Mastectomy and Breast Conserving Therapy Share Comparable Survival and Efficacy on Patients with Occult Breast Cancer: A Retrospective Study in China

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Abstract

Purpose This single-center retrospective study aimed to compare the efficacy of mastectomy and Breast Conserving Therapy (BCT) on overall survival (OS) and disease-free survival (DFS) and examine prognostic factors of Occult Breast Cancer (OBC) in China.

Methods We conducted a univariate Kaplan-Meier analysis and a multivariate Cox proportional hazards model on OBC patients in Cancer Hospital, Chinese Academy of Medical Science (CHCAMS), comparing prognostic factors including treatment plans, risk factors, TNM stages, metastasis, and recurrence.

Results Seventy patients with OBC undergoing axillary lymph node dissection (ALND) were included with median follow-up of 84.0 months. No statistically significant differences in OS (HR, 1.64; 95% CI, 0.59-4.51; *p*=0.327) and DFS (HR, 1.83; 95% CI, 0.60-4.89; *p*=0.200) were observed between mastectomy (n=23) and BCT (n=37). Positive estrogen receptor and progesterone receptor suggested better survival in univariate analysis. Patients with more severe N stage presented inferior survival. The association between radiotherapy and worse survival was probably because patients with higher TNM stages tended to receive radiotherapy. Low Ki-67 level (≤14%) predicted worse outcomes in both univariate and multivariate analyses.

Conclusion Mastectomy with ALND presented comparable prognosis outcomes to BCT with ALND for OBC patients.

Introduction

Breast cancer (BC) is the most prevalent malignancy and the main cause of cancer mortality in women [1]. Occult breast cancer (OBC) is a rare kind accounting for only 0.17-1% of all the breast tumors [2–4]. Patients with OBC have palpable axillary nodules with normal mammograms and chest radiographs rather than a prominent primary breast mass. Palpable axillary lymphadenopathy usually appears as a symptom of malignancy and metastasis [5]. Histologic examination via surgical excision biopsy or needle aspiration biopsy of axillary nodes can indicate an underlying breast tumor. OBC retains exclusive clinical characteristics, including an older age, a larger proportion of estrogen receptor (ER) and progesterone receptor (PR) negativity, a higher rate of human epidermal growth factor receptor-2 (HER2) positive status, 10 and more positive lymph nodes, and American Joint Committee on Cancer N2/3 stage, all of which have contributed to different survival outcomes [6–8]. Hidden lesions lead to less possibility for patients with OBC to receive surgical treatment than the non-OBC control. Mastectomy and axillary lymph node dissection (ALND) have been the recommended operative approach [5, 6].

OBC prognostic variables are under investigation, however, with few studies reported. Ongoing studies have been focusing on its optimal treatment plans, clinicopathological characteristics, accurate diagnosis, and prognosis. Recent retrospective studies and SEER population-based studies have mostly shown that OBC patients undergoing ALND alone or in combination with mastectomy or breast conserving therapy (BCT) shared similar treatment outcomes. Subsequent radiotherapy tends to improve

prognosis, implying the probability of conservative treatment [7, 9–13]. Several series reported that patients with OBC had a better or similar outcome than that of the non-OBC patients [7, 8, 14], particularly for those with N2/3 stage or positive ER/PR tumors [6]. Other series presented an unfavorable prognosis of OBC in comparison of Stage II non-OBC [15, 16]. The nodal status seems to be the strongest prognostic factor and other clinicopathological features (ER/PR negativity, triple-negative subtype, etc.) have also been postulated as predictors of survival [4, 6–9]. However, a large amount of the previous studies was based on heterogeneous public databases, most of which concentrated on North American and European populations. More attention is needed for the definitive treatments in Chinese and other Asian populations with denser and smaller breasts.

Herein, we conducted a retrospective study on OBC to investigate its prognosis factors and the efficacy of mastectomy with ALND and BCT with ALND at Cancer Hospital, Chinese Academy of Medical Science (CHCAMS). BC molecular subtypes, Ki-67 status, and the therapeutic effect of neoadjuvant chemotherapy on OBC prognosis were pioneeringly explored. This single-center study was conducted in one of the largest tumor-specialized hospitals in China recruiting a large cohort of Chinese OBC patients with sustainable follow-up and comprehensive information.

Methods

Data collection and study population

All participants were enrolled in Department of Breast Surgery at CHCAMS from September 1976 to September 2020 whose medical records were reviewed. *Clinical* OBC patients were eligible for recruitment if they had (1) a palpable axillary lymph node enlargement as the initial symptom; (2) axillary lymph node dissection (ALND); (3) pathologically confirmed metastatic adenocarcinoma of axillary lymph nodes via microscopic morphology and immunohistochemical analysis of biopsy specimens; (4) had no clear breast malignant space-occupying lesions in preoperative physical examinations, mammography, and ultrasonography [4, 8–10]. Patients with (1) axillary tail breast cancer; (2) previous history of ipsilateral or contralateral breast cancer; (3) other primary cancer origins rather than breast after relevant examinations; (4) confirmed distant metastases clinically, radiologically, or pathologically were excluded.

They were divided into BCT group and mastectomy group. BCT group included patients with/without radiotherapy undergoing breast conserving surgery or observation without other operation after ALND. Patients in the mastectomy group had a modified radical mastectomy with/without radiotherapy. Radiotherapy was applied to breast, chest wall, and lymph node drainage regions. The radiation target volume, dose, and location were prescribed according to patients' clinical conditions. Generally, radiotherapy was no longer given to axillary lymph nodes (LNs) after ALND but to the chest wall and LN drainage regions in the high recurrence risk population. Adjuvant and neoadjuvant therapy for each patient followed a standard protocol of the patient's molecular subtype.

Patient characteristics, including gender, age of diagnosis, preoperative imaging features, breast malignant evidence, TNM stage, family history, BC risk factor (drinking, smoking, exposures to toxic chemicals, overweight or obesity, non-children-bearing and non-breastfeeding), pathological signs (ER/PR status, HER2 and Ki-67 level), the number of LNs pathologically positive and resected, recurrence and metastasis status were analyzed as potential prognostic factors. Other treatment options (radiotherapy, adjuvant chemotherapy, and neoadjuvant chemotherapy) were also under research. Overall survival (OS) referred to the time from the random assignment to death due to any cause and Disease-free survival (DFS) was the time from the random assignment to the first appearance of any metastasis or recurrence (the endpoint was the time of last follow-up for lost patients and patients alive). Positive ER/PR was defined as more than 10% of tumor cells staining positive for ER/PR proteins [17]. HER2 positive cells were tumor cells that stained strongly (3+) for ERBB2 protein immunohistochemically or whose ERBB2 protein was stained (2+) with amplified ERBB2 gene in fluorescence in situ hybridization. Ki-67 was detected by MLB-1 antibody and its cutoff value was 14% [18].

Statistical Analyses

Data analyses were performed via R statistical software (version 4.1.0, R Foundation for Statistical Computing, Vienna, Austria). To include more potential prognostic factors, a two-sided p-value < 0.1 was considered statistically significant. Hazard ratios (HRs) were presented with 95% confidence interval (CI) and were calculated by R package ‘survival’. DFS and OS conditions were estimated via Kaplan-Meier method. Log-rank test was applied for the univariate analysis. Cox proportional hazards model was used for univariate and multivariate analyses to assess OS and DFS comparing the mastectomy and BCT group. Kaplan-Meier survival plots and the multivariate forest plots of OS and DFS were performed with ‘ggsurvplot’ and ‘ggforest’ functions in the R packages ‘survival’, ‘survminer’, and ‘ggplot2’.

Results

Characteristics of Patient Population

The study included seventy OBC patients initially presenting with axillary metastases as the only clinical manifestation at CHCAMS from September 1976 to September 2020. Table 1 demonstrated patient demographics, tumor, and other treatments received respectively in the mastectomy and BCT treatment group. All the patients were clinically diagnosed with OBC and received ALND. A mastectomy as one of the primary interventions was performed in 28 patients. Three patients with mastectomy had positive MRI results. Eight (28.6%) of the mastectomy group had pathological breast tumor evidence, two of whom also had MRI positivity (Supplementary Fig. 1). A primary tumor was detectable in 2/19 (10.5%) undergoing pathological examination in the BCT group of 42 patients. Five patients with BCT had positive MRI results, two of which were pathologically malignant (Supplementary Fig. 1). Of the 69 OBC patients with N stage information, 37 (53.6%) was N1, 18 (26.1%) was N2, and 14 (20.3%) had N3 disease. Of the 28 patients with mastectomy, 17 (60.7%) received radiotherapy. Among the 42 patients

with BCT, 28 (66.7%) had subsequent radiotherapy. Long-term follow-up was available with an average of 84.0 (5.6–217.7) months for 60 patients. Among the 23 women undergoing mastectomy, two (8.7%) experienced tumor recurrence, 1/2 (4.4%) developed metastasis, and five died. Among the 37 patients followed up in the BCT group, eight (21.6%) had metastatic tumors, 6/8 (16.2%) developed recurrence, and 7 patients died of BC.

Table 1
Basic characteristics of the 70 OBC patients with ALND

	Mastectomy + ALND n = 28	BCT + ALND n = 42	Total n = 70
Age in years: median	52.7	52.8	52.7
Gender female:male	28:0	41:1	69:1
	n (%)	n (%)	n (%)
BC family history	2 (7.1%)	3 (7.1%)	5 (7.1%)
BC risk factor	8 (28.6%)	14 (33.3%)	22 (31.4%)
Positive findings in MRI	3 (37.5%, 3/8)	5 (25.0% ,5/20)	8 (28.6%, 8/28)
Pathological malignance in breast	8 (28.6%, 8/28)	2 (10.5%, 2/19)	10 (21.3%, 10/47)
Discordance between MRI and pathology	3 (37.5%, 3/8)	1 (16.7%, 1/6)	4 (28.6%, 4/14)
T stage			
T0/TX	23 (82.1%)	40 (95.2%)	63 (90.0%)
T1	4 (14.3%)	2 (4.8%)	6 (8.6%)
unknown	1 (3.6%)	0	1 (1.4%)
N stage			
N1	17 (60.7%)	20 (47.6%)	37 (52.9%)
N2	4 (14.3%)	14 (33.3%)	18 (25.7%)
N3	6 (21.4%)	8 (19.0%)	14 (20.0%)
unknown	1 (3.6%)	0	1 (1.4%)
Histological stage			
II	10 (35.7%)	20 (47.6%)	30 (42.9%)
III	17 (60.7%)	22 (52.4%)	39 (55.7%)
unknown	1 (3.6%)	0	1 (1.4%)

OBC occult breast cancer, *BCT* breast conserving therapy, *ALND* axillary lymph node dissection, *BC* breast cancer, *MRI* magnetic reasoning imaging, *LNs* lymph nodes, *ER* estrogen receptor, *PR* progestogen receptor, *HER2* human epidermal growth factor receptor 2, *TNBC* triple negative breast cancer. *Unknown* means the original data was missing.

	Mastectomy + ALND n = 28	BCT + ALND n = 42	Total n = 70
ER			
negative	6 (21.4%)	18 (42.9%)	24 (34.3%)
positive	15 (35.7%)	15 (35.7%)	30 (42.9%)
unknown	7 (25.0%)	9 (21.4%)	16 (22.9%)
PR			
negative	7 (25.0%)	16 (38.1%)	23 (32.9%)
positive	14 (50.0%)	17 (40.5%)	31 (44.3%)
unknown	7 (25.0%)	9 (21.4%)	16 (22.9%)
HER2			
negative	12 (42.9%)	21 (50.0%)	33 (47.1%)
positive	6 (21.4%)	8 (19.0%)	14 (20.0%)
unknown	10 (10.7%)	13 (31.0%)	23 (32.9%)
Ki-67			
≤14%	1 (3.6%)	2 (4.8%)	3 (4.3%)
> 14%	10 (35.7%)	20 (47.6%)	30 (42.9%)
unknown	17 (60.7%)	20 (47.6%)	37 (52.9%)
Molecular Subtypes			
Luminal	11 (39.3%)	23 (54.8%)	34 (48.6%)
luminal A	1 (3.6%)	1 (2.4%)	2 (2.9%)
luminal B	6 (21.4%)	9 (21.4%)	15 (21.4%)
ErbB2+	1 (3.6%)	4 (9.5%)	5 (7.1%)
TNBC	3 (10.7%)	9 (21.4%)	12 (17.1%)
Recurrence or metastasis	2 (7.1%)	8 (19.0%)	10 (14.3%)
Radiotherapy	17 (60.7%)	28 (66.7%)	45 (64.3%)

OBC occult breast cancer, *BCT* breast conserving therapy, *ALND* axillary lymph node dissection, *BC* breast cancer, *MRI* magnetic reasoning imaging, *LNs* lymph nodes, *ER* estrogen receptor, *PR* progestogen receptor, *HER2* human epidermal growth factor receptor 2, *TNBC* triple negative breast cancer. *Unknown* means the original data was missing.

	Mastectomy + ALND n = 28	BCT + ALND n = 42	Total n = 70
Adjuvant Chemotherapy	22 (78.6%)	32 (76.2%)	54 (77.1%)
Endocrine therapy	13 (46.4%)	18 (42.9%)	31 (44.3%)
Neoadjuvant Chemotherapy	13 (46.4%)	9 (21.4%)	22 (31.4%)

OBC occult breast cancer, *BCT* breast conserving therapy, *ALND* axillary lymph node dissection, *BC* breast cancer, *MRI* magnetic reasoning imaging, *LNs* lymph nodes, *ER* estrogen receptor, *PR* progestogen receptor, *HER2* human epidermal growth factor receptor 2, *TNBC* triple negative breast cancer. *Unknown* means the original data was missing.

Os And Dfs Between Mastectomy And Bct Group In Univariate Analysis

Overall, patients followed-up who underwent mastectomy with ALND (n = 23) and BCT with ALND (n = 37) had a 5-year DFS rate of 69.6% and 40.5%, a 5-year OS rate of 73.9% and 47.2%, a 10-year DFS rate of 60.9% and 18.9%, and a 10-year OS rate of 60.9% and 22.2% respectively. Two treatments showed no difference in the prognosis of both OS (Cox: HR, 1.70; 95% CI, 0.58-5.00, $p = 0.332$; log-rank: HR, 1.64; 95% CI, 0.59–4.51, $p = 0.327$) (Supplementary Fig. 2a) and DFS (Cox: HR, 1.90; 95% CI, 0.60–5.97; $p = 0.275$; log-rank: HR, 1.83; 95% CI, 0.68–4.89; $p = 0.200$) (Supplementary Fig. 2b). Ruling out the ten with pathological malignancy, there was still no difference in the survival of the mastectomy group (n = 15) and the BCT group (n = 35) (OS: Cox: HR, 1.07; 95% CI, 0.34–3.50; $p = 0.906$; log-rank: HR, 1.07; 95% CI, 0.35–3.23; $p = 0.906$. DFS: Cox: HR, 1.36; 95% CI, 0.39–4.73; $p = 0.626$; log-rank: HR, 1.29; 95% CI, 0.43–3.85; $p = 0.625$) (Supplementary Table 2 and supplementary Fig. 5). Subgroup comparisons of four luminal molecular subtypes and three N stages were implemented. There was no difference in prognosis of different molecular subtypes, including luminal A (n = 2, 5.9%), luminal B (n = 15, 44.1%), ErbB2+ (n = 5, 14.7%), and TNBC (n = 12, 35.3%). In each of the BC subgroups, two treatments demonstrated similar outcomes, except that the mastectomy group of TNBC turned to have better OS (log-rank: HR, 4.61; 95% CI, 0.80-26.71; $p = 0.080$) (Supplementary Fig. 4). We also compare two therapies and their OS and DFS in N1, N2, and N3 stage subgroups distinctly, whose results indicated the similar prognoses of BCT and mastectomy (Supplementary Fig. 5).

OS overall survival, *DFS* disease free survival, *ALND* axillary lymph node dissection, *BCT* breast conserving therapy, *ER* estrogen receptor, *PR* progestogen receptor, *HER2* human epidermal growth factor receptor 2.

Predictive Prognosis Factors Of Os And Dfs In Univariate Analysis

Four statistical significant univariates were observed in OS (Supplementary Table 1), including N stage (Cox: HR, 1.62; 95% CI, 0.89–2.93; $p = 0.061$; log-rank: HR, 0.07; 95% CI, 0.28–4.76; $p = 0.105$) (Supplementary Fig. 3a), radiotherapy (Cox: HR, 4.07; 95% CI, 1.13–14.37; $p = 0.032$; log-rank: HR, 3.87; 95% CI, 1.41–10.66; $p = 0.021$) (Fig. 1a), ER positivity (Cox: HR, 0.18; 95% CI, 0.02–1.59; $p = 0.124$; log-rank: HR, 0.19; 95% CI, 0.04–0.94; $p = 0.086$) (Fig. 1c), and Ki-67 status (Cox: HR, 0.10; 95% CI: 0.01–1.68; $p = 0.110$; log-rank: HR, 0.14; 95% CI, 0.001–13.95; $p = 0.051$) (Fig. 1e). Recurrence (Cox: HR, 12.11; 95% CI: 3.15–46.53; $p < 0.001$; log-rank: HR, 10.04; 95% CI, 1.16–87.06; $p < 0.001$) (Supplementary Fig. 4a) and metastasis (Cox: HR, 7.86; 95% CI: 2.59–23.90; p 0.001; log-rank: HR, 7.15; 95% CI, 1.94–26.42; $p < 0.001$) status was also statistically significant (Supplementary Fig. 4b).

Statistically significance was observed according to six factors in DFS (Supplementary Table 1), including N stage (Cox: HR, 2.08; 95% CI, 1.11–3.92; $p = 0.023$; log-rank: HR, 1.11; 95% CI, 0.28–4.30; $p = 0.027$) (Supplementary Fig. 3b), histological stage (Cox: HR, 2.59; 95% CI, 0.84–7.99; $p = 0.099$; log-rank: HR, 2.38; 95% CI, 0.80–7.09; $p = 0.088$) (Supplementary Fig. 3d), radiotherapy (Cox: HR, 5.85; 95% CI, 1.28–26.83; $p = 0.023$; log-rank: HR, 1.11; 95% CI, 1.54–11.65; $p = 0.010$) (Fig. 1b), ER positivity (Cox: HR, 0.17; 95% CI, 0.02–1.47; $p = 0.107$; log-rank: HR, 0.18; 95% CI, 0.04–0.88; $p = 0.069$) (Fig. 1d), PR positivity (Cox: HR, 0.19; 95% CI, 0.02–1.68; $p = 0.137$; log-rank: HR, 0.20; 95% CI, 0.04–0.99; $p = 0.098$) (Supplementary Fig. 3f) and Ki-67 status (Cox: HR, 0.06; 95% CI, 0.003–0.89; $p = 0.041$; log-rank: HR, 0.07; 95% CI, 0.0002–33.52; $p = 0.005$) (Fig. 1f).

Os And Dfs Between Mastectomy And Bct Group In Multivariate Analysis

Multivariate analysis was performed among the statistically significant prognostic factors ($p < 0.1$) in either of univariate Cox regression analysis or log-rank test with Kaplan-Meier method (Fig. 2). The two treatment plans, as the main focus of our study, were also considered. N stage, ER, PR, Ki-67, and radiotherapy were included for OS and DFS survival analysis. Recurrence and metastasis, as the confounding factors, were excluded. They were closely related to and could be determined by other prognostic factors, including TNM stages, molecular subtypes, treatment modalities, etc. and were inappropriate to consider as independent variates. Only Ki-67 remained an independent prognostic variate for DFS (HR, 0.02; 95% CI, < 0.0001-1.28; $p = 0.062$). Higher Ki-67 proliferation index suggested better outcomes. In the sample with only strictly defined OBC population included, Ki-67 could also predict DFS independently (HR, 0.004; 95% CI: <0.0001-2.09; $p = 0.083$) (Supplementary Fig. 6). Ki-67 was still the only statistically significant independent prognostic factor relevant to poor DFS outcomes in multivariate Cox survival analysis (HR, 0.01; 95% CI: <0.0001-1.09; $p = 0.054$) when the two treatment options were not considered (Supplementary Fig. 7).

Discussion

In this study, OS and DFS of OBC patients with BCT + ALND were comparable to those of the patients with mastectomy + ALND. The result is consistent with previous findings, indicating that BCT with ALND demonstrates an adequate curative effect [6, 7, 9–16]. We observed that recurrence and metastasis happened to 8.7% and 4.4% of the patients in the mastectomy group, and 16.2% and 21.6% in the BCT group, which might suggest that mastectomy as a more effective therapy for local control in agreement with the past research [12, 19].

OBC is a challenging clinical manifestation with uncertain malignant etiology [6, 8]. Histologically proven metastatic axillary LNs probably derive from the primary breast neoplasm and other potential origins include ectopic breast tissue found in axillary LNs, lung, ovary, thyroid, etc. [4, 20]. Our study included *clinically* diagnosed OBC with/without MRI. Pathological testing reveals primary tumors of 27.3%-76.9% of OBC patients via other techniques including MRI [6, 19, 21, 22]. It is difficult to detect primary breast tumors from the conventional pathological sections in OBC due to its minor size. Consequently, patients receiving BCT may still have undetectable microscopic breast cancer foci left, which might have interfered with an accurate estimation on their prognosis. Whether OBC demonstrates better survival than non-OBC remains unclear. Rosen and Kimmel found that 48 patients with occult breast lesions had better prognoses than its Stage II control [23]. Huang et al. [8] and Ge et al. [7] discovered the superior outcomes of OBC compared to non-OBC, while Jackson et al. [16] reported conversely.

66.7% patients with BCT + ALND and 60.7% with mastectomy + ALND undergoing radiotherapy demonstrated worse OS and DFS than those without radiotherapy. The inconsistency with the previous findings might be impeded by the small sample size. Also, poor outcomes could be attributed to higher TNM stages and more tendency of positive MRI in patients who underwent radiotherapy. There is no definite consensus on locoregional treatment for OBC. Recent research and guideline recommendations promote locoregional management, including radiotherapy without mastectomy as a justifiable alternative to the preferred mastectomy [17, 24]. Other studies have demonstrated that radiotherapy provides comparable survival or improve the survival of OBC compared to mastectomy or BCT with ALND [4, 6, 9, 11, 12, 22], especially for patients with more than seven invasive lymph nodes [24]. Barton et al. reported better local recurrence-free survival and relapse-free survival in patients with radiotherapy to the breast conserved than those who did not, but there was no difference in OS [25]. Intriguingly, Hessler et al. discovered that patients with ALND + radiotherapy had significantly better OS than those with mastectomy + ALND + radiotherapy [26]. Overall, local surgery or radiation additionally benefits OBC survival outcomes compared to ALND only. This study has further supported the locoregional treatment regimens of either mastectomy + ALND or radiotherapy + ALND to enhance survival in OBC patients with axillary metastases. Due to improved cosmesis, ALND + RT may be the best local therapy for OBC with comparable survival results. Applying postoperative radiation for locoregional control even enables the avoidance of mastectomy and BCT for OBC patients without worrisome in-breast lesions on preoperative imaging [24].

Consistent with the previous studies, our results agree that severe lymph node status or higher N stage is one of the unfavorable prognostic factors [4, 9, 12]. OBC population tends to have a higher grade in N

stage [7, 24]. Our study observed no statistical difference considering the number of resected and pathologically positive lymph nodes to predict OBC prognosis. However, Walker et al. suggested that both more than 10 positive and fewer than 10 resected lymph nodes could indicate unfavorable survival [13]. He et al. discovered that four or more positive LNs may independently predict worse outcomes [9]. T stage was not statistically significant for OBC prognosis. Previous research has also compared the prognosis of T0/Tx to T1-T3 disease and discovered similar results [8, 14]. In a study of 80 OBC patients, Montagna et al. found no significant difference in DFS or OS between patients with T0 disease and the control [14]. Huang et al. discovered that T stage was not statistically significant in predicting OBC prognosis, but patients with OBC had a better outcome compared to non-OBC, particularly to those with N2/N3 stage or ER/PR-positive tumors [8]. The study of Sohn et al. partially conformed to our findings, in which T0/TxN1 patients had better survival than T1N1 patients, while T0/TxN2, T0/TxN3 patients had similar survival to the matched T1 patients [4]. As an important survival determinant for BC, nodal stage potentially overweighs tumor size contributing to OBC patients' survival, suggested by the different prognostic values of T and N stage in our study.

Most previous studies showed that OBC patients tended to retain positive ER and negative PR and HER2 status approached by the cohort population and SEER database [8, 11–13], among which Huang et al. [8] had enrolled up to 572 OBC out of the over 117 thousand BC patients. Our results, however, demonstrated that more than half of the OBC patients had positive ER/PR and negative HER2 status, which could be the characteristics of Chinese OBC population. Korean women have similar breast traits, while Korean OBC cohorts showed controversial HR and HER2 status [4, 10], as well as another Chinese cohort [9]. The discordance might originate from the small size of OBC series. Larger Asian cohorts could provide clearer evidence of HR and HER2 status in the future. Negative hormone receptor status is an adverse prognostic factor for OS and DFS in our study as the existing literature has shown. Walker et al. [13] and Sohn et al. [4] proved that negative ER was a poor prognostic predictor, which was partially confirmed by the univariate analysis of He et al. [9] but not in its multivariate analysis. Montagna et al. also found that ER/PR status was independent with survival outcomes, while triple negative OBC presented a significantly higher risk of recurrence and mortality [14].

Ki-67 emerges as the independent predictive factor in both univariate and multivariate analyses. Low Ki-67 (≤ 14%) indicated worse outcomes and was innovatively investigated in the present study. Active Ki-67 status might also be a feature of OBC. Oppositely, low Ki-67 has been proven as a prognostic factor for better survival of BC patients [27]. As a biomarker, Ki-67 estimates the proliferative phase (G1, G2, S, and M phase) of tumor cells and also helps to differentiate molecular subtypes according to ER, PR, and HER2 conditions. The four molecular subtypes showed no statistically different survival and two surgical options provided parallel outcomes in each subgroup, including luminal A, luminal B, ErbB2+, and TNBC. Our sample had a greater percentage of TNBC and luminal A/B subtypes than that of the previous studies [7, 8, 10]. The proportion of the ErbB2 + subtype ranged dramatically from 3.8% [7] to 52.9% [10], and our percentage lies between them. The measurement of Ki-67 also demonstrated its usefulness in predicting clinical outcomes and response to chemotherapy and neoadjuvant therapy [18, 28]. It is important to note that the number of patients with low Ki-67 was only 3 and may be limited to derive

reliable results. The standardization of tissue handling and immunohistochemical staining is also required to improve its reliability, and NCCN also have not recommended assessment of Ki-67 yet [17].

There are several limitations of our study. First, the cohort size is small. Due to the rarity of this untypical clinical condition, all the studies on OBC share a limited population. Our cohort has contained as many OBC patients as possible with a long follow-up up to 25 years. The retrospective and single-center nature may lead to bias and treatment patterns varied considerably over the long chronological span. BCT was applied more widely over time among patients who received ALND [13]. Pathological complete response (pCR) occurs during the neoadjuvant systemic therapy and may also have affected clinical decision-making [12] but was not considered due to the absence of pCR data. Additionally, the absence of HR, HER2, and Ki-67 status of some patients may render the uncertain conclusions. Two treatment groups had heterogeneous ER/PR status. 71.4% had positive ER and 37.5% had positive PR disease in the BCT group with 45.4% and 51.5% severally in the mastectomy group. We also failed to include adequate patients to differentiate the clinicopathological subgroups. The same is true for other factors, and given the limited number of events, this multivariate analysis remains an exploratory one.

Also, our limited sample failed to compare the different prognoses of patients with MRI positivity/pathological malignancy to those with MRI negativity. MRI has been playing an increasingly important role in identifying primary occult lesions and predicting therapeutic effects [29, 30]. If an occult focus is found via MRI, it should be excluded from the occult neoplasm in this study. MRI can identify approximately two-thirds of the primary neoplasms with sensitivity up to 96%. The specificity of 63% requires further confirmation by histological biopsy [31]. However, many patients only had LN metastasis without breast lesions, making it difficult to define their histologic tumor grade [12]. The routine application of breast MRI may alter the choice of the locoregional therapy for up to one-third of OBC patients [31] and may allow for BCT rather than mastectomy [32]. Future OBC studies with more MRI data will help to identify the previously undetected lesions for a more precise diagnosis under NCCN Guidelines [17].

Conclusion

In conclusion, this study finds that BCT + ALND and mastectomy + ALND do not yield different OS and DFS outcomes of OBC. Future studies on large-scale, well-designed, and multi-centered cohorts help to evaluate the prognosis of these two treatments with more accurate HR, HER2 and Ki-67 status and to provide more insights into OBC biology.

Declarations

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Author contributions Jiayi Li, Gang Liu, Ziqi Jia, Jiaqi Liu, and Xiang Wang conceived and designed the project. Jiayi Li, Fei Ren, Ziqi Jia, Gang Liu, and Menglu Zhang contributed to data extraction, analysis, and interpretation. Jiayi Li, Ziqi Jia, and Gang Liu generated the tables and figures and drafted the manuscript. All the authors participated in revising the manuscript before submission and the formal revision, including data processing, statistical analysis, generating figures and tables, and text modification. All authors had full access to the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors contributed to the article and approved the submitted version.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical approval The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Research Ethics Committee of CHCAMS (No. 21/087-2758).

Informed consent Individual informed consent for this retrospective analysis was waived.

References

1. Loibl S, Poortmans P, Morrow M et al (2021) Breast cancer. The Lancet 397(10286):1750–1769. http://doi.org/10.1016/s0140-6736(20)32381-3
2. Foroudi F, Tiver KW (2000) Occult breast carcinoma presenting as axillary metastases. Int J Radiat Oncol Biol Phys 47(1):143–147. http://doi.org/10.1016/s0360-3016(99)00542-8
3. Ofri A, Moore K (2020) Occult breast cancer: Where are we at? Breast 54:211–215. http://doi.org/10.1016/j.breast.2020.10.012
4. Sohn G, Son BH, Lee SJ et al (2014) Treatment and survival of patients with occult breast cancer with axillary lymph node metastasis: a nationwide retrospective study. J Surg Oncol 110(3):270–274. http://doi.org/10.1002/jso.23644
5. Blanchard DK, Farley DR (2004) Retrospective study of women presenting with axillary metastases from occult breast carcinoma. World J Surg 28(6):535–539. http://doi.org/10.1007/s00268-004-7290-y

6. Macedo FI, Eid JJ, Flynn J et al (2016) Optimal Surgical Management for Occult Breast Carcinoma: A Meta-analysis. Ann Surg Oncol 23(6):1838–1844. http://doi.org/10.1245/s10434-016-5104-8
7. Ge LP, Liu XY, Xiao Y et al (2018) Clinicopathological characteristics and treatment outcomes of occult breast cancer: a SEER population-based study. Cancer Manag Res 10:4381–4391. http://doi.org/10.2147/CMAR.S169019
8. Huang KY, Zhang J, Fu WF et al (2020) Different Clinicopathological Characteristics and Prognostic Factors for Occult and Non-occult Breast Cancer: Analysis of the SEER Database. Front Oncol 10:1420. http://doi.org/10.3389/fonc.2020.01420
9. He M, Tang LC, Yu KD et al (2012) Treatment outcomes and unfavorable prognostic factors in patients with occult breast cancer. Eur J Surg Oncol 38(11):1022–1028. http://doi.org/10.1016/j.ejso.2012.08.022
10. Woo SM, Son BH, Lee JW et al (2013) Survival outcomes of different treatment methods for the ipsilateral breast of occult breast cancer patients with axillary lymph node metastasis: a single center experience. J Breast Cancer 16(4):410–416. http://doi.org/10.4048/jbc.2013.16.4.410
11. Wu SG, Zhang WW, Sun JY et al (2017) Comparable Survival between Additional Radiotherapy and Local Surgery in Occult Breast Cancer after Axillary Lymph Node Dissection: A Population-based Analysis. J Cancer 8(18):3849–3855. http://doi.org/10.7150/jca.21217
12. Tsai C, Zhao B, Chan T et al (2020) Treatment for occult breast cancer: A propensity score analysis of the National Cancer Database. Am J Surg 220(1):153–160. http://doi.org/10.1016/j.amjsurg.2019.11.023
13. Walker GV, Smith GL, Perkins GH et al (2010) Population-based analysis of occult primary breast cancer with axillary lymph node metastasis. Cancer 116(17):4000–4006. http://doi.org/10.1002/cncr.25197
14. Montagna E, Bagnardi V, Rotmensz N et al (2011) Immunohistochemically defined subtypes and outcome in occult breast carcinoma with axillary presentation. Breast Cancer Res Treat 129(3):867–875. http://doi.org/10.1007/s10549-011-1697-6
15. Svastics E, Ronay P, Bodo M (1993) Occult breast cancer presenting with axillary metastasis. Eur J Surg Oncol 19(6):575–580
16. Jackson B, Scott-Conner C, Moulder J (1995) Axillary metastasis from occult breast carcinoma: diagnosis and management. Am Surg 61(5):431–434
17. William JG, Meena SM, Jame A et al (2021) NCCN breast 2021.6. National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed 18 August 2021
18. Goldhirsch A, Wood WC, Coates AS et al (2011) Strategies for subtypes–dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol 22(8):1736–1747. http://doi.org/10.1093/annonc/mdr304
19. Wang X, Zhao Y, Cao X (2010) Clinical benefits of mastectomy on treatment of occult breast carcinoma presenting axillary metastases. Breast J 16(1):32–37. http://doi.org/10.1111/j.1524-

4741.2009.00848.x

20. Terada M, Adachi Y, Sawaki M et al (2018) Occult breast cancer may originate from ectopic breast tissue present in axillary lymph nodes. Breast Cancer Res Treat 172(1):1–7. http://doi.org/10.1007/s10549-018-4898-4
21. Butler RS, Chen C, Vashi R et al (2013) 3.0 Tesla vs 1.5 Tesla breast magnetic resonance imaging in newly diagnosed breast cancer patients. World J Radiol 5(8):285–294. http://doi.org/10.4329/wjr.v5.i8.285
22. Vlastos G, Jean ME, Mirza AN et al (2001) Feasibility of breast preservation in the treatment of occult primary carcinoma presenting with axillary metastases. Ann Surg Oncol 8(5):425–431. http://doi.org/10.1007/s10434-001-0425-6
23. Rosen PP, Kimmel M (1990) Occult breast carcinoma presenting with axillary lymph node metastases: a follow-up study of 48 patients. Hum Pathol 21(5):518–523. http://doi.org/10.1016/0046-8177(90)90008-s
24. Kim BH, Kwon J, Kim K (2018) Evaluation of the Benefit of Radiotherapy in Patients with Occult Breast Cancer: A Population-Based Analysis of the SEER Database. Cancer Res Treat 50(2):551–561. http://doi.org/10.4143/crt.2017.189
25. Barton SR, Smith IE, Kirby AM et al (2011) The role of ipsilateral breast radiotherapy in management of occult primary breast cancer presenting as axillary lymphadenopathy. Eur J Cancer 47(14):2099–2106. http://doi.org/10.1016/j.ejca.2011.05.010
26. Hessler LK, Molitoris JK, Rosenblatt PY et al (2017) Factors Influencing Management and Outcome in Patients with Occult Breast Cancer with Axillary Lymph Node Involvement: Analysis of the National Cancer Database. Ann Surg Oncol 24(10):2907–2914. http://doi.org/10.1245/s10434-017-5928-x
27. Harbeck N, Rastogi P, Martin M et al (2021) Adjuvant Abemaciclib Combined With Endocrine Therapy for High-Risk Early Breast Cancer: Updated Efficacy and Ki-67 Analysis From the monarchE Study. http://doi.org/10.1016/j.annonc.2021.09.015. Ann Oncol
28. Dowsett M, Nielsen TO, A'Hern R et al (2011) Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. J Natl Cancer Inst 103(22):1656–1664. http://doi.org/10.1093/jnci/djr393
29. Kim H, Park W, Kim SS et al (2020) Outcome of breast-conserving treatment for axillary lymph node metastasis from occult breast cancer with negative breast MRI. Breast 49:63–69. http://doi.org/10.1016/j.breast.2019.10.017
30. Harada TL, Uematsu T, Nakashima K et al (2021) Evaluation of Breast Edema Findings at T2-weighted Breast MRI Is Useful for Diagnosing Occult Inflammatory Breast Cancer and Can Predict Prognosis after Neoadjuvant Chemotherapy. Radiology 299(1):53–62. http://doi.org/10.1148/radiol.2021202604
31. Fayanju OM, Stoll CR, Fowler S et al (2013) Geographic and temporal trends in the management of occult primary breast cancer: a systematic review and meta-analysis. Ann Surg Oncol 20(10):3308–3316. http://doi.org/10.1245/s10434-013-3157-5

32. Ettinger DS, Agulnik M, Cates JM et al (2011) NCCN Clinical Practice Guidelines Occult primary. J Natl Compr Canc Netw 9(12):1358–1395. http://doi.org/10.6004/jnccn.2011.011

Figures

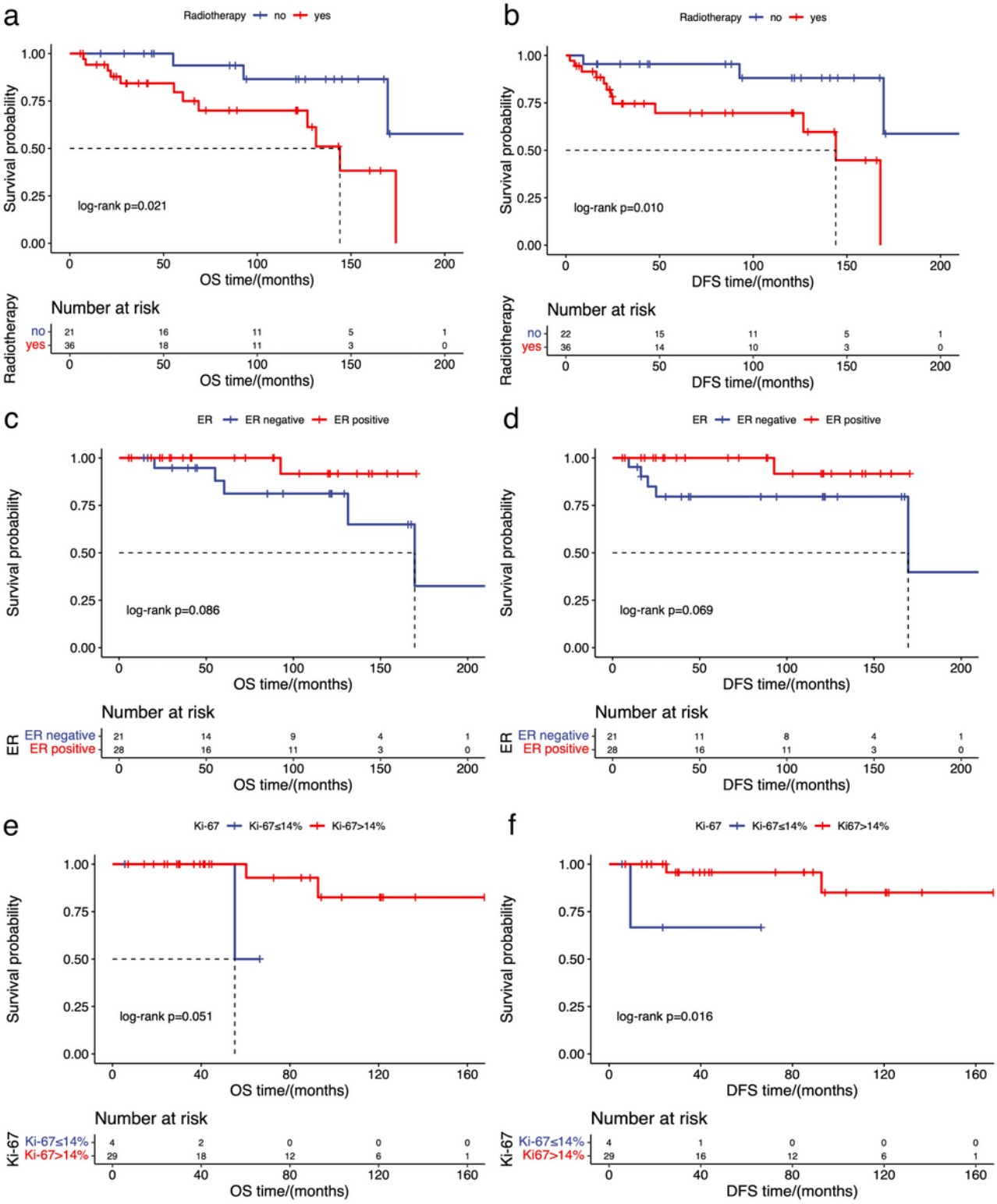

Figure 1

Univariate Kaplan-Meier survival plots of a radiotherapy of OS; b radiotherapy of DFS; c ER status of OS; d ER status of DFS; e Ki-67 status of OS; f Ki-67 status of DFS

OS overall survival, *DFS* disease free survival, *ALND* axillary lymph node dissection, *BCT* breast conserving therapy, *ER* estrogen receptor, *PR* progestogen receptor, *HER2* human epidermal growth factor receptor 2.

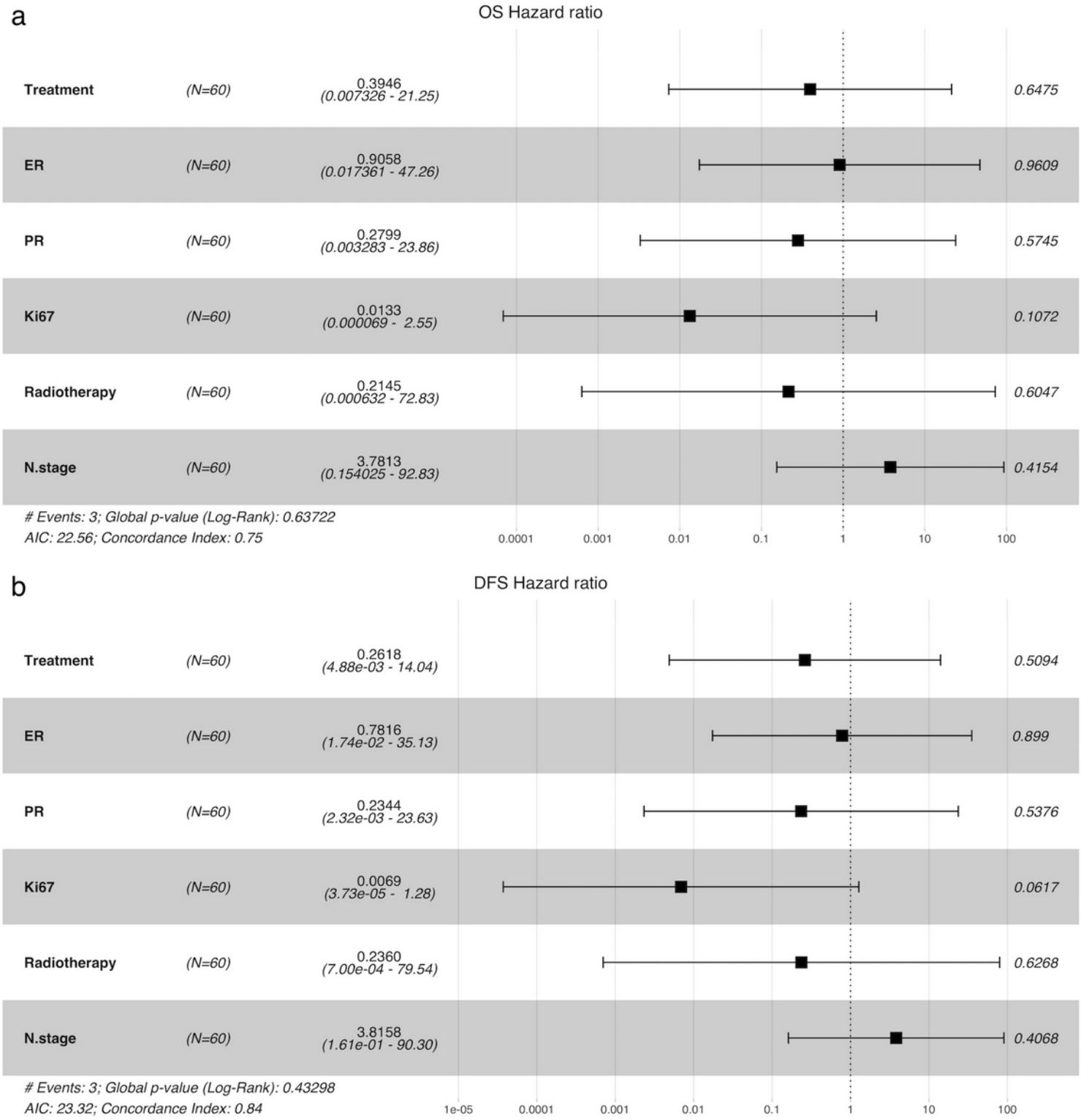

Figure 2

Forest plots of multivariate Cox proportional hazards model of a treatment, ER, PR, Ki-67, radiotherapy, and N stage of OS; b treatment, ER, PR, Ki-67, radiotherapy, and N stage of DFS

OS overall survival, *DFS* disease free survival, *ALND* axillary lymph node dissection, *BCT* breast conserving therapy, *ER* estrogen receptor, *PR* progestogen receptor, *HER2* human epidermal growth factor receptor 2. Treatment, mastectomy+ALND vs. BCT+ALND. ER, estrogen receptor negative vs. positive. PR, progestogen receptor negative vs. positive. Ki-67 status, ≤14% vs. >14%. Radiotherapy, no vs. yes. N stage, N1, N2, vs. N3

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