Occult Breast Cancer Presenting with Axillary Lymph Node Metastasis: A Clinicopathological Analysis and Survival Outcomes

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Abstract

Aim: Occult breast cancer (OBC) is a rare clinical entity characterized by axillary lymph node metastasis without a detectable primary tumor in the breast. This study aimed to evaluate the clinicopathological features and the impact of different treatment modalities on survival in patients diagnosed with OBC.

Methods: A total of 14 patients diagnosed with OBC between 2016 and 2024 were retrospectively analyzed. Diagnosis was confirmed clinically and through multimodal imaging, including ultrasonography, mammography, magnetic resonance imaging (MRI), and positron emission tomography/computed tomography (PET-CT). Demographic data, immunohistochemical profiles, surgical interventions, systemic therapies, and survival rates were evaluated.

Results: The cohort was predominantly female (92.9%), with a mean age of 54.6 years. The most common presenting symptom was a palpable axillary mass (71.4%). Molecular subtypes were identified as Luminal A (50%), Luminal B (35.7%), and Triple-Negative (14.3%). The 5-year survival rate was 100% in patients who underwent either modified radical mastectomy (MRM) or breast-conserving surgery (BCS) combined with axillary lymph node dissection (ALND). In contrast, the survival rate was 50% for those who underwent ALND alone and 0% for those who received no surgical intervention (p=0.003). While radiotherapy was associated with a higher 5-year survival rate compared to no radiotherapy (90.9% vs. 50%), this difference was not statistically significant (p=0.083). No significant associations were found between survival and age, smoking status, neoadjuvant chemotherapy, or endocrine therapy (p>0.05).

Conclusions: Multimodal treatment is essential for OBC. Breast-directed surgery combined with axillary dissection significantly improves survival compared to either axillary dissection alone or no surgical intervention.

Keywords: *Axillary lymph node metastases; occult breast carcinoma; radiotherapy; surgery; survival*

1. Introduction

Occult breast cancer (OBC) is described as an axillary metastatic carcinoma without a detectable primary tumor in the breast, accounting for approximately 0.3–1% of all breast cancers[1,2]. The diagnostic foundation of OBC is the inability to identify a primary lesion in the breast via clinical examination, mammography, ultrasonography (USG), and magnetic resonance imaging (MRI)[3]. This rare clinical presentation complicates the diagnostic process and leads to significant debates regarding treatment strategies. Various hypotheses have been proposed in the literature concerning the etiology of OBC, including the microinvasive nature of the primary tumor, spontaneous regression of the tumor, or origin from ectopic breast tissue in the axillary region[4,5].

Breast carcinoma is the most common cause of axillary lymph node metastases, followed by carcinomas originating from the lungs, gastrointestinal system, and prostate. Therefore, patients must undergo a systematic and comprehensive physical examination along with advanced imaging methods to detect the primary tumor[6]. Due to the limited sensitivity of conventional methods such as mammography and ultrasonography, advanced imaging techniques like MRI and positron emission tomography/computed tomography (PET-CT) play a critical role in the investigation of the primary focus[7,8].

There is no consensus in the literature regarding the prognosis and optimal treatment of OBC. Some studies have found no significant difference in survival between patients undergoing axillary lymph node dissection (ALND) alone and those undergoing ALND in addition to modified radical mastectomy (MRM) or breast-conserving surgery (BCS)[9].

Studies reporting that radiotherapy (RT) improves survival have been documented[10-12]. Furthermore, lymph node stage and the extent of involvement have been emphasized as significant prognostic factors in many studies[9,13].

The aim of this study is to examine the clinical and pathological characteristics of patients diagnosed with OBC followed at our cen-

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ter, to evaluate the effects of different treatment modalities on survival, and to contribute to optimal management strategies for this rare disease in light of current literature.

2. Materials and Methods

This study was conducted in accordance with decision No. 10/14, dated June 19, 2025, granted by the Clinical Research Ethics Committee of Antalya Training and Research Hospital. The study adhered to the Declaration of Helsinki.

A total of 14 patients who were diagnosed with breast carcinoma metastasis via axillary lymph node biopsy between 2016 and 2024, but in whom no primary breast tumor was detected through clinical examination, breast USG, mammography, breast MRI, and PET-CT examinations, were included in this study. All cases were radiologically and pathologically confirmed as occult breast cancer.

Demographic data (age, sex), smoking and alcohol consumption habits, presenting complaints, radiological methods used for screening, selected surgical procedures, and administered treatments were recorded from the hospital's electronic information system and patient files. Nodal involvement was staged as pN according to the American Joint Committee on Cancer (AJCC) TNM Staging System (8th Edition).

Histopathological evaluation of the axillary lymph node metastases was performed using hematoxylin-eosin staining and immunohistochemical (IHC) stains (CK 7, CK 20, Pan CK, LCA, GATA-3, Mammaglobin, GCDFP-15, CDX2) for differential diagnosis. ER, PR, HER2, and Ki-67 expressions were evaluated, and molecular subtypes were classified. HER2 status was evaluated according to the ASCO/CAP guidelines. Cases with an IHC score of 2+ (equivocal) were definitively categorized based on Fluorescence in situ hybridization (FISH) results.

Descriptive statistics were presented as frequency, percentage, mean, and standard deviation. Survival rates were estimated using the Kaplan-Meier method. Survival times between groups were compared using the Log-rank test. Univariate analyses were performed using the Log-rank test. All analyses were conducted using SPSS 23.0 software, and a p-value of <0.05 was considered statistically significant.

3. Results

Demographic and Clinical Characteristics

Of the 14 patients included in the study, the vast majority were female (92.9%, n=13), while one patient (7.1%) was male. The mean age at the time of diagnosis was 54.64 ± 10.97 years (range: 31–73). Analysis of the presenting complaints revealed that 10 patients (71.4%) had a palpable mass in the axillary region, one patient had swelling in the neck region, and one patient had erythema of the breast skin. In two patients (14.3%), axillary lymphadenopathy (LAP) was detected incidentally during examinations performed for other reasons. Metastatic lymph nodes were located in the left axilla in 8 patients (57.1%) and in the right axilla in 6 patients (42.9%). Regarding habits, 78.6% of the patients (n=11) were non-smokers. No history of alcohol consumption was identified in any patient. The demographic and clinical characteristics of the patients are presented in Table 1.

Diagnostic Process and Treatment

Regarding the diagnostic method, core biopsy of the axillary lymph node was preferred in 85.8% (n=12) of the patients, while excisional biopsy was performed in 14.2% (n=2). The mean diameter of the pathological lymph nodes was measured as 31.71 ± 13.87 mm (range: 12–65 mm).

Figure 1

Mammographic findings of two different patients. In both cases, there is no evidence of suspicious parenchymal lesions in the breast. (A) Multiple axillary lymphadenopathies and (B) A single axillary lymphadenopathy are visualized.

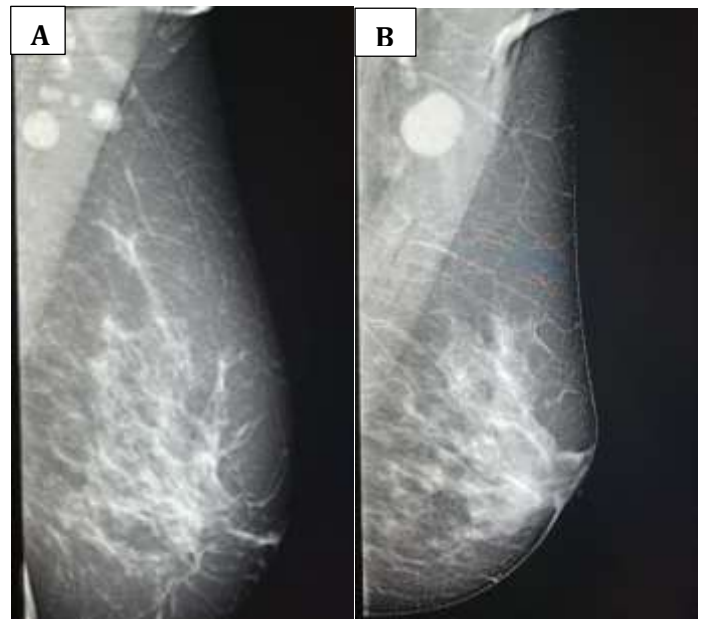


Table 1

Baseline Demographic and Clinicopathological Characteristics of the Study Cohort

		n	Percent (%)
Gender	Female	13	92.9
	Male	1	7.1
Vital Status	Alive	11	78.6
	Deceased	3	21.4
Laterality	Right	6	42.9
	Left	8	57.1
Diagnostic Method	LND	5	35.7
	LNB	9	64.3
Smoking Status	Smoker	3	21.4
	Non-smoker	11	78.6
Alcohol Use	Yes	0	0
	No	14	100
Age (year)	Mean±SD (Min-Max)	54.64±10.97 (31-73)	
Overall Survival (days)	Mean±SD (Min-Max)	1880.79 ± 1071.68 (217-3323)	
Lymph Node Diameter (mm)	Mean±SD (Min-Max)	31.71±13.87 (12-65)	

LND, Lymph node dissection; LNB, lymph node biopsy; SD, Standard Deviation

Following the diagnosis of breast carcinoma metastasis to the axillary lymph node, bilateral mammography (Figure 1), breast USG, breast MRI, and PET-CT were performed for all patients during the screening phase; no primary tumor focus was detected in the breast tissue of any patient. MRM + ALND was performed in 10 patients (71.4%), ALND alone in 2 patients (14.3%), and BCS + ALND in 1 patient (7.1%). One patient died before surgical intervention could be performed. In 75% (n=9) of the lymph node dissection materials, 10 or more lymph nodes were retrieved. In pathological staging, all patients were classified as pT0; the nodal stage distribution was identified as 78.5% pN1, 14.2% pN2, and 7.3% pN3. Regarding systemic involvement, the male patient had supraclavicular and distant lymph node metastases at the time of diagnosis, while one female patient had bone and lung metastases.

Neoadjuvant chemotherapy (CT) was administered to 42.8% (n=6) of the patients. Adjuvant CT was administered to 42.8% (n=6), of whom 2 patients continued with systemic CT. Ipsilateral breast and axillary radiotherapy was administered to 85.7% (n=12) of the patients. Endocrine therapy was administered to 78.5% (n=11) of the patients, consisting of anastrozole in seven cases and tamoxifen in three cases.

Immunohistochemical Profile

In the IHC panel applied for differential diagnosis, Pan-CK, CK 7, GATA-3, and GCDFP-15 expressions were positive in all cases, while CK 20, CDX2, and LCA were negative (Figure 2). Regarding the hormone receptor profile, ER positivity was detected in 56.5% of cases, PR positivity in 39.6%, and HER2 positivity in 35.8% (Figure 3). In all cases, tumor cells showed a positive immunoreaction with E-cadherin, and metastatic tumor cells exhibited invasive ductal carcinoma morphology. According to molecular subtypes, 50% (n=7) of the patients were classified as Luminal A, 35.7% (n=5) as Luminal B, and 14.3% (n=2) as Triple negative.

Survival Analyses

The mean overall survival (OS) time in the study group was calculated as 1880.79 ± 1071.68 (217-3323). No mortality was observed during the follow-up period in patients under 50 years of age, while the 5-year overall survival rate in patients aged 50 and over was 72.9%. The 5-year survival rate was 100% in the right axillary localization group and 75% in the left group; however, lateralization had no statistically significant effect on survival (p=0.908). No significant relationship was found between age or smoking and survival (p>0.05) (Table 2).

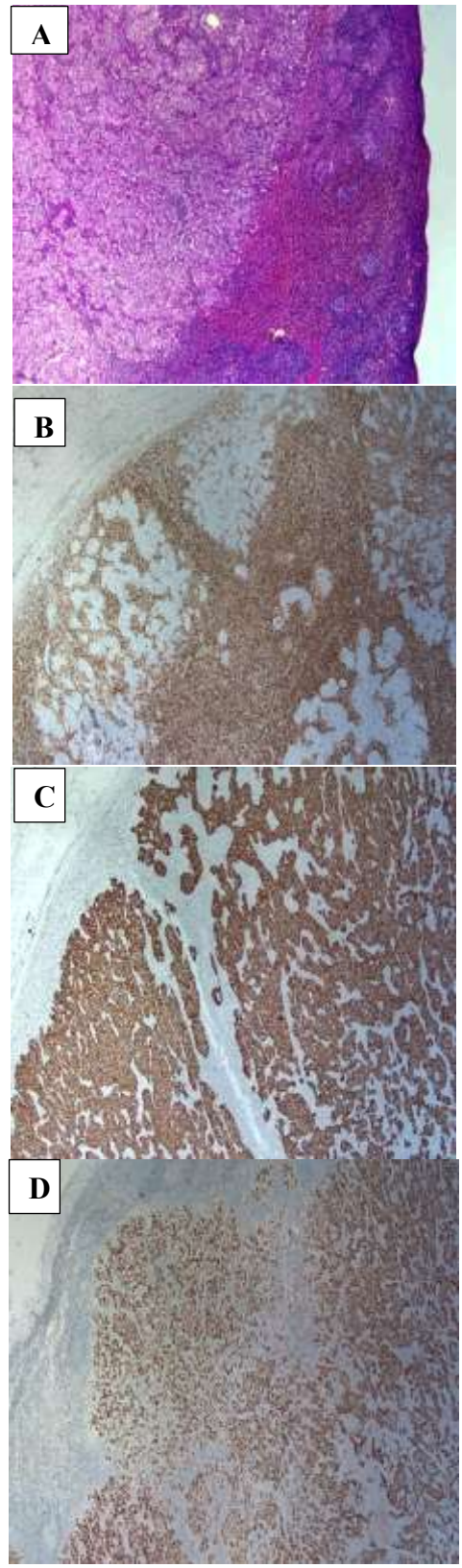
When the effect of surgical techniques on survival was evaluated, the 5-year survival rate was 100% in patients treated with MRM+ALND and BCS+ALND, 50% in those treated with ALND alone, and 0% in the patient who did not undergo surgery. In pairwise comparisons, the difference between the MRM+ALND group and the non-surgical group was statistically significant (p=0.002). No statistical significance was found in other pairwise comparisons (p>0.05). One patient who did not undergo surgery died of heart failure while undergoing diagnostic procedures due to comorbid conditions.

Although the 5-year survival rate was higher in patients receiving RT (90.9% vs. 50%), this difference did not reach statistical significance (p=0.083). No significant relationship was found between neoadjuvant CT or endocrine therapy variables and survival (p>0.05) (Table 3).

The mean survival times were 1683.14 ± 1085.55 days for the Luminal A type, 1757.80 ± 1131.53 days for the Luminal B type, and 2880.00 ± 626.50 days for the Triple negative type. In Kaplan–Meier analysis, the 5-year overall survival was 71.4% in the Luminal A group, while it was 100% in the Luminal B and Triple negative groups due to the absence of events during the follow-up period.

Figure 2

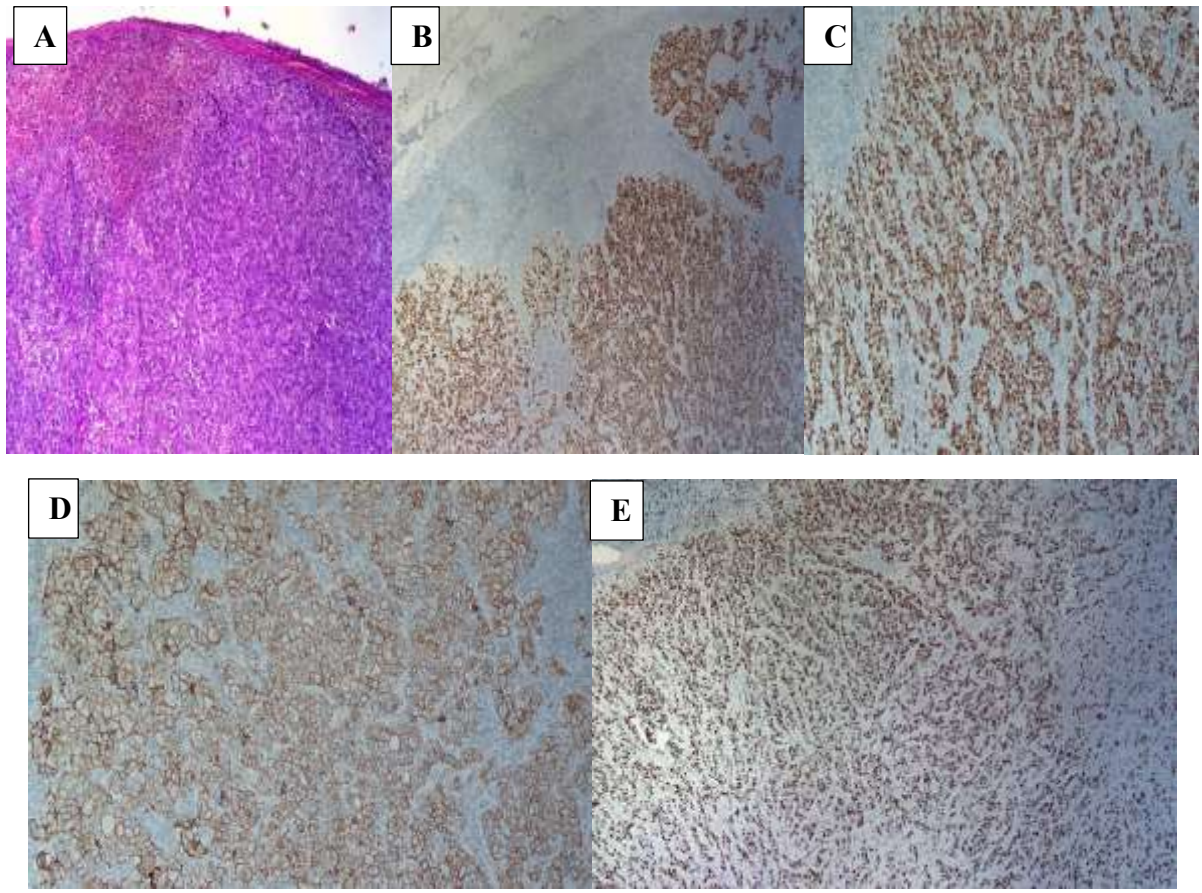
Immunohistochemical stains performed for differential diagnosis of a metastatic axillary lymph node



(A) Tumoral infiltration disrupting the architecture of the lymph node (Hematoxylin & Eosin, X40). (B) Diffuse LCA positivity in lymphoid cells. Metastatic tumor cells showed no staining with LCA. (X40). (C) Infiltrative tumor cells exhibiting cytoplasmic Pan-CK expression (X40). (D) Strong nuclear GATA-3 positivity in infiltrative tumor cells (X40).

Figure 3

Prognostic immunohistochemical stains applied to metastatic tumor cells



(A) Hematoxylin & Eosin (H&E) staining (X40). (B) Strong nuclear ER expression (X40). (C) Nuclear PR positivity (X40). (D) Strong membranous HER2 staining (X100). (E) Ki-67 proliferation index (X40).

Table 2

Univariate Analysis of 5-Year Overall Survival Rates According to Clinicopathological Characteristics

		n	Mortality (n)	5-year survival rate (%)	Log-rank p
Age	<50	6	0	100	0.098
	≥50	8	3	72.9	
Localization Site	Right	6	1	100	0.908
	Left	8	2	75	
Smoking Status	Non-smoker	11	2	80.8	0,698
	Smoker	3	1	100	
ER	Negative	2	0	100	0,404
	Positive	12	3	82.5	
HER2	Negative	9	3	77.8	0,24
	Positive	5	0	100	
KI-67	≤%40	7	1	85.7	0,763
	>%40	7	2	83.3	
pN	N1	11	2	80.8	0,771
	N2–N3	3	1	100	
Molecular subtyping	Luminal A	7	3	71.4	0.223
	Luminal B	5	0	100	
	Triple negative	2	0	100	

ER, Estrogen Receptor; HER2, Human Epidermal Growth Factor Receptor 2; Ki-67, Marker of proliferation Ki-67; pN, Pathological nodal stage

Table 3
Comparison of 5-Year Overall Survival Rates Stratified by Treatment Modalities

Treatment	Group	n	Mortality (n)	5-year survival rate (%)	Log-rank p	Pairwise Comparison
Surgical treatment	MRM+ALND	10	1	100	0,003	p_1=0,327 p_2=0,480 p_3=0,002 p_4=0,157 p_5=0,317
	ALND	2	1	50		
	BCS+ALND	1	0	100		
	No Surgery	1	1	0		
Neoadjuvant chemotherapy	With	6	1	83,3	0,829	
	Without	8	2	58,3		
Radiotherapy	With	12	2	90.9	0,083	
	Without	2	1	50		
Endocrine therapy	Yes	11	2	90	0.6	
	No	3	1	66.7		

p1: MRM+ALND vs ALND, p2: ALND vs BCS+ALND, p3: MRM+ALND vs No Surgery, p4: ALND vs No Surgery, p5: BCS+ALND vs No Surgery
ALND, Axillary lymph node dissection; BCS, Breast-conserving surgery; MRM, Modified radical mastectomy

No statistically significant difference was found when survival was compared among subtypes using the Log-rank (Mantel–Cox) test ($\chi^2(2)=3.00$; p=0.223).

Three mortality events were observed during the follow-up period. Due to the limited number of events and the insufficient number of patients in the subgroups, independent risk factors affecting survival could not be evaluated using multivariate Cox regression analysis.

4. Discussion

Occult breast cancer is an exceptionally rare entity characterized by axillary lymph node metastasis where the primary focus cannot be detected through clinical and radiological examinations[1,3]. Representing 0.3–1% of all breast cancers in the literature, many aspects of this disease, from diagnostic processes to treatment strategies, remain controversial[1,2]. The incidence of OBC in men is an extremely rare condition, occurring in less than 1% of cases, and the single male case in our study is consistent with this low incidence reported in the literature[14,15].

Recent guidelines strongly recommend the use of breast MRI due to its high sensitivity in cases where conventional methods remain insufficient[7,16]. Furthermore, the inability to detect a primary focus in PET-CT examinations performed on all our patients led to the classification of OBC as "pathologically occult" (pOBC)[2,8].

Several hypotheses regarding the pathogenesis of OBC have been proposed, such as the "spontaneous regression of the primary focus" or its "origin from axillary ectopic breast tissue"[4,5]. During the diagnostic stage, the presence of breast histomorphology in the metastatic tissue and IHC positivity for CK 7, GATA-3, GCDFP-15, or mammaglobin, along with negativity for CK 20 and TTF-1, confirms primary breast cancer[17]. Specific markers such as GATA-3 and GCDFP-15 are particularly diagnostic in ER- and PR-negative cases[18]. In our cases, positivity for Pan-CK, CK 7, GATA-3, and GCDFP-15, alongside negativity for CK 20, CDX2, and LCA, fully met the breast origin criteria in the literature. The fact that the axillary lymph node diagnosis for all patients in our series was invasive ductal carcinoma metastasis and the detection of positive IHC markers for breast origin supports the view that these foci originate from ectopic breast tissue or undetectable microinvasive foci[17]. Although some literature reports higher hormone receptor positivity in male OBC cases compared to females[14,19], the data from the single male patient in our study did not allow for a generalization. In our male case, the tumor cells showed diffuse positivity with ER and PR IHC stains and were negative for HER2.

Treatment management is the most debated topic in OBC literature. Numerous studies argue that there is no significant difference in survival between the classical approach of MRM and less invasive options such as BCS or ALND + RT alone[9]. However, the most striking finding of our study is the statistically significant difference detected between surgical methods regarding 5-year survival (p=0.003). The survival rate, which was 100% in the group treated with MRM+ALND or BCS+ALND, dropped to 50% in those treated with ALND alone, and to 0% in those who did not undergo surgery. However, it should be noted that the death of one patient in the non-surgical group was due to heart failure during the diagnostic workup phase rather than disease progression. While this limits the establishment of a direct causal link between survival and surgical intervention, it highlights that patients who were clinically suitable for surgery had a more favourable clinical course in the present series. Further studies with a larger number of patients are needed to confirm these findings.

The role of radiotherapy in OBC management is considered a prognostic factor strong enough to be a primary treatment modality[11]. It is observed that surgical interventions encompassing both RT and MRM/BCS increase both breast cancer-specific survival and overall survival in OBC patients[20]. In our study, the 5-year survival rate was higher in those receiving RT compared to those who did not (90.9% vs. 50%); although this did not reach statistical significance (p=0.083), it is clinically consistent with the thesis in the literature that "RT prolongs survival"[12,21].

Nodal status is accepted as one of the most important independent prognostic factors in OBC; it has been reported that the risk of mortality increases as the number of positive lymph nodes

increases and the stage advances (N2–N3)[9,22]. Furthermore, the presence of supraclavicular or distant lymph node metastasis is associated with poorer outcomes[10].

In our study, mortality was observed in two patients who had distant metastases at the time of diagnosis. Regarding molecular subtypes, although it has been reported that the triple negative group and non-luminal subtypes have a worse prognosis[23,24], no survival difference was detected between the luminal groups and the triple negative group in our series (p=0.223); this is thought to result from our small sample size.

Although Cox regression analysis could not be performed due to the limited number of patients and low mortality rate in our study, the decisive effect of surgical treatment (especially MRM+ALND) on survival comes to the fore. While the inclusion of detailed data regarding systemic treatments (CT, RT, and endocrine therapy) increases the strength of our results, the small number of patients—particularly the limited number of male patients—prevented the evaluation of interactions between variables through multivariate analyses. Due to the rare nature of OBC, large-scale prospective and randomized studies are required for more definitive treatment protocols.

The prognosis in OBC patients is directly related to nodal stage, the presence of distant metastasis, and the extent of surgical intervention. In our study, it was determined that multimodal approaches, particularly those where MRM or BCS is combined with axillary dissection, offer superior survival outcomes compared to cases undergoing ALND alone. The tendency of ipsilateral breast and axillary region radiotherapy to increase survival rates stands out as a clinical advantage, even if it did not reach the level of statistical significance. Although the rarity of the disease and sample limitations make it difficult to determine independent risk factors, the integration of personalized treatment strategies and systemic therapies plays a key role in optimizing survival success.

Statement of ethics

This study was conducted in accordance with decision No. 10/14, dated June 19, 2025, which was granted by the Clinical Research Ethics Committee of Antalya Training and Research Hospital. The study adhered to the Helsinki Declaration.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author contributions

Surgical and Medical Practices: B.R.K, Ö.V.G.; Concept: Ş.Y., A.K.; Design: Ş.Y., Ö.V.G.; Data Collection or Processing: Ş.Y., A.H.Ö., Ö.V.G.; Analysis or Interpretation: Ş.Y., A.K.; Literature Search: Ş.Y., A.H.Ö.; Writing: Ş.Y., B.R.K.

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