Article

Assessing Surgical Benefits and Creating a Prognostic Model for Breast Cancer with Lung-only Metastasis: An Analysis of the National Cancer Database

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AIM: The decision to perform surgery on breast cancer patients with lung-only metastasis is a subject of ongoing debate. Our investigation seeks to assess the survival rates following surgical intervention among individuals diagnosed with breast cancer experiencing isolated metastasis to the lungs. Additionally, we endeavor to devise a predictive nomogram aimed at forecasting the long-term survival.

METHODS: We analyzed patients diagnosed with primary lung metastases from breast cancer between 2010 and 2015, utilizing datasets obtained from the National Cancer Database (NCDB). We employed the Cox proportional hazards regression model and the Kaplan-Meier method to analyze survival data. Additionally, we constructed nomograms to forecast survival outcomes.

RESULTS: The study comprised 2403 patients, with 1058 (44.0%) undergoing breast-specific surgery and 1345 (56.0%) not receiving surgical treatment. The group that underwent surgical procedures exhibited a significantly enhanced overall survival (OS) compared to the non-surgery group (multivariate analysis: hazard ratio [HR] = 0.64; 95% confidence interval [CI], 0.54–0.75; $p < 0.001$). Surgical intervention consistently improved survival across nearly all patient subgroups. The research successfully established a predictive nomogram designed to calculate the likelihood of long-term survival, attaining a concordance index (C-index) of approximately 0.7 in both validation and training cohorts. By integrating multiple clinicopathological variables, the nomogram efficiently classified patients into categories reflecting different survival forecasts.

CONCLUSIONS: The findings of this investigation support the notion that surgical treatment can enhance the overall survival of patients with initial lung-only metastasis from breast cancer. The investigation further introduces a nomogram demonstrating reasonable accuracy in forecasting long-term survival of patients in this cohort.

Keywords: breast cancer; lung metastasis; surgery; NCDB

Introduction

Breast cancer remains a major cause of both morbidity and mortality on a global scale [1, 2]. It is estimated that approximately 6% of individuals with breast cancer present experiencing distant metastases at initial diagnosis [3]. The most common metastatic sites of breast cancer were lung, bone, liver, and brain [4]. Patients with metastatic breast cancer (MBC) typically have a median survival of 18 to 24 months, with the 5- and 10-year post-diagnosis survival rates dipping to 27% and 13%, respectively [5]. The emergence of lung metastasis marks a critical juncture in the progression of the breast cancer and significantly influences patient prognosis [6]. Despite progress in early detection and therapeutic interventions, the occurrence of metastasis confined to the lungs still poses a distinct clinical challenge, calling for a refined understanding of patient prognoses and the formulation of prognostic models that can inform treatment choices.

Recent retrospective analyses and a prospective clinical trial conducted in India have not substantiated a survival advantage for surgical intervention in patients with metastatic breast cancer [7, 8]. Recent research indicates that surgical removal might confer a survival advantage in selected instances of lung-only metastasis [9]. However, the selection criteria for surgical candidates and the extent of the potential benefits remain to be fully clarified [10]. Furthermore, there still exists a degree of uncertainty among practitioners regarding the advisability of performing surgery on the primary tumor in breast cancer patients with metastasis limited to the lungs.

The development of a precise prognostic model would greatly influence clinical decision-making, facilitating tailored treatment approaches that could enhance both the quality of life and survival rates for these patients [11]. Constructing such a model necessitates considering a wide array of elements, encompassing tumor biology, demographic characteristics of patients, and specifics of both systemic and surgical interventions.

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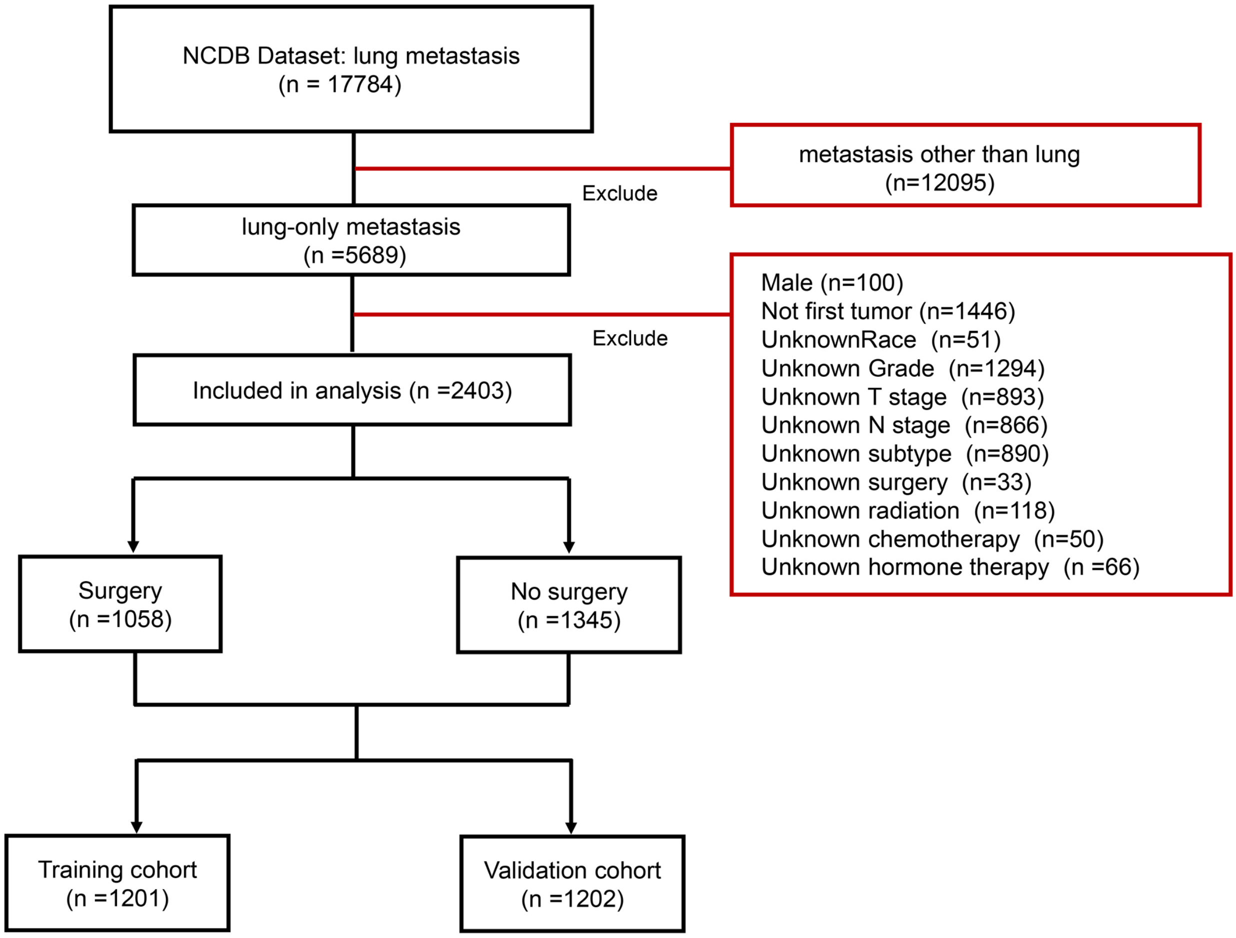

Fig. 1. A flowchart illustrating the process of patient selection. NCDB, National Cancer Database.

Therefore, this study seeks to thoroughly evaluate the potential surgical advantages for patients with breast cancer that has metastasized only to the lungs and to suggest a prognostic model based on data from the National Cancer Database (NCDB). Clinicians could benefit from this approach by making better treatment decisions and by giving prognostic advice to patients who are at risk for such conditions.

Materials and Methods

Collection of Data and Selection of Participants

Information was sourced from the NCDB (https://www.facs.org/quality-programs/cancer-programs/national-cancer-database/), capturing approximately 70% of all new cancer diagnoses in the United States, and NCDB is a collaborative effort of the American Cancer Society and the American College of Surgeons. This study focused on individuals diagnosed with breast cancer and concurrent lung metastasis during the years 2010 to 2015.

Participants were disqualified for any of these conditions: (1) being male; (2) presence of metastatic sites other than the lung; (3) cases not representing the first primary tumor; (4) incomplete medical records regarding race, diagnosis year, grade, American joint committee on cancer (AJCC) T and N stage, cancer subtype, surgical and radiation treatments, chemotherapy, or hormone therapy. In adherence with these criteria, the study enrolled 2403 patients (Fig. 1). These patients were then evenly distributed into a training set and a validation set at a 1:1 ratio. The training set was instrumental in the creation of the nomogram, which was later assessed in the validation set. The primary endpoint evaluated was overall survival (OS).

Statistical Methodology

The study summarized demographic and clinicopathological attributes using descriptive statistical measures. The Pearson chi-square (χ^2) test was employed to discern associations among clinicopathological factors. Survival analysis was conducted using Kaplan-Meier curves, and differences in survival rates between the surgical and non-surgical cohorts were compared using a two-tailed log-rank test. Additionally, both univariate and multivariate Cox regression analyses were carried out to calculate hazard ratios (HRs), with 95% confidence intervals (CIs). Furthermore, prognostic nomograms were constructed to project 1-year, 3-year, and 5-year OS.

Table 1. Baseline characteristics of breast cancer with lung-only metastasis.

Characteristic	Total cohort	No surgery cohort	Surgery cohort	χ^2 value	p-value
	n (%)	n (%)	n (%)		
Age, year				46.2	<0.001
<35	58 (2.4)	25 (1.9)	33 (3.1)		
35–49	380 (15.8)	166 (12.3)	214 (20.2)		
50–69	1173 (48.8)	650 (48.3)	523 (49.4)		
≥70	792 (33.0)	504 (37.5)	288 (27.2)		
Race				1.3	0.533
White	1749 (72.8)	969 (72.0)	780 (73.7)		
Black	539 (22.4)	313 (23.3)	226 (21.4)		
Others	115 (4.8)	63 (4.7)	52 (4.9)		
Diagnosis year				50.4	<0.001
2010–2012	1059 (44.1)	507 (37.7)	552 (52.2)		
2013–2015	1344 (55.9)	838 (62.3)	506 (47.8)		
Grade				24.5	<0.001
1	104 (4.3)	69 (5.1)	35 (3.3)		
2	677 (28.2)	424 (31.5)	253 (23.9)		
3–4	1622 (67.5)	852 (63.3)	770 (72.8)		
Subtype				19.4	<0.001
HR+/HER2–	1027 (42.7)	615 (45.7)	412 (38.9)		
HR+/HER2+	350 (14.6)	187 (13.9)	163 (15.4)		
HR–/HER2+	332 (13.8)	197 (14.6)	135 (12.8)		
TNBC	694 (28.9)	346 (25.7)	348 (32.9)		
T stage				7.4	0.061
T0–1	223 (9.3)	126 (9.4)	97 (9.2)		
T2	749 (31.2)	390 (29.0)	359 (33.9)		
T3	430 (17.9)	243 (18.1)	187 (17.7)		
T4	1001 (41.7)	586 (43.6)	415 (39.2)		
N stage				27.3	<0.001
N0	576 (24.0)	278 (20.7)	298 (28.2)		
N1	1118 (46.5)	669 (49.7)	449 (42.4)		
N2	383 (15.9)	198 (14.7)	185 (17.5)		
N3	326 (13.6)	200 (14.9)	126 (11.9)		
Radiotherapy				264.1	<0.001
No	1879 (78.2)	1215 (90.3)	664 (62.8)		
Yes	524 (21.8)	130 (9.7)	394 (37.2)		
Chemotherapy				67.0	<0.001
No	787 (32.8)	534 (39.7)	253 (23.9)		
Yes	1616 (67.2)	811 (60.3)	805 (76.1)		
Hormone therapy				1.2	0.273
No	1404 (58.4)	799 (59.4)	605 (57.2)		
Yes	999 (41.6)	546 (40.6)	453 (42.8)		

HR+, hormone receptor-positive; HER2, Human Epidermal Growth Factor Receptor 2; HER2+, HER2-positive; TNBC, triple-negative breast cancer.

To evaluate the accuracy of the nomogram predictions, calibration curves were plotted, comparing predicted survival with observed outcomes. Statistical computations, including descriptive statistics, Pearson χ^2 test, and Cox proportional hazards modeling, were conducted using SPSS software version 24.0 (IBM Corp., Armonk, NY, USA). Kaplan-Meier survival analysis was performed with R software (version 4.0.0; R Foundation for Statistical Computing, Vienna, Austria), and the nomogram was generated using the "rms" and "survival" packages in R. A p-value less than 0.05 in a two-tailed test was deemed statistically significant.

Results

Baseline Characteristics

In the analyzed cohort, 2403 patients were considered, with 1058 (44.0%) having undergone specialized breast surgery and 1345 (56.0%) not receiving such treatment. The baseline characteristics of both cohorts were statistically compared using the Pearson χ^2 test, as detailed in Table 1. A significantly higher proportion of younger patients opted for surgical intervention (35–49 years: 20.2% vs. 12.3%). Those who did not undergo surgery tended to have a diagnosis within the more recent years of the study period (2013–2015: 62.3%). In terms of clinicopathological attributes, the surgery group had a greater incidence of poorly differentiated tumors (72.8% vs. 63.3%), as well as a higher frequency of the triple-negative breast cancer subtype (32.9% vs. 25.7%). Additionally, patients who had surgery were more likely to receive adjunct treatments, such as radiotherapy (37.2% vs. 9.7%) and chemotherapy (76.1% vs. 60.3%), but not hormone therapy (42.8% vs. 40.6%).

Survival Analyses

The OS of patients with lung-only metastasis undergoing surgical intervention versus those who did not was compared using the Kaplan-Meier method. The resulting survival curves, as depicted in Fig. 2, demonstrate a clear survival benefit for the cohort that underwent surgery compared to those who did not receive this intervention. To further elucidate the impact of surgery on survival, a Cox regression model was employed. The multivariate analysis from this model indicated a significant improvement in OS for the surgery cohort (hazard ratio [HR] = 0.64, $p < 0.001$). This suggests that surgery is associated with a 34% reduction in the hazard of death compared to no surgery, which is statistically significant. The analysis of survival benefits stratified by patient subgroups revealed that the advantage of surgery extended across most subgroups. However, there were exceptions noted in the study. Patients with histological grade 1 and those with hormone receptor-positive/HER2-positive (HR+/Human Epidermal Growth Factor Receptor 2 [HER2]+) subtypes did not exhibit a statistically significant survival benefit from surgery (Table 2).

The entire patient cohort was initially divided into two groups: a training cohort and a validation cohort, with an equal allocation, as depicted in Fig. 1. Evaluation of the baseline characteristics revealed no significant disparities between the two cohorts, as illustrated in Table 3. Following this, both univariate and multivariate Cox regression analyses were conducted to pinpoint factors demonstrating a significant correlation with OS among patients with metastases confined to the lungs, as delineated in Table 4. The examination unveiled that older age (70 years or older vs. 35 years and younger; hazard ratio [HR] = 2.49, $p = 0.003$), higher histological grades (grades 3–4 vs. grade 1; HR = 1.91, $p = 0.001$), the triple-negative breast cancer (TNBC) subtype (TNBC vs. HR+/HER2–; HR = 1.29, $p = 0.023$), and larger primary tumors (T4 vs. T0–1; HR = 1.59, $p = 0.001$) typically correlated with a poorer prognosis. Conversely, a more favorable survival outlook was

Table 2. Cox regression analysis conducted to assess the survival advantage of surgery among breast cancer patients with metastases limited to the lungs.

Variables	Multivariate analysis	
	HR (95% CI)	*p*-value
All patients	0.64 (0.54–0.75)	<0.001
Subgroup		
Age, year		
<35	0.26 (0.07–0.99)	0.049
35–49	0.73 (0.55–0.95)	0.021
50–69	0.60 (0.50–0.71)	<0.001
≥70	0.68 (0.56–0.81)	<0.001
Race		
White	0.64 (0.56–0.73)	<0.001
Black	0.69 (0.54–0.88)	0.003
Others	0.72 (0.39–1.33)	0.298
Diagnosis year		
2010–2012	0.63 (0.54–0.74)	<0.001
2013–2015	0.66 (0.56–0.78)	<0.001
Grade		
1	0.75 (0.39–1.43)	0.381
2	0.70 (0.54–0.89)	0.004
3–4	0.64 (0.57–0.73)	<0.001
Subtype		
HR+/HER2–	0.58 (0.48–0.70)	<0.001
HR+/HER2+	0.81 (0.58–1.14)	0.225
HR–/HER2+	0.56 (0.39–0.81)	0.002
TNBC	0.68 (0.57–0.81)	<0.001
T stage		
T0–1	0.51 (0.34–0.76)	0.001
T2	0.56 (0.45–0.70)	<0.001
T3	0.74 (0.57–0.97)	0.026
T4	0.75 (0.64–0.89)	0.001
N stage		
N0	0.64 (0.51–0.80)	<0.001
N1	0.63 (0.53–0.76)	<0.001
N2	0.76 (0.57–1.01)	0.056
N3	0.73 (0.53–0.99)	0.046
Radiotherapy		
No	0.74 (0.65–0.83)	<0.001
Yes	0.39 (0.30–0.50)	<0.001
Chemotherapy		
No	0.63 (0.52–0.76)	<0.001
Yes	0.66 (0.57–0.76)	<0.001
Hormone therapy		
No	0.63 (0.55–0.73)	<0.001
Yes	0.68 (0.56–0.82)	<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; TNBC, triple-negative breast cancer.

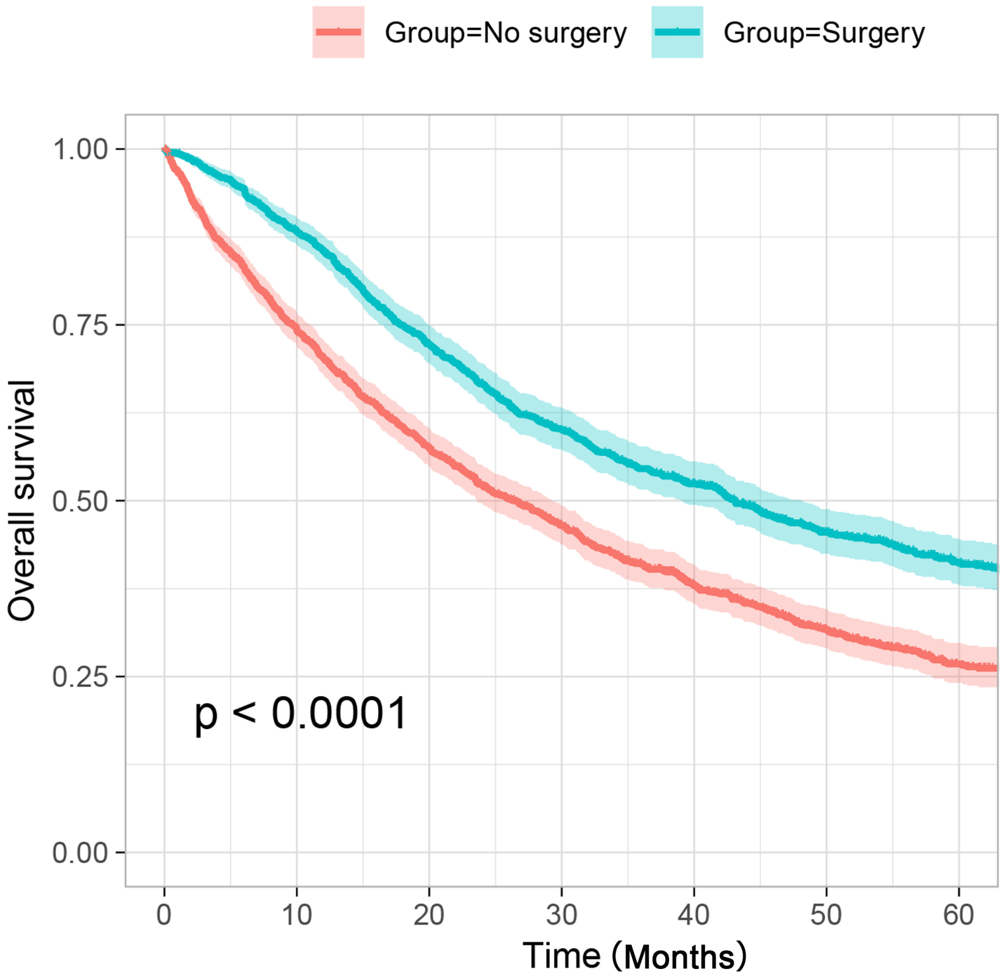

Fig. 2. The Kaplan-Meier curve illustrates the overall survival (OS) of breast cancer patients with lung-only metastases, comparing those who underwent surgical intervention with those who did not. Surgery cohort (n = 1058); No surgery cohort (n = 1345).

linked to tumors that were HER2-positive (HR+/HER2+ vs. HR+/HER2–, HR = 0.68, $p = 0.006$; HR–/HER2+ vs. HR+/HER2–, HR = 0.47, $p < 0.001$), as well as to patients who underwent surgical intervention (HR = 0.64, $p < 0.001$), received chemotherapy (HR = 0.62, $p < 0.001$), or received endocrine therapy (HR = 0.45, $p < 0.001$).

Nomogram and Risk Stratifications

To enhance the prediction of survival rates in breast cancer patients who had only lung metastases, a prognostic nomogram was developed. This tool incorporates multiple independent prognostic indicators including age, tumor grade, cancer subtype, tumor stage, and treatment modalities such as surgery, chemotherapy, and hormone therapy. The nomogram, depicted in Fig. 3, enables the calculation of a cumulative score for each patient by matching their individual characteristics with the corresponding points on the scale. This approach simplifies the prediction of survival probabilities at 1, 3, and 5 years. As an example, based on the clinical attributes of a hypothetical patient, a score of 389 was obtained, translating to 1-, 3-, and 5-year OS rates of 96.7%, 90.8%, and 86%, respectively. Generally, a greater total score suggested a less favorable patient prognosis. The Harrell's concordance index (C-index), used to evaluate the predictive accuracy of the nomogram for OS, was recorded at 0.714 for the training set and 0.690 for the validation set. Additionally, calibration curve analysis demonstrated a commendable alignment between the nomogram's predicted survival rates and the actual observed rates, as illustrated in **Supplementary Fig. 1**. Patients were stratified into low- and high-risk categories based on their median risk scores from the nomogram. As demonstrated in Fig. 4, those classified in the high-risk category exhibited significantly lower survival rates compared to their low-risk counterparts.

Discussion

Our investigation provides a detailed evaluation of outcomes in breast cancer patients with lung-only metastases following surgical treatment. The findings demonstrate

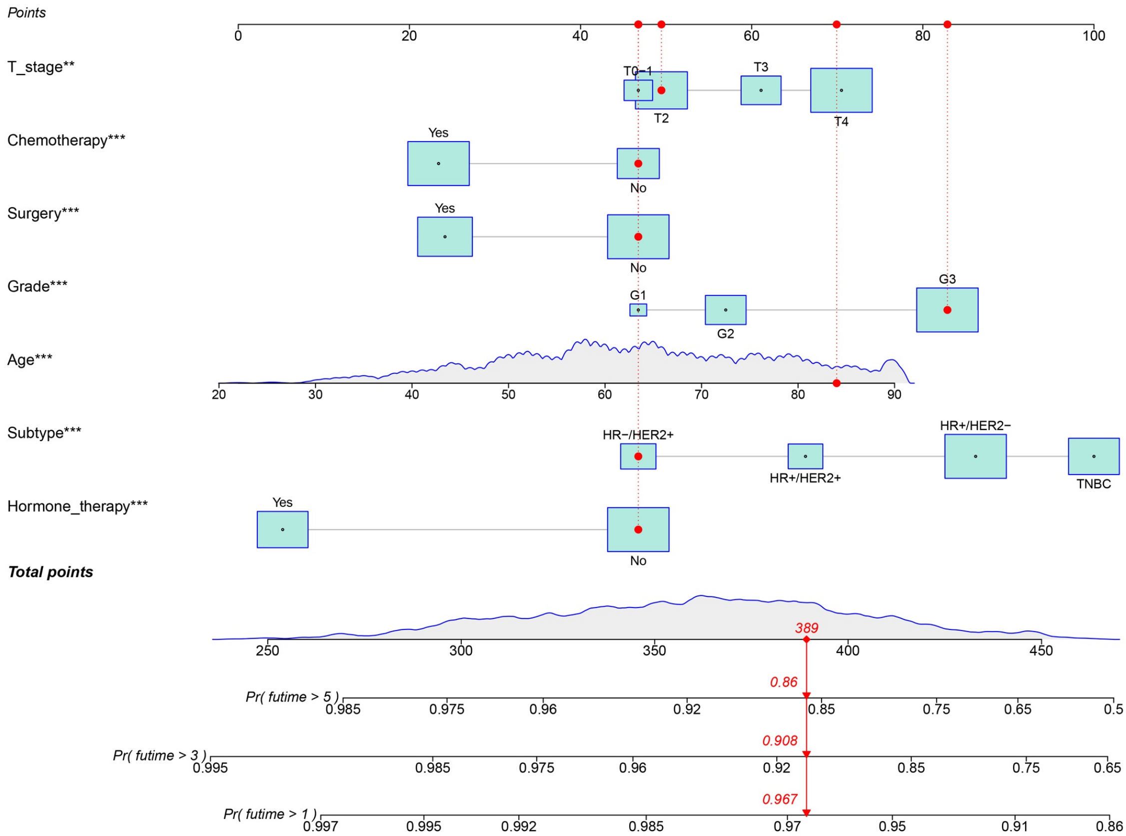

Fig. 3. Nomogram developed for forecasting overall survival likelihood. $^{**}p < 0.01$, $^{***}p < 0.001$.

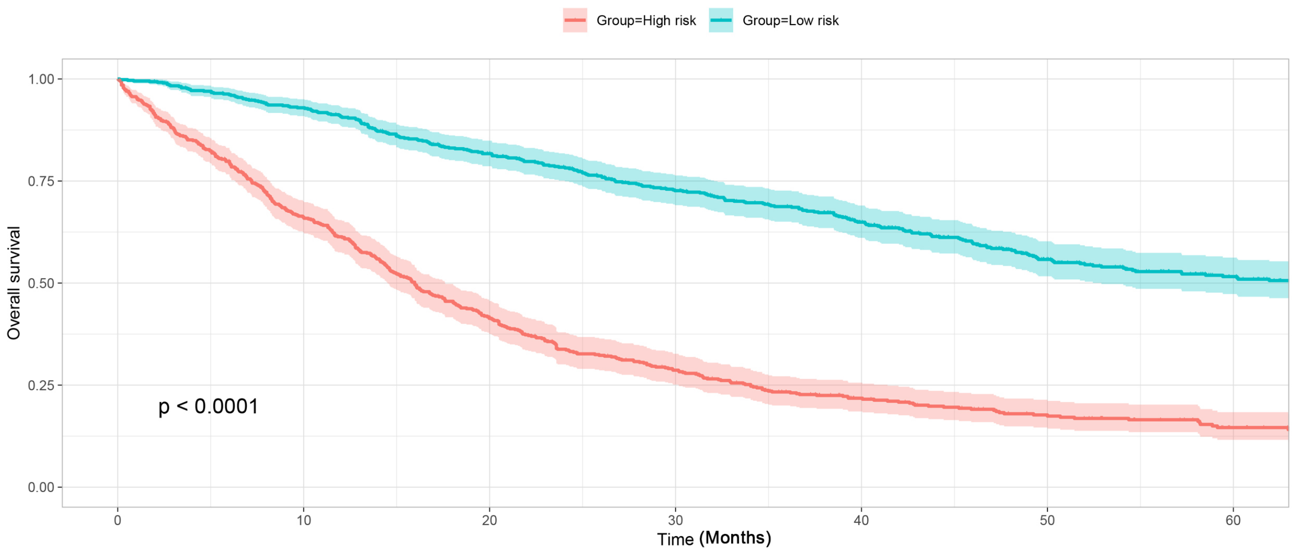

Fig. 4. Kaplan-Meier curve of overall survival for patients with high or low risk stratified by nomogram. Low risk cohort (n = 599); High risk cohort (n = 602). Median risk score: 1.96.

a distinct advantage in survival for those who received surgery for breast cancer, reinforcing previous research that highlighted the importance of rigorous local management, including surgical procedures, in metastatic breast cancer [12, 13]. This advantage in survival remained consistent, even after adjusting for various confounding elements using a multivariate Cox regression analysis, emphasizing the critical role that surgical intervention may play in treating this group of patients.

Interestingly, our research observed a higher propensity for younger patients to undergo surgery, potentially indicating a general preference for more assertive treatment strategies

Table 3. Baseline characteristics of training and validation cohort.

Characteristic	Training cohort No. (%)	Validation cohort No. (%)	χ^2 value	*p*-value
Age, year			3.9	0.275
<35	25 (2.1)	33 (2.7)		
35–49	184 (15.3)	196 (16.3)		
50–69	576 (48.0)	597 (49.7)		
≥70	416 (34.6)	376 (31.3)		
Race			4.4	0.112
White	892 (74.3)	857 (71.3)		
Black	261 (21.7)	278 (23.1)		
Others	48 (4.0)	67 (5.6)		
Diagnosis year			0.78	0.378
2010–2012	540 (45.0)	519 (43.2)		
2013–2015	661 (55.0)	683 (56.8)		
Grade			3.13	0.209
1	59 (4.9)	45 (3.7)		
2	348 (29.0)	329 (27.4)		
3–4	794 (66.1)	828 (68.9)		
Subtype			1.73	0.631
HR+/HER2–	515 (42.9)	512 (42.6)		
HR+/HER2+	164 (13.7)	186 (15.5)		
HR–/HER2+	170 (14.2)	162 (13.5)		
TNBC	352 (29.3)	342 (28.5)		
T stage			0.9	0.827
T0–1	110 (9.2)	113 (9.4)		
T2	365 (30.4)	384 (31.9)		
T3	216 (18.0)	214 (17.8)		
T4	510 (42.5)	491 (40.8)		
N stage			5.5	0.141
N0	274 (22.8)	302 (25.1)		
N1	573 (47.7)	545 (45.3)		
N2	179 (14.9)	204 (17.0)		
N3	175 (14.6)	151 (12.6)		
Surgery			0.03	0.855
No	670 (55.8)	675 (56.2)		
Yes	531 (44.2)	527 (43.8)		
Radiotherapy			0.4	0.546
No	933 (77.7)	946 (78.7)		
Yes	268 (22.3)	256 (21.3)		
Chemotherapy			0.8	0.369
No	383 (31.9)	404 (33.6)		
Yes	818 (68.1)	798 (66.4)		
Hormone therapy			1.0	0.309
No	714 (59.5)	690 (57.4)		
Yes	487 (40.5)	512 (42.6)		

among this demographic, likely due to their better general health and greater ability to withstand intense treatments. This tendency for younger patients to choose surgery might also stem from an anticipation of a more extended survival, making the benefit of long-term survival more attractive [14, 15].

Our results underline the significance of complementary treatments such as radiotherapy and chemotherapy, which were more frequently used alongside surgery. This integrated treatment approach, merging surgical and systemic therapies, appears to contribute significantly to the survival advantage observed, suggesting a combined effect that merits further exploration.

However, it is important to recognize that surgical intervention did not benefit all patient groups uniformly. Particularly, those with histological grade 1 tumors and HR+/HER2+ subtypes did not experience a marked survival improvement from surgery. This lack of signifi-

Table 4. Cox regression analysis for breast cancer with lung-only metastasis.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age, year		<0.001		<0.001
<35	Reference		Reference	
35–49	1.44 (0.77–2.69)	0.250	1.26 (0.68–2.36)	0.465
50–69	1.67 (0.91–3.04)	0.096	1.61 (0.88–2.95)	0.121
≥70	2.80 (1.53–5.11)	0.001	2.49 (1.35–4.58)	0.003
Race		0.152	NA	
White	Reference			
Black	1.16 (0.98–1.38)	0.081		
Others	0.88 (0.59–1.30)	0.505	NA	
Diagnosis year		0.467		
2010–2012	Reference			
2013–2015	0.95 (0.82–1.10)	0.467		
Grade		<0.001		<0.001
1	Reference		Reference	
2	1.05 (0.72–1.54)	0.792	1.19 (0.81–1.74)	0.378
3–4	1.68 (1.17–2.41)	0.005	1.91 (1.31–2.78)	0.001
Subtype		<0.001		<0.001
HR+/HER2–	Reference		Reference	
HR+/HER2+	0.59 (0.46–0.77)	<0.001	0.68 (0.52–0.90)	0.006
HR–/HER2+	0.78 (0.62–0.99)	0.044	0.47 (0.35–0.62)	<0.001
TNBC	2.01 (1.71–2.37)	<0.001	1.29 (1.04–1.61)	0.023
T stage		<0.001		0.001
T0–1	Reference		Reference	
T2	1.03 (0.77–1.38)	0.834	1.07 (0.80–1.44)	0.636
T3	1.24 (0.91–1.68)	0.177	1.34 (0.98–1.83)	0.064
T4	1.49 (1.13–1.97)	0.005	1.59 (120–2.11)	0.001
N stage		0.349		
N0	Reference		NA	
N1	0.98 (0.81–1.17)	0.796		
N2	1.16 (0.92–1.47)	0.200		
N3	1.09 (0.85–1.38)	0.503		
Surgery				
No	Reference		Reference	
Yes	0.59 (0.51–0.68)	<0.001	0.64 (0.54–0.75)	<0.001
Radiotherapy				
No	Reference		Reference	
Yes	0.71 (0.59–0.84)	<0.001	1.00 (0.83–1.21)	1.000
Chemotherapy				
No	Reference		Reference	
Yes	0.73 (0.63–0.85)	<0.001	0.62 (0.51–0.75)	<0.001
Hormone therapy				
No	Reference		Reference	
Yes	0.51 (0.44–0.59)	<0.001	0.45 (0.36–0.56)	<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; TNBC, triple-negative breast cancer; NA, not applicable.

cant benefit might be due to the effectiveness of current endocrine therapies and the swift advancements in anti-HER2-targeted treatments, highlighting the importance of tailoring treatment plans to specific tumor features and patient characteristics to maximize outcomes.

The creation of a prognostic nomogram that includes variables such as age, tumor grade, cancer subtype, tumor stage, and treatment approaches mark a considerable progression towards personalized care for patients. This tool, by offering tailored survival predictions, aids in making more informed choices for both patients and healthcare providers. The nomogram's accuracy, as shown by its C-index, is comparable to many well-recommended nomograms [16], and the agreement between predicted and observed survival rates, underlines its value in a clinical context.

Notably, a unique advantage of this study shows that categorizing patients into low- and high-risk groups based on nomogram scores provides a useful way to pinpoint those who might gain the most from aggressive treatments, including surgery. This categorization could prove especially helpful in guiding therapeutic decisions and optimizing the use of resources in clinical settings.

Conclusions

In conclusion, our analysis sheds light on the complex role of surgical treatment in managing breast cancer patients with lung-only metastases. While surgery presents a significant survival advantage for a substantial patient subgroup, the decision for surgery should be carefully considered, after taking into account the specific characteristics of the patient and the tumor. Future studies should focus on refining prognostic tools and investigating the possible synergies between surgical and systemic therapies, aiming to further tailor treatment to improve outcomes for breast cancer patients.

Availability of Data and Materials

The data generated and/or analyzed during the current study are available in the NCDB database (https://www.facs.org/quality-programs/cancer-programs/national-cancer-database/).

Author Contributions

WZ and XJ designed the research study. WZ, GZ, WY, XJ analyzed the data. WZ and XJ wrote the manuscript. All authors revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62713/aic.3365.

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