be sufficiently documented. We also cannot emphasize enough the need to implement a standardized definition of MF and MC to unify our results. Additionally, in the case of BCT in MF and MC, we also cannot emphasize enough the need to design prospective trials addressing this issue. These efforts could provide the ability to improve upcoming breast cancer guidelines on the issues of multifocality and multicentricity in breast cancer.

Conclusion

With the current evidence addressing the issue of MF and MC breast cancers, we are confronted with conflicting results concerning the impact on survival. This trial demonstrated an inferior outcome in MF and MC breast cancer patients. However, guideline-adherent adjuvant treatment was associated with an improvement in survival parameters throughout UF, MF, and MC breast cancers. After adjusting our data, we could not find a significant difference in RFS and OAS between UF, MF, and MC carcinomas if 100 %-guideline-adherent treatment was applied. Our data suggest that the poorer prognostic factors in MF and MC breast cancers could be the reason for the inferior outcome.

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Ethical standard This study and the BRENDA project have been approved by the ethics committee of the University of Ulm.

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