Caspian Journal of Internal Medicine 2026 (Spring); 17(2): 347-359
DOI: 10.22088/cjim.17.2.347

Original Article

Relapse-free survival and metastasis-free survival between patients with breast cancer receiving adjuvant or neoadjuvant therapy: A retrospective study in Iran

Mina Azarnia (MD) [1]
Mehran Sharifi (MD) [2*]
Zahra Rezaeian (MD) [3]
Saeedeh Arabzadeh (MD) [3]
Shaghayegh Haghjooy Javanmard (MD) [4]

1. Department of Internal Medicine, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
2. Department of Internal Medicine, School of Medicine, Cancer Prevention Research Center, Seyyed Al-Shohada Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
3. Cancer Prevention Research Center, Seyyed Al-Shohada Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
4. Applied Physiology Research Center, Department of Physiology, Isfahan, Iran

*** Correspondence:**
Mehran Sharifi, Department of Internal Medicine, School of Medicine, Cancer Prevention Research Center, Seyyed Al-Shohada Hospital, Isfahan University of Medical Sciences, Isfahan, Iran

E-mail:
sharifi.mehran5056@gmail.com
Tel: +98 3136201991

Received: 4 May 2025
Revised: 14 Aug 2025
Accepted: 23 Sep 2025
Published: 10 March 2026

Abstract

Background: Breast cancer is the most common malignancy among women in Iran and worldwide. Although both neoadjuvant and adjuvant chemotherapies are widely used, their impact on relapse-free survival (RFS) and metastasis-free survival (MFS) in real-world settings remains unclear. This study aimed to compare RFS and MFS between neoadjuvant and adjuvant chemotherapy in breast cancer patients.

Methods: A retrospective cohort study was conducted on patients who had received adjuvant or neoadjuvant therapy at Seyed Al-Shohada Hospital during July 2016 and July 2020. The cut-off date was July 202. Kaplan-Meier analysis and Cox regression models were used to evaluate RFS and MFS. To address potential confounding by indication due to non-randomized treatment assignment, inverse probability of treatment weighting (IPTW) was applied using propensity scores based on age, tumor grade, and molecular subtype.

Results: Neoadjuvant therapy was significantly associated with increased relapse risk compared to adjuvant therapy in both multivariate (HR = 3.06, P = 0.030) and IPTW-weighted models (HR = 6.10, P = 0.002). No significant difference in MFS was observed between treatment groups. TNBC was identified as the strongest predictor of metastasis (HR = 6.45, P = 0.001). Subtype-specific analyses revealed better outcomes with adjuvant therapy in Luminal A and improved MFS/RFS with neoadjuvant therapy in TNBC.

Conclusion: Adjuvant therapy was associated with better local disease control (RFS), while MFS was primarily influenced by tumor subtype. These findings highlighted the importance of subtype-tailored therapeutic strategies and supported the use of causal methods such as IPTW in observational oncology research.

Keywords: Breast cancer, Adjuvant treatment, Neoadjuvant therapy, Metastasis-free survival (MFS), Relapse-free survival (RFS).

Citation:
Azarnia M, Sharifi M, Rezaeian Z, Arabzadeh S, Haghjooy Javanmard Sh. Relapse-free survival and metastasis-free survival between patients with breast cancer receiving adjuvant or neoadjuvant therapy: A retrospective study in Iran. Caspian J Intern Med 2026; 17(2): 347-359.

Breast cancer, the most prevalent cancer among women worldwide, is a leading cause of death within this group (1). It is also the most common cancer among Iranian women, with an unfortunate growing incidence (2). Breast cancer is mainly categorized into four subtypes based on the expression of estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2), and Ki67 (3). Accurate diagnosis and treatment strategies for the management of breast cancer mainly rely on subtype differentiation.In recent decades, therapeutic approaches toward breast cancer, including adjuvant and neoadjuvant therapies, have become increasingly effective, resulting in improved survival rates (4).

 Publisher: Babol University of Medical Sciences

Adjuvant therapy, which is given after surgery, aims to eradicate any remaining cancer cells. Therefore, it reduces the risk of cancer recurrence and increases overall survival (5). Neoadjuvant therapy is a type of treatment administered before a surgical procedure. It is often prescribed to reduce the size of the tumor, thus facilitating breast-conserving surgery. In the past, neoadjuvant chemotherapy was typically utilized for patients with locally advanced or inoperable breast cancer (6). However, it is now available for patients with early-stage, operable breast cancer. Evidence has indicated that neoadjuvant chemotherapy can potentially reduce post-operative complications, such as lymphedema (7). Clinical research has provided evidence that neoadjuvant chemotherapy significantly reduces the rate of metastasis and also improves survival rates in patients with breast cancer (7, 8).

Cancer recurrence, defined as the reappearance of cancer cells that were part of the original tumor after primary treatment, can occur locally or distantly. Local recurrence is the return of cancer to the breast or adjacent lymph nodes, while distant recurrence refers to the spread of cancer to other areas of the body, known as metastasis. Bones, lungs, liver, and brain are the most prone sites for breast cancer metastasis (9). Despite significant progress in early detection and treatment of breast cancer, metastasis continues to be the leading cause of mortality in breast cancer patients (10).The effectiveness of cancer therapeutic strategies is commonly evaluated using several indicators, including relapse-free survival (RFS) and metastasis-free survival (MFS). RFS quantifies the duration of a patient's post-treatment life without cancer recurrence, representing the period from the completion of treatment to cancer recurrence. MFS measures the duration of a patient's post-treatment life without cancer spreading to other body parts, denoting the period from the end of treatment to the cancer metastasis.

The NSABP B-18 trial, conducted in 1997, was the first clinical study to compare the use of the same chemotherapy regimen in neoadjuvant and adjuvant settings. Results did not reveal statistically significant differences in terms of disease-free survival and overall survival (11). Similarly, the EORTC trial compared neoadjuvant and adjuvant treatments for operable breast cancer patients using the same chemotherapy regimen. Results indicated that there was no statistically significant difference between the two groups in terms of overall survival (OS), disease-free survival (DFS), or loco-regional recurrence rate (12).To the best of our knowledge, a comparison of MFS and RFS outcomes in Iranian breast cancer patients who received either neoadjuvant ;or adjuvant chemotherapy has not yet been undertaken to date. Randomized controlled trials (RCTs) remain the gold standard for evaluating comparative therapeutic effects and have shown no significant differences in OS and DFS outcomes between neoadjuvant and adjuvant therapies. However, many RCTs are not designed to assess certain survival outcomes in real-world settings and often apply strict eligibility criteria, which may limit the generalizability of their findings to broader patient populations encountered in routine practice. In this context, retrospective observational studies, such as ours, can complement RCT evidence by assessing actual treatment patterns, diverse patient subgroups, and long-term outcomes under routine clinical conditions. Therefore, we conducted this study to compare the effectiveness of neoadjuvant and adjuvant chemotherapy in improving long-term survival outcomes, including RFS and metastasis-free survival, among breast cancer patients in Isfahan province, Iran, from 2016 to 2020. The findings of this study aimed to provide additional context to existing RCT evidence and to help inform treatment decisions in real-world clinical practice.

Methods

Study design and patients: This study was retrospectively designed to compare MFS and RFS in breast cancer patients who received adjuvant or neoadjuvant therapy at Seyed Al-Shohada Hospital, Isfahan, between July 2016 and July 2020. Data were extracted from the Breast Cancer Registry. All patients treated during this period were included, while those with incomplete registry data or missing medical records in the hospital archive were excluded. The follow-up period was extended to July 2021 (cutoff date). In this study, the primary outcomes were the incidence of distant metastasis and local recurrence during follow-up. In addition, data on patient demographics (age, menopausal status at diagnosis, family history of breast cancer) and tumor characteristics (histological grade, molecular subtype, and receptor status: ER, PR, HER2) were also collected (table 1).

Outcome definition: In this study, MFS was defined as the time from the start point the date of surgery for patients receiving neoadjuvant therapy or the date of last adjuvant intervention for the patients in adjuvant group to the first occurrence of distant metastasis. RFS was measured from the same start point to the date of the first local recurrence. Patients without events, i.e. no distant metastasis or local recurrence, by the end of follow-up were censored at the cutoff date (July 2021), while those lost to follow-up were censored at their last known follow-up date.

Statistical analysis: Data were analyzed using SPSS (v 26.0) and survival curves were generated using GraphPad Prism (v 8.0). Continuous variables were expressed as mean±standard deviation (SD), and categorical variables were reported as frequency (percentage). Baseline characteristics between the adjuvant and neoadjuvant groups were compared using the chi-square test or Fisher's exact test, as appropriate, for categorical variables. Continuous variables were compared using the independent samples t-test. For tumor grade and breast cancer molecular subtypes, per-category group comparisons were performed using Bonferroni correction.

Survival analysis was conducted using the Kaplan-Meier method to evaluate RFS and MFS rates. The log-rank test was utilized to compare RFS and MFS curves between neoadjuvant and adjuvant groups and across each molecular subtype. A Cox proportional hazards regression analysis was conducted to identify predictors of MFS and RFS. Initially, univariate Cox regression was performed to assess the crude association of each variable with MFS and RFS. Variables with p-values < 0.20 in the univariate analysis were subsequently included in the multivariate Cox regression model to identify independent predictors while adjusting for potential confounders. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. Tumor grade was treated as an ordinal variable (I to III), while molecular subtype was considered a categorical variable using dummy coding. A sensitivity analysis was conducted using inverse probability of treatment weighting (IPTW) to minimize confounding by indication. Propensity scores were estimated from age, tumor grade, and molecular subtype, and used to construct weighted Cox models for RFS and MFS. Univariate, multivariate, and IPTW Cox models were performed using complete case analysis; cases with unknown tumor grade (n = 40) or uncommon/unknown molecular subtype (n = 20) were excluded from the analyses. Statistical significance was defined as $p < 0.05$. For analyses involving Bonferroni correction, the significance threshold was adjusted to 0.05/n, where n represents the number of categories compared.

Results

A total of 411 patients were included in the analysis, with 111 receiving neoadjuvant and 300 receiving adjuvant treatment. The median follow-up duration was 20 months (range: 1 to 53 months) in the neoadjuvant treatment group and 25 months (range: 1 to 58 months) in the adjuvant treatment group. Patient demographics and tumor characteristics are summarized in table 1. The mean age at diagnosis of patients in the adjuvant and neoadjuvant groups was 49±12.4 and 44±10.6 years, respectively. All participants had undergone local and systemic treatments. Local treatment included surgical procedures and/or radiotherapy. Systemic treatments included chemotherapy, hormone therapy, or targeted therapy.

Table 1. Summary of patient demographics and tumor characteristics. Data are presented as mean±standard deviation for age, and as number (percentage) for all other variables.

Characteristic	Adjuvant group (N=300)	Neoadjuvant group (N=111)	P-value
Age at diagnosis (yr)	49±12.4	44±10.6	< 0.0001
Menopause Status (%)			0.674
Menopause	17 (5.7)	5 (4.5)	
Perimenopause	4 (1.3)	0	
premenopause	60 (20)	22 (19.8)	
Unknown	219 (73)	74 (66.7)	
Familial breast cancer history (%)			0.918
Yes	26 (8.7)	11 (9.9)	
No	51 (17)	18 (16.2)	
Unknown	223 (74.3)	82 (73.9)	
Tumor grade (%)			< 0.0001
I	32 (10.7)	3 (2.7)	
II	170 (56.7)	37 (33.3)	
III	84 (28)	51 (46)	
Unknown	14 (4.7)	20 (18)	

Characteristic	Adjuvant group (N=300)	Neoadjuvant group (N=111)	P-value
Tumor behavior (%)			0.911
In situ	5 (1.7)	1 (0.9) *	
Malignant; primary site	295 (98.3)	110 (99.1)	
Tumor laterality (%)			0.273
Right; origin of primary	120 (40)	43 (38.7)	
Left; origin of primary	173 (57.7)	61 (55)	
One breast involvement; unspecified side	2 (0.6)	2 (1.8)	
Paired site	5 (1.7)	5 (4.5)	
Receptor status (%)			
Estrogen receptor (ER)			< 0.0001
Positive	270 (90)	57 (51.4)	
Negative	22 (7.3)	46 (41.4)	
Unknown	8 (2.7)	8 (7.2)	
Progesterone receptor (PR)			< 0.0001
Positive	253 (84.3)	50 (45)	
Negative	39 (13)	53 (47.8)	
Unknown	8 (2.7)	8 (7.2)	
Human Epidermal Growth Factor Receptor 2 (HER-2)			0.002
Positive	81 (27)	43 (39)	
Negative	210 (70)	59 (53)	
Unknown	9 (3)	9 (8)	
Breast cancer subtype (%)			< 0.0001
Luminal A	191 (63.6)	38 (34)	
Luminal B	78 (26)	19 (17)	
HER2-enriched	12 (4)	25 (23)	
TNBC	8 (2.7)	20 (18)	
Uncommon subtypes	2 (0.7)	0	
Unknown	9 (3)	9 (8)	

* This patient was diagnosed with synchronous ductal carcinoma in situ (DCIS) with microinvasion. Due to high-risk features on imaging and biopsy, the multidisciplinary tumor board had recommended neoadjuvant chemotherapy at the time of diagnosis.TNBC: Triple-negative breast cancer

As presented in table 1, there were statistically significant differences in the distribution of tumor grade and molecular subtypes between the adjuvant and neoadjuvant groups (overall $p < 0.0001$ for both comparisons). Further analysis using per-category group comparison revealed that patients with Grade I and II tumors were significantly more frequent in the adjuvant group (p-value = 0.009 and $p < 0.0001$, respectively), while those with Grade III tumors were more common in the neoadjuvant group ($P = 0.001$). Regarding molecular subtypes, Luminal A was significantly more prevalent in the adjuvant group (63.6% vs. 34.2%; $p < 0.0001$), while HER2-enriched and TNBC subtypes were more common in the neoadjuvant group (23% vs. 4% and 18% vs. 2.7%, respectively; $p < 0.0001$ for both). This pattern suggests that patients with more aggressive molecular profiles, particularly HER2-enriched and TNBC, had been more assigned to neoadjuvant therapy. Therefore, these baseline disparities between adjuvant and neoadjuvant groups should be considered when interpreting the comparative survival outcomes. The frequency of local recurrence and distant metastasis, categorized by molecular subtype and treatment group (adjuvant vs. neoadjuvant), was illustrated in table 2. The adjuvant group showed a 2.7% local recurrence rate, with TNBC patients

experiencing the highest incidence at 12.5%. In this group, the rate of distant metastasis was 7.3%, again highest in the TNBC subtype at 50%. In contrast, the local recurrence rate was 9.8 % in neoadjuvant groups, which was more prevalent among patients with Luminal A subtype (15.8%). Distant metastasis in this group was 10.8%, with the highest rate observed in TNBC (15%). Conversely, the neoadjuvant group had a 9.8% local recurrence rate, most prevalent in the Luminal A subtype (15.8%). Distant metastasis in this group was 10.8%, with the highest rate observed in TNBC (15%). The primary objective of this study was to compare MFS and RFS between patients with breast cancer who underwent neoadjuvant or adjuvant therapy.

Figures 1 displays the Kaplan-Meier curves for MFS and RFS for both treatment groups.As shown in Figure 1a, both groups had an unreached median MFS and demonstrated high MFS rates during the first 30 months. While the neoadjuvant group experienced a decrease in MFS around 48 months, the adjuvant group maintained a consistently high MFS rate, suggesting a potentially greater long-term preventive effect against metastasis. Despite this observed difference, the Log-rank test showed no statistically significant difference in MFS between the two groups ($\chi^2(1) = 44.56$, P = 0.120). As illustrated in Figure 1b, RFS rate was significantly higher in the adjuvant group compared to the neoadjuvant treatment group (Log-rank test: $\chi^2(1) = 9.47$, P = 0.002). This finding indicated that the patients in the neoadjuvant group experienced a significantly higher incidence of local recurrence than those in the adjuvant group. Considering the observational nature of the study and the non-randomized assignment of treatment, there was a risk of confounding by indication.

Specifically, differences in baseline characteristics such as tumor grade and molecular subtype distribution, both of which were significantly more aggressive in the neoadjuvant group, may have contributed to the observed survival outcomes and biased the treatment comparisons. To address this, subsequent analyses were conducted to account for baseline imbalances. These included stratified analyses within each treatment group, subtype-specific comparisons, multivariate Cox regression models adjusting for key clinical variables, and a sensitivity analysis using inverse probability of treatment weighting (IPTW) based on propensity scores. To perform stratified analyses within treatment groups, specifically, to compare MFS and RFS across the Luminal A, Luminal B, HER2-enriched, and triple-negative breast cancer (TNBC) subtypes, separate log-rank tests were conducted for MFS and RFS in each group. The results for the adjuvant treatment group are presented in figure 2, and those for the neoadjuvant group are shown in figure 3

Table 2. Local recurrence and distal metastasis in each molecular subtype of the adjuvant and neoadjuvant treatment groups. Data are shown as a number (percentage)

Molecular subtypes	Treatment group	Local recurrence	Distal metastasis
Luminal A	Adjuvant (n=191)	3 (1.6)	11 (5.8)
	Neoadjuvant (n=38)	6 (15.8)	5 (13.2)
Luminal B	Adjuvant (n=78)	3 (3.8)	5 (6.4)
	Neoadjuvant (n=19)	2 (10.5)	0
HER2-enriched	Adjuvant (n=12)	0	2 (16.7)
	Neoadjuvant (n=25)	2 (8.0)	3 (12.0)
TNBC	Adjuvant (n=8)	1 (12.5)	4 (50)
	Neoadjuvant (n=20)	0	3 (15.0)
Unknown or uncommon	Adjuvant (n=11)	1 (9.1)	0
	Neoadjuvant (n=9)	0	1 (11.1)
Total	Adjuvant (n=300)	8 (2.7)	22 (7.3)
	Neoadjuvant (n=111)	10 (9.0)	12 (10.8)

TNBC: Triple-negative breast cancer

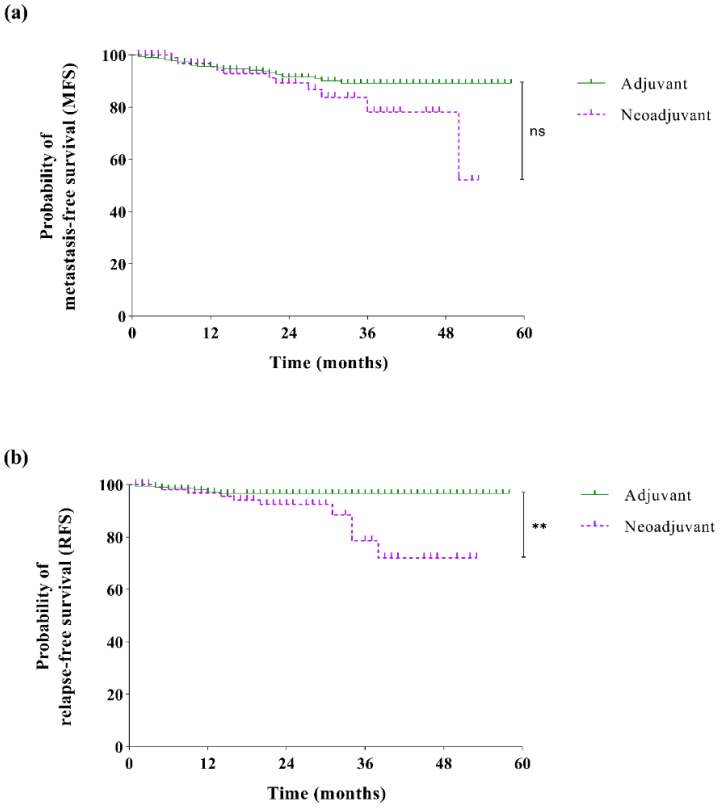

Figure 1. Kaplan-Meier curves comparing (a) metastasis-free survival (MFS) rate and (b) relapse-free survival (RFS) rate between adjuvant and neoadjuvant therapy groups.

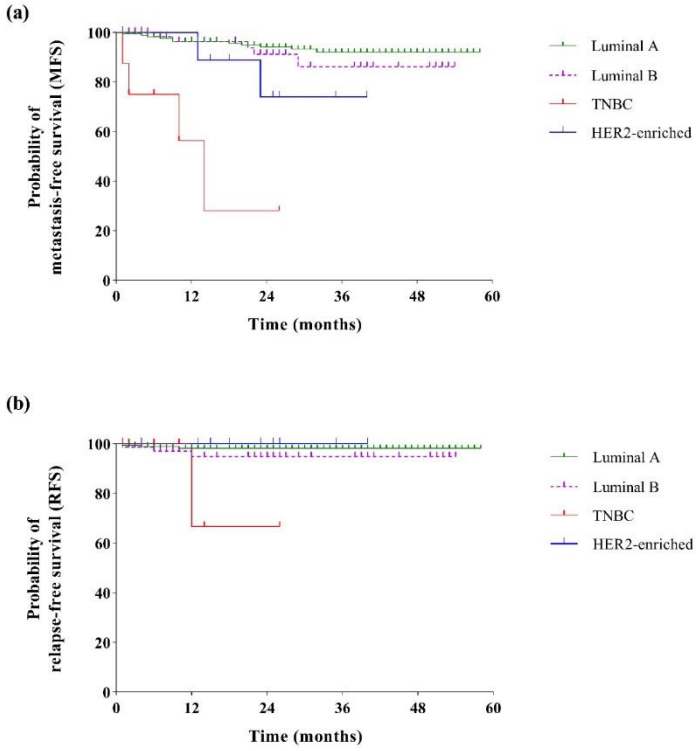

Figure 2. Comparison of (a) metastasis-free survival (MFS) and (b) relapse-free survival (RFS) rates among molecular subtypes of breast cancer in adjuvant group.

The median MFS for TNBC subtype was 14 (95% CI, 7.8 to 20.2) months, while the median MFS for Luminal A, Luminal B, and HER2-enriched subtypes was not reached. As indicated in figure 2a, there was a statistically significant difference in MFS distributions among four subtypes, $\chi^2(3) = 51.06$, $p < 0.0001$. Pairwise comparisons were conducted to determine which subtypes had different survival distributions. A Bonferroni correction was made with statistical significance accepted at the $p < 0.008$ level. There was a statistically significant difference in MFS distributions between Luminal A and TNBC subtypes, $\chi^2(1) = 44.56$, $p < 0.0001$, as well as Luminal B and TNBC subtypes, $\chi^2(1) = 26.05$, $p < 0.0001$. These findings suggest that patients with Luminal A and Luminal B tumor subtypes may experience more benefit from adjuvant chemotherapy in terms of preventing metastasis compared to patients with triple-negative tumors. These findings also highlighted the limited effectiveness of adjuvant therapy in controlling disease progression in TNBC compared to other subtypes. Figure 2b shows the RFS for each subtype. Luminal A, Luminal B, and HER2-enriched subtypes demonstrated similarly high RFS, whereas the TNBC had a lower RFS, especially in the early time periods. Further analysis revealed the difference in RFS distributions among the subtypes was not statistically significant ($\chi^2(3) = 6.99$, $P = 0.072$).

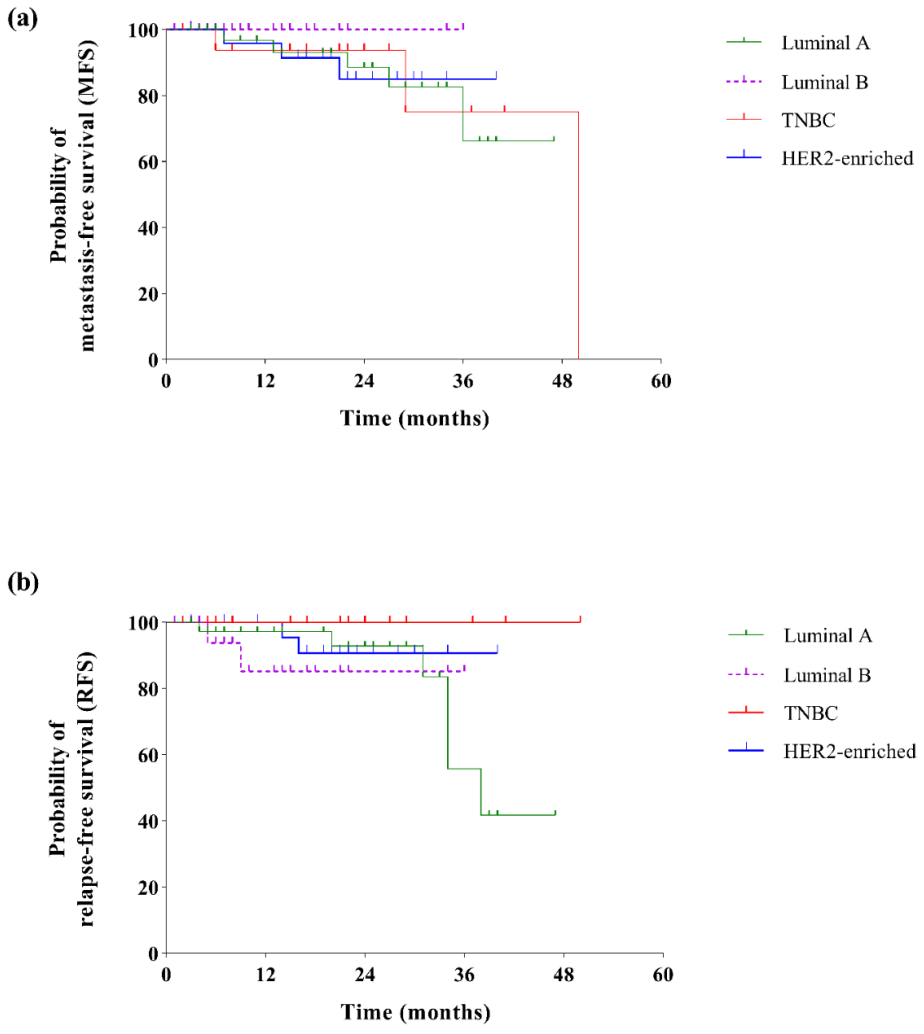

Figure 3. Comparison of (a) metastasis-free survival (MFS) and (b) relapse-free survival (RFS) rates among molecular subtypes of breast cancer in neoadjuvant group.

In the neoadjuvant group, the median MFS for TNBC subtype was 50 (95% CI, not reached) months and those for the other subtypes were not reached. There were no significant differences in MFS (Figure 3a) and RFS (Figure 3b) distributions among four subtypes of breast cancer, $\chi^2(3) = 1.37$, $P = 0.710$ and $\chi^2(3) = 3.28$, $P = 0.350$, respectively.

The median RFS for luminal A was 38 (95% CI, not reached) months, while that for the other subtypes was not reached. The lack of significant differences in survival outcomes across subtypes may indicate that neoadjuvant therapy helps to reduce the prognostic impact of tumor biology. This observation highlights the potential role of early systemic treatment in improving outcomes in high-risk subtypes such as TNBC.

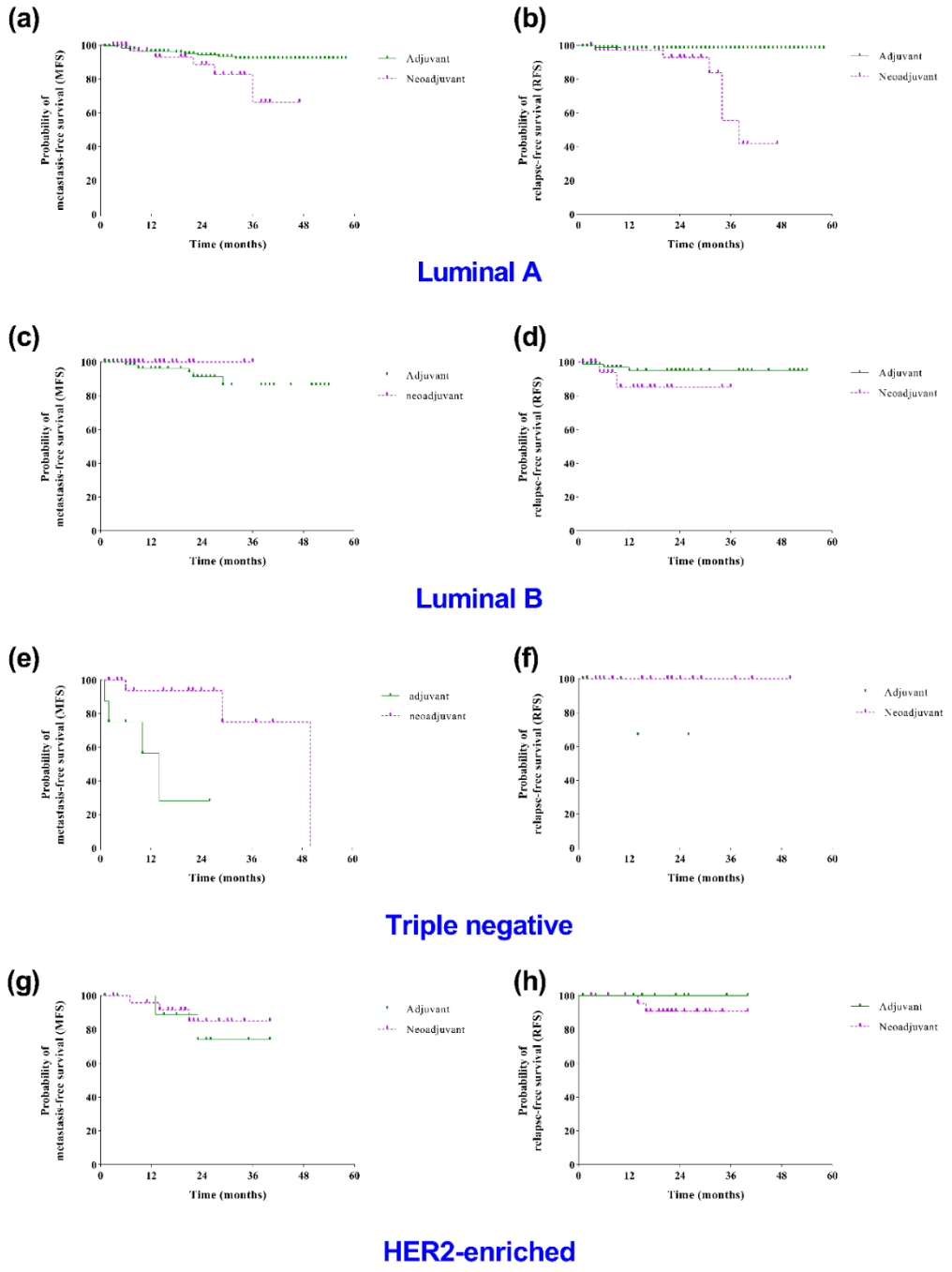

Figure 4. Kaplan-Meier survival curves comparing MFS (a, c, e, g) and RFS (b, d, f, h) between adjuvant and neoadjuvant therapy groups for four different breast cancer subtypes: Luminal A, Luminal B, Triple-negative (TNBC), and HER2-enriched (top to bottom)

The comparison of MFS and RFS curves for each molecular subtype between the two treatments groups (figure 4) revealed distinct treatment efficacy patterns across breast cancer subtypes. For Luminal A adjuvant therapy was significantly better than neoadjuvant therapy for MFS ($\chi^2(1) = 3.82$, $p = 0.049$, figure 4a) and RFS ($\chi^2(1) = 23.53$, $p < 0.0001$, figure 4b), demonstrating the strong

benefit of prescribing adjuvant therapy in the Luminal A subtype.

Conversely, for the triple-negative subtype, the neoadjuvant group showed significantly higher MFS ($\chi^2(1) = 8.99$, Pp = 0.003, figure 4e) and RFS ($\chi^2(1) = 4$, P = 0.045, figure 4f) rates than the adjuvant group. Notably, the median MFS was 14 and 50 months in the adjuvant and neoadjuvant groups, respectively. These findings showed the potential advantage of adopting neoadjuvant therapy in patients with the most aggressive form of breast cancer, suggesting that early systemic intervention may significantly improve MFS and RFS in this high-risk population. In contrast, the MFS and RFS in Luminal B ($\chi^2(1) = 0.75$, P = 0.380; figure 4c and $\chi^2(1) = 1.44$, P = 0.230, figure 4d, respectively) and HER2-enriched ($\chi^2(1) = 0.16$, P = 0.690; figure 4g and $\chi^2(1) = 0.71$, P = 0.390, Figure 4h, respectively) subtypes showed no significant differences between adjuvant and neoadjuvant therapies. These results highlight the necessity for subtype-tailored treatment approaches to optimize outcomes in breast cancer management. While Kaplan–Meier curves provided a visual and statistical comparison of survival distributions between groups and across molecular subtypes, further analysis using Cox proportional hazards regression was conducted to identify independent predictors of RFS and MFS. Of the 411 patients initially entered survival analyses, 40 lacked histopathological grade and 20 lacked molecular subtype data. These 60 cases were therefore excluded from the survival models, resulting in a complete-case cohort of 351 women.

Univariate Cox regression analysis results for both RFS and MFS are presented in table 3. For RFS, neoadjuvant therapy was associated with a significantly higher risk of relapse compared to adjuvant therapy (HR = 3.88, 95% CI: 1.49–10.08; P = 0.004). Additionally, each one-level increase in tumor grade (from I to III) tripled the relapse risk (HR = 3.11, 95% CI: 1.34–7.20; P = 0.008). However, age and molecular subtype were not significantly related to RFS (all p > 0.300). For MFS, TNBC demonstrated the poorest prognosis, with a more than fivefold increased hazard of distant metastasis compared to the Luminal A subtype (HR = 5.25, 95% CI: 2.28–12.07; p < 0.0001). Although neoadjuvant therapy, higher tumor grade, and the HER2-enriched subtype met the threshold of p < 0.20, they did not reach statistical significance in univariate analysis.

Table 3. Univariate Cox regression assessing predictors of RFS and MFS (complete-case n=351)

Variable	RFS			MFS		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age (year)	0.98	0.94 to 1.02	0.285	0.99	0.96 to 1.02	0.720
Tumor grade (I to III)	3.11	1.34 to 7.20	0.008	1.48	0.86 to 2.56	0.162
Molecular subtype						
Luminal A *	1	-	-	1	-	-
Luminal B	1.63	0.58 to 4.55	0.361	0.75	0.29 to 1.93	0.548
HER2-enriched	1.36	0.31 to 6.08	0.687	2.02	0.77 to 5.32	0.153
TNBC	1.13	0.15 to 8.61	0.909	5.25	2.28 to 12.07	< 0.0001
Type of treatment						
Adjuvant *	1	-	-	1	-	-
Neoadjuvant	3.88	1.49 to 10.08	0.004	1.76	0.86 to 3.58	0.124

Tumor grade was treated as an ordinal variable.
Complete-case analysis (n=351); patients with unknown grade (n=40) or unknown subtype (n=20) were excluded.
*: reference category
RFS: relapse-free survival; MFS: metastasis-free survival; HR: hazard ratio; CI: confidence interval; TNBC: triple-negative breast cancer.

Variables with a univariable p-value < 0.20 were entered into the multivariate Cox regression model to adjust for potential confounders. The multivariate Cox regression results for both RFS and MFS are shown in Table 4. After adjustment, both neoadjuvant chemotherapy (adjusted HR = 3.06, 95% CI: 1.11–8.47; P = 0.030) and higher tumor

grade (adjusted HR = 2.63, 95% CI: 1.07–6.49; P = 0.036) remained significant independent predictors of relapse in the RFS model.

In the corresponding MFS model, following adjustment for treatment type, tumor grade, and molecular subtype, only TNBC remained a statistically significant independent predictor of distant metastasis (adjusted HR = 6.45, 95% CI: 2.13–19.53; P = 0.001). Neoadjuvant therapy (adjusted HR = 1.07; P = 0.880), tumor grade (adjusted HR = 1.31; P = 0.386), and the HER2-enriched subtype (adjusted HR = 2.92; P = 0.056) were not statistically significant after adjustment.

Table 4. Multivariate Cox proportional-hazards model identifying independent predictors of RFS and MFS (complete-case analysis,n=351)

Variable	RFS			MFS		
	aHR	95% CI	P-value	aHR	95% CI	P-value
Tumor grade (I to III)	2.63	1.04 to 6.49	0.036	1.31	0.70 to 2.39	0.386
Molecular subtype						
Luminal A *	1	-	-	1	-	-
Luminal B	-	-	-	-	0.98 to 8.71	0.0.56
HER2-enriched	-	-	-	2.92	2.13 to	0.001
TNBC	-	-	-	6.45	19.53	
Type of treatment						
Adjuvant *	1	-	-	1	-	-
Neoadjuvant	3.06	1.11 to 8.47	0.030	1.07	0.42 to 2.70	0.880

Tumor grade was treated as an ordinal variable. Complete-case analysis (n=351); patients with unknown grade (n=40) or unknown subtype (n=20) were excluded. *: reference category. RFS: relapse-free survival; MFS: metastasis-free survival; aHR: adjusted hazard ratio; CI: confidence interval; TNBC: triple-negative breast cancer

As a final step to minimize confounding by indication, a sensitivity analysis was conducted using an inverse probability of treatment weighting (IPTW) Cox regression model. Propensity scores for treatment assignment were initially estimated based on age, tumor grade, and molecular subtype. These scores were then used to construct weighted Cox models for RFS and MFS, with the results presented in table 5. In the IPTW-weighted Cox regression model, patients receiving neoadjuvant therapy had a significantly higher hazard of relapse compared to those receiving adjuvant therapy (wHR: 6.10, 95% CI: 1.97–18.90, P = 0.002), consistent with the multivariate Cox model (aHR: 3.06, 95% CI: 1.11–8.47, P = 0.030). For MFS, no significant difference was observed between treatment groups in either model (IPTW wHR: 1.63, 95% CI: 0.74–3.56, P = 0.224; multivariate aHR: 1.07, 95% CI: 0.42–2.70, P = 0.880). These findings reinforced the robustness of the statistically significant difference in RFS between the adjuvant and neoadjuvant groups, reducing concerns regarding confounding by indication.

Table 5. IPTW-weighted Cox regression analysis of RFS and MFS by treatment type.

Type of treatment	RFS			MFS		
	wHR	95% CI	P-value	wHR	95% CI	P-value
Adjuvant *	1	-	-	1	-	-
Neoadjuvant	6.10	1.97 to 18.90	0.002	1.63	0.74 to 3.56	0.224

Complete-case analysis (n=351); patients with unknown grade (n=40) or unknown subtype (n=20) were excluded.*: reference category. RFS: relapse-free survival; MFS: metastasis-free survival; wHR: weighted hazard ratio; CI: confidence interval.

Breast cancer remains the most frequently diagnosed malignancy among women. Advances in chemotherapy regimens, surgical techniques, and targeted hormonal therapies have led to substantial improvements in survival outcomes (13). The present study focused on comparing metastasis-free survival (MFS) and recurrence-free survival

(RFS) between breast cancer patients receiving neoadjuvant and adjuvant therapies in a real-world cohort at Seyed Al-Shohada Hospital, Isfahan, between July 2016 and July 2020.The results of this study should be interpreted in light of its retrospective and observational nature. In standard clinical practice, neoadjuvant therapy is typically administered for patients with more locally advanced or biologically aggressive tumors, who inherently have a higher baseline risk of both local recurrence and distant metastasis. To account for this clinical context, we applied two complementary analytical strategies: multivariate Cox regression, which adjusted for key prognostic factors, and IPTW-weighted Cox regression, specifically designed to reduce possible confounding by indication resulting from the non-randomized treatment allocation.

In the unadjusted analysis, neoadjuvant therapy was associated with a significantly higher risk of relapse compared to adjuvant treatment. This association remained statistically significant in both the multivariate-adjusted and IPTW-weighted models, suggesting that the increased relapse risk cannot be fully attributed to differences in baseline tumor characteristics. While the neoadjuvant group included patients with more aggressive tumor biology, the consistency of results across modeling approaches reinforces the validity of the observed treatment effect. In contrast, MFS did not significantly differ between the treatment groups before and after adjustment. These findings emphasized the importance of individualized treatment decisions based on a combination of clinical and pathological factors.

The existing literature regarding the comparison of MFS and RFS between adjuvant and neoadjuvant therapies is limited. Most previous research has primarily focused on comparing overall survival (OS) and disease-free survival (DFS) between these two treatments. For example, a nine-year randomized trial published in 2001 examined patients with operable breast cancer who received either adjuvant or neoadjuvant chemotherapy, utilizing a chemotherapy protocol consisting of four cycles of doxorubicin/cyclophosphamide. The results of this trial demonstrated no statistically significant differences in OS and DFS between the two treatment groups (14). In addition, the 2018 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) analysis (15) found that while neoadjuvant therapy increases the chance of breast-conserving surgery, it may also be associated with higher local recurrence rates, a finding consistent with our observation that patients in the neoadjuvant group had significantly higher rates of local recurrence (P= 0.002). Based on this result, it is suggested that adjuvant therapy may provide better long-term protection against local recurrence.

Furthermore, our analysis by molecular subtype revealed that TNBC had the poorest MFS outcomes, with a median time to metastasis of just 14 months. This finding aligns with prior literature describing TNBC as a highly aggressive subtype with limited treatment options (16). Our findings revealed that in patients with Luminal A breast cancer, adjuvant therapy is associated with lower rates of local recurrence and distant metastasis compared to neoadjuvant therapy, suggesting that adjuvant therapy may be an appropriate therapeutic strategy for this molecular subtype. This result was in agreement with existing literature, indicating that Luminal A breast cancers generally have a favorable prognosis and respond well to adjuvant therapy (17, 18). Conversely, our results demonstrated that neoadjuvant treatment is significantly more effective than adjuvant therapy in improving MFS and RFS rates among patients with TNBC, indicating a greater protective effect against local and distant recurrence. This finding supports the common practice of administering neoadjuvant chemotherapy in TNBC (19). However, it was in contrast to the finding reported by Clifton et al., who observed no significant difference in DFS between patients with triple-negative breast cancer who received adjuvant or neoadjuvant chemotherapy (20).

In 2022, Akbari et al. reported the results of a 10-year follow-up study analyzing survival rates in 845 Iranian patients diagnosed with stage III locally advanced breast cancer who received either adjuvant or neoadjuvant treatment between 2009 and 2019. They found no significant difference in OS between the two treatment groups. Moreover, they reported that factors, including education level, hormone therapy, estrogen/progesterone receptor status, and tumor grade, were not significantly associated with OS. However, the researchers found that age and a family history of breast cancer were significant factors affecting survival outcomes (21).

In our study, age was not a significant predictor of RFS or MFS in multivariate models, while TNBC was a strong predictor of poorer MFS. Moreover, neoadjuvant therapy and tumor grade remained independent predictors of lower RFS. However, family history of breast cancer could not be assessed due to missing data.

Taken together, these findings highlighted the importance of tailoring treatment strategies to tumor biology and underscore the complexity of interpreting survival outcomes in non-randomized, real-world settings. The application of IPTW modeling in this study helped mitigate confounding by indication, reinforcing the

robustness of the observed associations between treatment type and relapse risk.

This study has some limitations that warrant consideration. As a non-randomized observational study conducted at a single center, there is a possibility of confounding by indication, where treatment assignment may have been influenced by tumor characteristics such as grade or molecular subtype. However, the use of both multivariable Cox regression and inverse probability of treatment weighting (IPTW) helped address these imbalances and strengthened causal inference. Despite these efforts, the possibility of residual confounding cannot be entirely excluded, particularly given the high proportion of missing data for certain important variables such as clinical stage and family history. Another limitation of our study is the relatively short median follow-up duration, which may not fully reflect long-term survival outcomes.

Nonetheless, we believe that our methodological approach supports the credibility of our findings. Moreover, this study provided valuable real-world insights into treatment effectiveness and helped improve the understanding of neoadjuvant and adjuvant strategies in breast cancer.In conclusion, our study demonstrated that adjuvant therapy was associated with significantly better RFS compared to neoadjuvant treatment, even after accounting for baseline tumor characteristics and potential confounding by indication. While MFS did not differ significantly between treatment groups, molecular subtype remained a critical determinant of metastasis, with TNBC showing the poorest outcomes. These findings highlighted the importance of personalized treatment planning based on tumor biology and offered practical insights that can inform real-world clinical decision-making in the management of breast cancer.

Acknowledgments

The authors would like to thank the staff of the Isfahan Cancer Prevention Center and all clinicians involved in the diagnosis, treatment, and follow-up of breast cancer patients included in this study.

Funding: The research was conducted as part of a thesis project financially supported by Isfahan University of Medical Sciences.

Ethics approval: This study was ethically approved by the Ethics Committee of Isfahan University of Medical Sciences (Reference number: IR.MUI.MED.REC.1400.829) and the requirement for written informed consent was waived. The research was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki and its subsequent amendments.

Conflict of interests: The authors have no conflicts of interest.

Authors' contribution: Mina Azarnia was responsible for writing the manuscript, performing the statistical analyses, and interpreting the study findings. Mehran Sharifi conceptualized and designed the study. Shaghayegh Haghjooy Javanmard and Mehran Sharifi critically reviewed and revised the manuscript. Zahra Rezaeian and Saeedeh Arabzadeh were involved in data extraction and collection. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

References

1. Nardin S, Mora E, Varughese FM, et al. Breast cancer survivorship, quality of life, and late toxicities. Front Oncol 2020; 10: 864.
2. Haghighat S, Omidi Z, Ghanbari MA. Trend of breast cancer incidence in Iran during a fifteen-year interval according to national cancer registry reports. Iran Quarterly Breast Dis 2022; 15: 4-17.
3. Smolarz B, Nowak AZ, Romanowicz H. Breast cancer-epidemiology, classification, pathogenesis and treatment (Review of literature). Cancers (Basel) 2022; 14: 2569.
4. Bilal E, Dutkowski J, Guinney J, et al. Improving breast cancer survival analysis through competition-based multidimensional modeling. PLoS Comput Biol 2013; 9: e1003047.
5. Anampa J, Makower D, Sparano JA. Progress in adjuvant chemotherapy for breast cancer: an overview. BMC Med 2015; 13: 1-13.
6. Schegerin M, Tosteson AN, Kaufman PA, Paulsen KD, Pogue BW. Prognostic imaging in neoadjuvant chemotherapy of locally-advanced breast cancer should be cost-effective. Breast Cancer Res Treat 2009; 114: 537-47.
7. Asaoka M, Gandhi S, Ishikawa T, Takabe K. Neoadjuvant chemotherapy for breast cancer: past, present, and future. Breast Cancer (Auckl) 2020; 14: 1178223420980377.
8. Zhang J, Sun M, Chang E, et al. Pathologic response as predictor of recurrence, metastasis, and survival in breast cancer patients receiving neoadjuvant chemotherapy and total mastectomy. Am J Cancer Res 2020; 10: 3415.

9. Yousefi M, Nosrati R, Salmaninejad A, et al. Organ-specific metastasis of breast cancer: molecular and cellular mechanisms underlying lung metastasis. Cell Oncol (Dordr) 2018; 41: 123-40.
10. Park M, Kim D, Ko S, et al. Breast cancer metastasis: mechanisms and therapeutic implications. Int J Mol Sci2022; 23: 6806.
11. Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol 1997; 15: 2483-93.
12. Van Nes JG, Putter H, Julien J-P, et al. Preoperative chemotherapy is safe in early breast cancer, even after 10 years of follow-up; clinical and translational results from the EORTC trial 10902. Breast Cancer Res Treat 2009; 115: 101-13.
13. Miller E, Lee HJ, Lulla A, et al. Current treatment of early breast cancer: adjuvant and neoadjuvant therapy. F1000Res 2014; 3: 198.
14. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: Nine-year results from national surgical adjuvant breast and bowel project B-18. J Natl Cancer Inst Monogr 2001; 2001: 96-102.
15. Asselain B, Barlow W, Bartlett J, et al. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol 2018; 19: 27-39.
16. Reis-Filho J, Tutt A. Triple negative tumours: a critical review. Histopathology 2008; 52: 108-18.
17. Ye J, Wang W, Xin L, et al. The clinicopathological factors associated with disease progression in Luminal a breast cancer and characteristics of metastasis: a retrospective study from a single center in China. Anticancer Res 2017; 37: 4549-56.
18. Diessner J, Wischnewsky M, Blettner M, et al. Do patients with luminal a breast cancer profit from adjuvant systemic therapy? A retrospective multicenter study. PloS One 2016; 11: e0168730.
19. Bagegni NA, Tao Y, Ademuyiwa FO. Clinical outcomes with neoadjuvant versus adjuvant chemotherapy for triple negative breast cancer: A report from the National Cancer database. PloS One 2019; 14: e0222358.
20. Clifton K, Gutierrez-Barrera A, Ma J, et al. Adjuvant versus neoadjuvant chemotherapy in triple-negative breast cancer patients with BRCA mutations. Breast Cancer Res Treat 2018; 170: 101-9.
21. Akbari M-e, Ghelichi-Ghojogh M, Nikeghbalian Z, et al. Neoadjuvant VS adjuvant chemotherapy in patients with locally advanced breast cancer; a retrospective cohort study. Ann Med Surg (Lond) 2022; 84: 104921.