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Nonmass lesions on preoperative MRI in breast cancer patients: clinical implications and prognostic significance

Joon Suk Moon[2], Tae Kyung Yoo[1], Jisun Kim[1], Il Yong Chung[1], Beom Seok Ko[1], Hee Jeong Kim[1], Jong Won Lee[1], Byung Ho Son[1] & Sae Byul Lee[1]✉

This study aimed to investigate the clinical importance and prognostic value of nonmass lesions (NMLs) identified via preoperative magnetic resonance imaging (MRI) in patients with breast cancer, with an emphasis on understanding how these lesions affect treatment decisions and survival outcomes. A retrospective analysis was conducted on 6971 patients diagnosed with breast cancer who underwent surgery at Asan Medical Center, Seoul, between January 2000 and December 2021. Patients were categorized based on the presence or absence of NMLs on preoperative MRI. Various clinicopathological parameters were compared, and survival outcomes, such as overall survival (OS), distant metastasis-free survival (DMFS), regional recurrence-free survival (RFS), and local recurrence-free survival (LFS), were analyzed using Kaplan–Meier and Cox regression methods. Subgroup analyses were performed based on the type of surgery and the administration of neoadjuvant chemotherapy and adjuvant radiation therapy. Of the total cohort, 21.9% ($n = 1524$) had NMLs. The presence of NMLs was associated with a significant improvement in OS ($P = 0.017$) for the entire patient group. Multivariate analysis revealed the presence of NMLs as a favorable prognostic factor (hazard ratio 0.47, 95% confidence intervals 0.25–0.90, $P = 0.022$). Subgroup analyses demonstrated significantly improved OS, DMFS, and RFS outcomes for patients with NMLs who underwent mastectomy after neoadjuvant chemotherapy. NMLs on preoperative MRI in patients with breast cancer are associated with improved overall survival (OS) and serve as an independent prognostic factor. However, further research is needed to elucidate the underlying reasons for these outcomes.

Keywords Breast cancer, MRI, Nonmass lesion, Mastectomy, Neoadjuvant chemotherapy, Radiation therapy

Breast cancer, recognized as the most frequently diagnosed malignancy worldwide, has undergone significant advancements in both diagnostic and therapeutic modalities over the past several decades[1]. These advancements have elevated the importance of radiological imaging, especially magnetic resonance imaging (MRI), as an indispensable tool in the comprehensive assessment of breast malignancies. MRI findings offer crucial information not only for the detection but also for the characterization of various pathological features of breast tumors[2–6].

In the past, research predominantly aimed at separating benign from malignant nonmass lesions (NMLs) to increase the specificity of MRI[2,7–12]. Recent studies have focused on the pathological characterization of NMLs after core needle biopsy (CNB), the results of which indicate the incidence of cancer[2,13]. Furthermore, other studies have examined the MRI patterns of NMLs to determine their correlation with malignancy, emphasizing the key role that pathological correlation and thorough imaging provide in the precise diagnosis and treatment of breast cancer[7,11,12]. However, knowing the clinical implications of NMLs extends beyond mere detection and classification. Prognostic information inferred from NMLs can guide treatment decisions and patient counseling, ensuring a more tailored approach to breast cancer management[7,9,14,15]. Figure 1. presents representative MRI images of cases with and without NML, illustrating key radiological features to facilitate the accurate identification and understanding of NMLs by readers. Previous studies have demonstrated that

[1]Division of Breast Surgery, Department of Surgery, University of Ulsan College of Medicine, Asan Medical Center, 88, Olympic-ro 43-gil, Songpa-Gu, Seoul 05505, Republic of Korea. [2]Department of Surgery, School of Medicine, Kyungpook National University, Kyungpook National University Chilgok Hospital, Daegu, Republic of Korea. ✉email: newstar153@hanmail.net

Captions

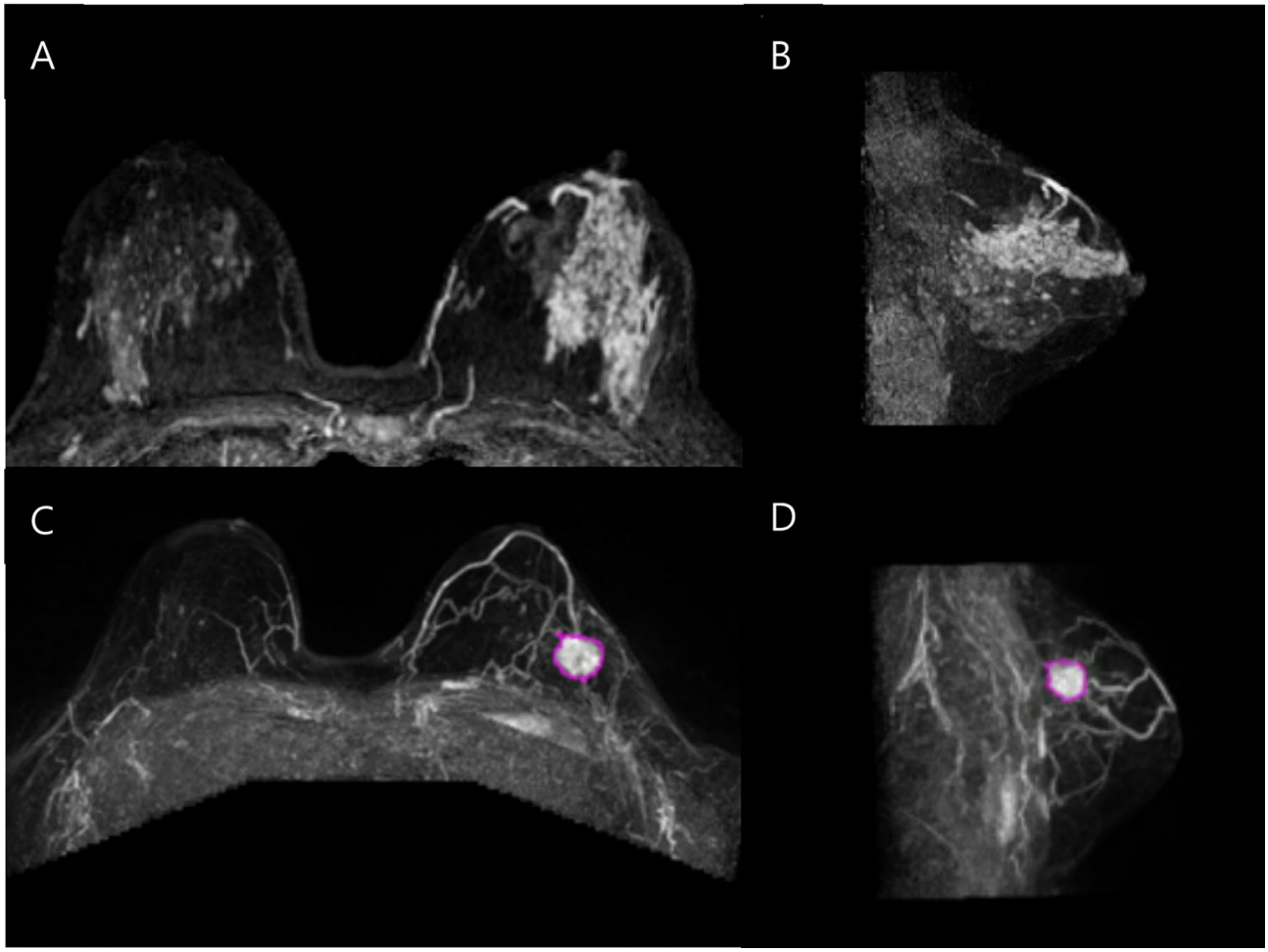

Fig. 1. Representative magnetic resonance imaging (MRI) images of breast cancer with and without nonmass Lesions (NMLs). (**A**,**B**) Preoperative MRI images of breast cancer patients with NMLs showing characteristic enhancement patterns. (**C**,**D**) Preoperative MRI images of breast cancer patients without NMLs demonstrating absence of enhancement indicative of NMLs.

patients who had NMLs detected on preoperative MRI and underwent breast conserving surgery (BCS) after neoadjuvant chemotherapy exhibited worse local-regional recurrence free survival[14]. Another study found that in cases where NMLs extended to the nipple and resolved after neoadjuvant chemotherapy, pathologic analysis confirmed that tumor invasion of the nipple was rare[15]. The above studies were limited to the group that received neoadjuvant chemotherapy, and the analysis of recurrence was also limited to local-regional recurrence.

This study aimed to determine the clinical implications of NMLs on preoperative MRI in breast cancer patients, focusing on their significance as prognostic indicators by expanding the analysis to include all patients with preoperative MRI and incorporating a survival analysis.

Materials and methods

Study population

This retrospective study was conducted on patients who underwent breast cancer surgery at Asan Medical Center, Seoul, between January 2000 and December 2021. From an initial cohort of 7660 patients with available preoperative MRI data, we included those diagnosed with breast cancer who underwent surgical treatment. These patients were diagnosed with breast cancer through ultrasound (US) or mammography (MMG) guided biopsy before preoperative initial MRI. The following patients were excluded from the study: (i) patients who underwent vacuum-assisted breast excision (VABE), (ii) those who underwent surgical excision due to suspected benign lesions prior to breast cancer surgery, and (iii) patients with stage IV breast cancer. Because MRI is highly sensitive, there are often instances of enhancement immediately after surgery or VABE due to reactive changes from hematoma or inflammation. These cases were excluded from the analysis because it was challenging to determine whether NMLs were present around the carcinoma before surgery or VABE. After applying these

criteria, our final cohort comprised 6971 patients. BCS was defined as a lumpectomy procedure, irrespective of whether an oncoplastic technique was performed. Patients were categorized as having undergone mastectomy if they underwent simple, skin-sparing, or nipple-sparing mastectomy, with or without immediate reconstruction. All procedures involving human participants were performed per the ethical standards of the institutional and/or national research committee, in line with the tenets of the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was reviewed and approved by the Institutional Review Board of Asan Medical Center (2022-0282). Given that the study was based on retrospective clinical data, the need for informed consent was waived by Asan Medical Center institutional review board, and the data were analyzed anonymously.

MRI acquisition

Bilateral MRI scans were conducted using either a 1.5T or 3.0T MR scanner, including models such as Avanto and Skyra from Siemens Medical Solutions (Erlangen, Germany) and Ingenia from Philips (Amsterdam, Netherlands). During the scan, patients lay in a prone position, and an 18-channel phased-array breast coil, specifically from Siemens Medical Solutions, was utilized. The imaging protocols included a T2-weighted short tau inversion recovery turbo spin–echo sequence. For the 1.5T scanner, the parameters used were as follows: repetition time (TR)/echo time (TE) of 1300/131 ms, matrix size of 384 × 384, field of view (FOV) of 340 × 340 mm^2, and slice thickness of 1.5 mm. For the 3.0T scanner, the parameters differed slightly, with a TR/TE of 1100/131 ms, a matrix size of 256 × 416, an FOV of 341 × 210 mm^2, and a section thickness of 1.5 mm. Furthermore, a dynamic contrast-enhanced fat-saturated axial three-dimensional T1-weighted sequence was applied. For the 1.5T scanner, the parameters were as follows: a TR/TE of 5.0/2.4 ms, a matrix size of 384 × 384, an FOV of 340 × 340 mm^2, and a section thickness of 0.9 mm. The 3.0T scanner had parameters set at a TR/TE of 5.6/2.5 ms, a matrix size of 384 × 384, an FOV of 360 × 360 mm^2, and a section thickness of 0.9 mm, comprising both unenhanced and five contrast-enhanced phases. The contrast agents used were gadoterate meglumine (UNIRAY®, Dongkook Pharmaceutical Co., Seoul, Korea), which was administered at 0.2 mL/kg using a power injector (Spectris, Medrad, Pittsburgh, PA, USA) at a flow rate of 1 mL/s immediately followed by a saline flush of 20 mL.

MRI interpretation and pathologic assessment of NMLs

In this study, the MRI interpretations were performed independently by several radiologists who specialize in breast imaging. All MRI were reviewed on a Picture Archiving and Communication System (PACS) workstation (Petavision, Asan Medical Center). NMLs on MRI were defined using the Breast Imaging Reporting and Data System (BI-RADS) lexicon. According to BI-RADS, NMLs on breast MRI is defined as an area wherein internal enhancement characteristics do not have distinct features of a mass and can be distinguished from the normal surrounding breast parenchyma. NMLs is characterized by various distributions such as focal area, linear, ductal, segmental, regional, multiple regions, and diffuse enhancement, and internal enhancement patterns including homogenous, heterogeneous, clumped, stippled, and reticular. These definitions were consistently applied to all images to enhance the consistency and reproducibility of the study. Each patient's images were evaluated independently. With in this research, tumors + NML refers to patients diagnosed with breast cancer who also have NMLs on MRI. It does not specifically refer to breast cancer confirmed by biopsy or surgery of the NMLs alone, but rather to the coexistence of breast cancer and NMLs as identified on MRI.

The final pathology of NMLs is difficult to determine precisely. During the post-operative diagnosis, the pathologist reports the extent of carcinoma but does not specify it by comparing it with the area identified as NMLs on MRI. In the case of BCS, while it is confirmed that the resection margin is negative for malignancy, it is challenging to ascertain whether all the NMLs seen on MRI have been removed. Therefore, in the final pathology, the NMLs seen on the initial MRI could range from benign to malignant.

Statistical analysis

To understand the clinical implications of NMLs in breast cancer MRI, we categorized patients into two distinct cohorts: those who manifested NMLs and those who did not. To compare the baseline characteristics between these two groups, we investigated several parameters. This included age; pathological T and N stage; overall stage; method of breast surgery; axillary staging method; histologic and nuclear grades; presence of lymphovascular invasion; hormone receptor status; and administration status of radiotherapy (RT), endocrine therapy, neoadjuvant chemotherapy, and adjuvant chemotherapy. Continuous variables, such as age, were statistically analyzed using the independent sample *t* test. Categorical variables were examined for significant differences between the groups using the chi-square test. Overall survival (OS) was calculated by measuring the period from diagnosis to death, regardless of the cause. Distant metastasis-free survival (DMFS) was defined as the duration from the initial operation to the time of the first occurrence of cancer spreading to distant organs or tissues or to the date of the last follow-up in the absence of distant metastasis. Regional recurrence-free survival (RFS) was defined as the period subsequent to initial breast cancer operation during which no cancer reappeared in the regional lymph nodes. LFS was defined as the duration of time from the initial operation on the breast cancer site during which no cancer was found in the breast tissue or chest wall. We utilized the Kaplan–Meier method to construct survival curves. Differences in survival rates between the two cohorts were discerned using the log-rank test. To isolate factors that potentially influenced OS and DMFS while adjusting for potential confounders, we employed the Cox proportional hazards model.

All our statistical evaluations were two-sided, and we set our threshold for statistical significance at $p < 0.05$. The analyses were carried out using SPSS statistics version 21 (IBM Corp., New York, USA), and to bolster the rigor and precision of our statistical findings, both the primary investigator and a dedicated biostatistician reviewed the results.

Results

Patient demographics and clinicopathological characteristics

A cohort of 6,971 patients with breast cancer was analyzed, and 50.7% ($n=3537$) of the patients were < 50 years old (Table 1). Regarding TNM staging, 49.6% of patients ($n=3461$) were classified as T1 stage, and 70.7% ($n=4929$) were classified as N0 stage. Furthermore, 47.5% of patients ($n=3313$) were classified as having pathologic Stage 1 disease, and 64.3% ($n=4483$) underwent BCS. A predominant proportion of patients were found to have histologic or nuclear grade 2 (63.1%, $n=4400$ and 68.7%, $n=4787$, respectively). Lymphovascular invasion was absent in 78.6% ($n=5481$) of the patients, hormone receptor status was 70.7% ($n=4926$) of the patients were estrogen receptor (ER) positive, and 56.3% ($n=3924$) were progesterone receptor (PR) positive. Most patients received RT (77.1%, $n=5376$) and endocrine therapy (70.8%, $n=4938$). Neoadjuvant chemotherapy was administered to 34.9% ($n=2436$) of the patients, while 57.0% ($n=3971$) underwent adjuvant chemotherapy.

Comparison between patients with and without NMLs

Among the total patients, 1524 (21.9%) were identified to have NMLs (NML+), and 5447 (78.1%) did not have NMLs (NML−) (Table 1). No significant differences were found between the two groups in terms of sex ($P=0.592$) or age ($P=0.393$). However, significant disparities were observed in the pathological T stage ($P<0.001$), with a notably greater percentage of patients with T1mi in the NML + group (14.2%) than in the NML− group (3.9%). Moreover, the proportion of patients with pathological T2-weighted images was greater in the NML (−) group than in the NML (+) group. Regarding pathologic N stage, a significantly greater percentage of patients with N0 disease were found in the NML (+) group (73.2%) than in the NML (−) group (70.0%) ($P=0.033$). The type of breast surgery also differed significantly between the groups ($P<0.001$), with an especially greater percentage of patients undergoing mastectomy in the NML (+) group (65.2%) than in the NML (−) group (27.4%). Regarding axillary staging, a greater proportion of patients in the NML (+) group did not undergo staging ($P=0.006$). Histologic grade 3 ($P=0.003$) and nuclear grade 3 ($P=0.005$) were more prevalent in the NML (+) group, whereas lymphovascular invasion was more common in the NML (−) group ($P<0.001$). A greater percentage of patients in the NML (−) group were positive for estrogen and progesterone receptors ($P=0.004$ and 0.001, respectively). Human epidermal growth factor receptor 2 (HER2) positivity was more common in the NML (+) group ($P<0.001$).

Survival analysis

The differences in survival outcomes between patients with and without NMLs (−) were evaluated and are illustrated in Fig. 2. Compared to those in the NML (−) group, the OS in the NML (+) group significantly improved ($P=0.017$). Specifically, the 3-year survival rate was 98.2% in the NML (−) group and 99.2% in the NML (+) group. Although Kaplan–Meier curves for DMFS, RFS, and LFS were constructed, the present study did not find any significant differences between the NML (+) and NML (−) groups.

Multivariate Cox regression analysis for overall survival

Multivariate Cox regression analysis was performed to evaluate the independent prognostic impact of various clinicopathological variables on OS in patients with breast cancer. The presence of NMLs was identified as a strong favorable prognostic factor related to improved OS. Specifically, compared with patients without NML, patients with NML exhibited a hazard ratio (HR) of 0.47 (95% confidence interval (CI) 0.25–0.90, $P=0.022$) (Table 2). These findings corroborate the Kaplan–Meier survival analysis, which also demonstrated a greater survival outcome in the NML (+) group.

Subgroup analysis: survival outcomes based on surgery type

A subgroup analysis of patients who had undergone different types of breast surgery was carried out to elucidate the effect of NMLs on survival outcomes in various clinical circumstances. Among patients who underwent total mastectomy, the NML (+) group had a better prognosis than the NML (−) group did. The 3-year OS rates were compared between the NML (−) and NML (+) groups, revealing a 96.3% survival rate in the NML (−) group versus a 98.8% survival rate in the NML (+) group ($P=0.001$) (Fig. 3). Similarly, the 3-year DMFS rate was 91.4% in the NML (−) group and 96.2% in the NML (+) group ($P<0.001$). RFS also differed significantly between the two groups, with 95.3% 3-year RFS for the NML (−) group compared to 98.2% for the NML (+) group ($P=0.001$). However, the LFS rates at 3 years were similar between the groups, with 96.6% for NML (−) patients and 97.7% for NML patients ($P=0.166$). In contrast, the outcome of a subgroup analysis limited to individuals who underwent BCS revealed no significant differences in OS, DMFS, RFS, or LFS based on the presence of NMLs (Fig. 3).

Subgroup analysis: survival outcomes of patients who underwent mastectomy following neoadjuvant chemotherapy

In the cohort that received neoadjuvant chemotherapy followed by surgery, the presence of NMLs was associated with significantly improved survival outcomes (Fig. 4). The 3-year OS rate was notably greater in the NML (+) group (98.1%) than in the NML (−) group (95.7%) ($P=0.039$). Similarly, the 3-year RFS was more favorable in the NML (+) group (98.1%) than in the NML (−) group (94.8%) ($P=0.004$). However, DMFS and LFS were not significantly different between the two groups. Conversely, in the upfront surgery group, the survival outcomes did not exhibit any substantial variation with respect to NML status. Consequently, the analysis was further refined by subdividing the patients into subgroups to specifically evaluate patients who underwent mastectomy following neoadjuvant chemotherapy. The 3-year OS rate was notably greater in the NML (+) group (97.5%) than in the NML (−) group (93.7%) ($P=0.013$) (Fig. 5). Similarly, the 3-year DMFS was more favorable in the NML (+) group (92.1%) than in the NML (−) group (86.5%) ($P=0.008$). Moreover, the 3-year RFS was

Parameter	Total (%)	NML (−) *n* = 5447 *n* (%)	NML (+) *n* = 1524 *n* (%)	*P* value
Age				0.393
≥ 50 years	3434 (49.3)	2698 (49.5)	736 (48.3)	
< 50 years	3537 (50.7)	2749 (50.5)	788 (51.7)	
Pathologic T stage				< 0.001
T0	669 (9.6)	512 (9.4)	157 (10.3)	
T1	3461 (49.6)	2787 (51.2)	674 (44.2)	
T2	1866 (26.8)	1553 (28.5)	313 (20.5)	
T3	281 (4.0)	194 (3.6)	87 (5.7)	
T4	28 (0.4)	22 (0.4)	6 (0.4)	
T1mi	429 (6.2)	213 (3.9)	216 (14.2)	
Tis	237 (3.4)	166 (3.0)	71 (4.7)	
Pathologic N stage				0.033
N0	4929 (70.7)	3814 (70.0)	1115 (73.2)	
N1	1522 (21.8)	1226 (22.5)	296 (19.4)	
N2	372 (5.3)	297 (5.5)	75 (4.9)	
N3	148 (2.1)	110 (2.0)	38 (2.5)	
Pathologic stage				< 0.001
Stage 0	222 (3.2)	155 (2.8)	67 (4.4)	
Stage 1	3313 (47.5)	2534 (46.5)	779 (51.1)	
Stage 2	2175 (31.2)	1800 (33.0)	375 (24.6)	
Stage 3	642 (9.2)	485 (8.9)	157 (10.3)	
Pathologic CR	619 (8.9)	473 (8.7)	146 (9.6)	
Breast surgery				< 0.001
Mastectomy	2488 (35.7)	1494 (27.4)	994 (65.2)	
Breast conserving surgery	4483 (64.3)	3953 (72.6)	530 (34.8)	
Axillary staging				0.006
No operation	96 (1.4)	88 (1.6)	8 (0.5)	
SNB	5159 (74.0)	4018 (73.8)	1141 (74.9)	
SNB + ALND	1479 (21.2)	1150 (21.1)	329 (21.6)	
ALND	237 (3.4)	191 (3.5)	46 (3.0)	
Histologic grade				0.003
1	272 (3.9)	230 (4.2)	42 (2.8)	
2	4400 (63.1)	3468 (63.7)	932 (61.2)	
3	2029 (29.1)	1538 (28.2)	491 (32.2)	
Unknown	270 (3.9)	211 (3.9)	59 (3.9)	
Nuclear grade				0.005
1	87 (1.2)	69 (1.3)	18 (1.2)	
2	4787 (68.7)	3791 (69.6)	996 (65.4)	
3	2097 (30.1)	1587 (29.1)	510 (33.5)	
LVI				< 0.001
Absent	5481 (78.6)	4232 (77.7)	1249 (82.0)	
Present	1490 (21.4)	1215 (22.3)	275 (18.0)	
ER				0.004
Negative	2045 (29.3)	1553 (28.5)	492 (32.3)	
Positive	4926 (70.7)	3894 (71.5)	1032 (67.7)	
PR				0.001
Negative	3047 (43.7)	2323 (42.6)	724 (47.5)	
Positive	3924 (56.3)	3124 (57.4)	800 (52.5)	
HER2 status				< 0.001
Negative	5162 (74.0)	4219 (77.5)	943 (61.9)	
Positive	1535 (22.0)	1017 (18.7)	518 (34.0)	
Unknown	274 (3.9)	211 (3.9)	63 (4.1)	
Ki67 (%)				0.842
20 ≥	3376 (48.4)	2628 (48.2)	748 (49.1)	
Continued				

Parameter	Total (%)	NML (−) *n* = 5447 *n* (%)	NML (+) *n* = 1524 *n* (%)	*P* value
20 <	3295 (47.3)	2583 (47.4)	712 (46.7)	
Unknown	300 (4.3)	236 (4.3)	64 (4.2)	
Radiation therapy				< 0.001
No	1595 (22.9)	901 (16.5)	694 (45.5)	
Yes	5376 (77.1)	4546 (83.5)	830 (54.5)	
Endocrine therapy				0.001
No	2033 (29.2)	1537 (28.2)	496 (32.5)	
Yes	4938 (70.8)	3910 (71.8)	1028 (67.5)	
Neoadjuvant chemotherapy				0.646
No	4535 (65.1)	3536 (64.9)	999 (65.6)	
Yes	2436 (34.9)	1911 (35.1)	525 (34.4)	
Adjuvant chemotherapy				< 0.001
No	3000 (43.0)	2283 (41.9)	717 (47.0)	
Yes	3971 (57.0)	3164 (58.1)	807 (53.0)	

Table 1. Comparison of baseline characteristics between patients with and without nonmass lesions. All the data are expressed as numbers (percentages). NML, nonmass lesion; LVI, lymphovascular invasion; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

significantly greater in the NML (+) group (97.8%) than in the NML (−) group (92.9%) ($P = 0.002$). However, LFS was not significantly different between the two groups ($P = 0.137$).

Subgroup analysis: proportion of NML (+) patients receiving adjuvant RT in the neoadjuvant chemotherapy and upfront surgery groups

Table 3 presents a detailed stratification of the patients, focusing on the proportion receiving adjuvant RT, considering the combined tumor and NML size (> 5 cm vs. ≤5 cm) as a criterion for postmastectomy radiation therapy (PMRT). Patients were further categorized by the administration of neoadjuvant chemotherapy versus upfront surgery. Among those who received neoadjuvant chemotherapy, 75.8% of patients who had tumors + NML > 5 cm, which is the criterion for PMRT, underwent RT. In contrast, in the upfront surgery group, only 27.6% of patients with tumors + NML > 5 cm underwent RT. Similar results were found when examining patients who underwent mastectomy. In the group that underwent mastectomy following neoadjuvant chemotherapy, 71.1% of patients with tumors + NML > 5 cm underwent RT, but in the group that underwent upfront mastectomy, only 12.3% of patients with tumors + NML > 5 cm underwent RT.

Discussion

Herein, we elucidated the clinical implications of NMLs identified via preoperative MRI in patients with breast cancer, with a focus on their prognostic potential. Our study revealed a notable association between the presence of NMLs and OS enhancement, which was substantiated through multivariate Cox regression analyses (HR 0.45, 95% CI 0.24–0.85, $P = 0.013$). Similarly, the NML was identified as a significant factor according to Kaplan–Meier survival and multivariate Cox regression analyses, underscoring its potential role as an independent prognostic factor in breast cancer. The subsequent subgroup analysis stratified based on breast surgery (mastectomy vs. BCS) and neoadjuvant chemotherapy (neoadjuvant vs. upfront surgery) further reinforced this association. Notably, when patients were segregated into groups based on the type of surgery (mastectomy or BCS) and subsequently categorized based on the presence of NMLs, a distinct pattern emerged in survival outcomes. In contrast to those in the mastectomy cohort, in which the NML (+) cohort demonstrated significantly superior survival outcomes to the NML (-) cohort, the BCS group, which may retain NMLs, did not show a significant difference in survival outcomes depending on NML status.

An additional analysis focused on the administration of neoadjuvant chemotherapy was also performed to determine the underlying factors that resulted in the significant differences observed within the mastectomy group. This subgroup analysis, categorized based on whether neoadjuvant chemotherapy was administered, yielded noteworthy results. Specifically, within the cohort that underwent neoadjuvant chemotherapy followed by mastectomy, the NML (+) subset demonstrated significantly superior outcomes in terms of OS, DMFS, and RFS. In the mastectomy group, the improved prognosis associated with NMLs may be attributable to several factors. First, it is possible that patients with NMLs on preoperative MRI were more likely to receive PMRT, as clinical staging based on the combined tumor and NML size may have classified them as T3. This might have contributed to enhanced local-regional control. Additionally, the presence of NMLs could reflect specific tumor biology or microenvironmental characteristics that are more responsive to systemic therapies such as neoadjuvant chemotherapy. While further investigation is required, these factors might partly explain the improved outcomes observed in this cohort. Consequently, the presence/absence of NMLs emerges as a crucial factor, especially in the context of patients who are strategized for surgery after neoadjuvant chemotherapy, in view of the potential

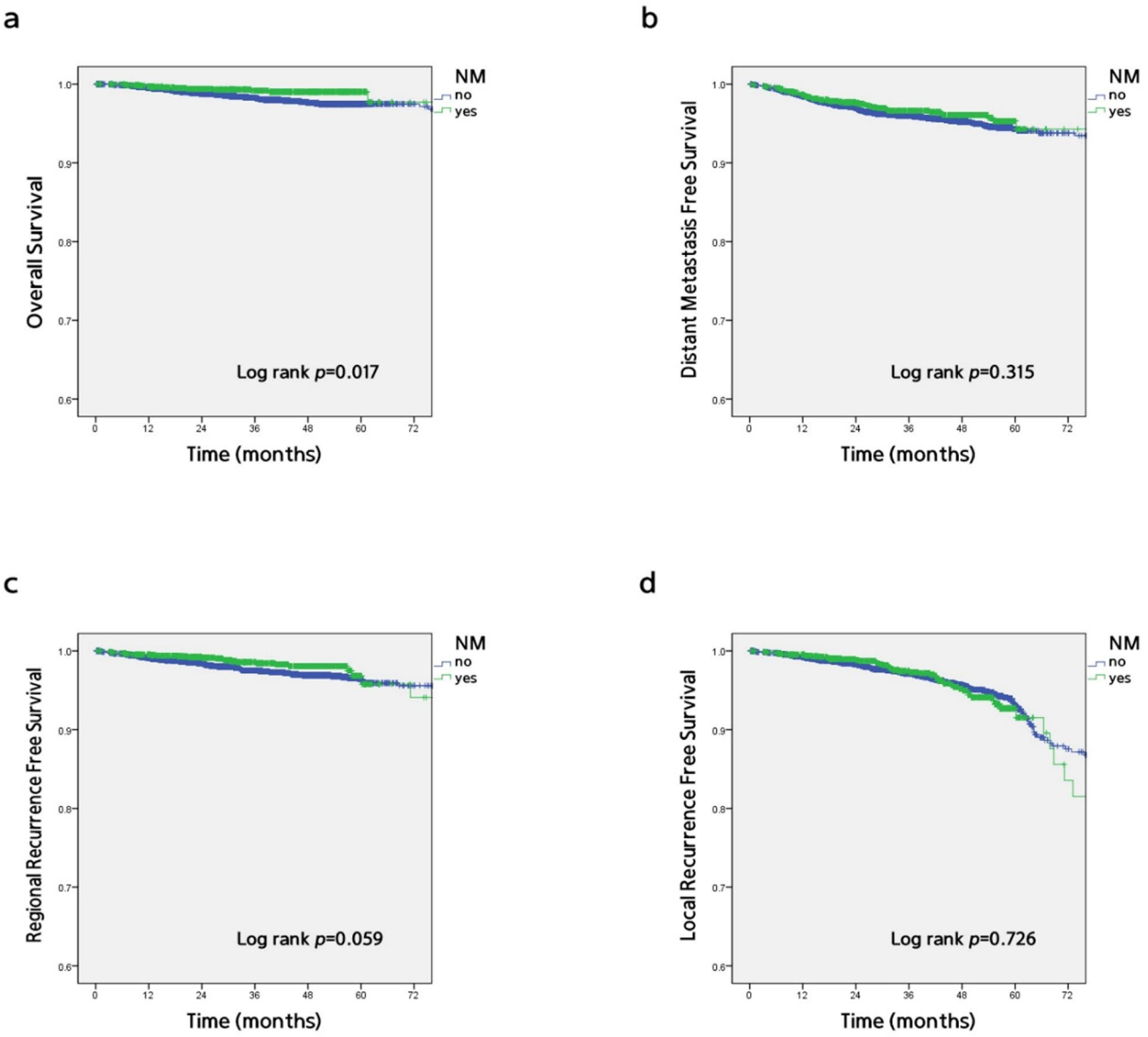

Fig. 2. Kaplan–Meier curves for the entire patient cohort comparing (**a**) overall survival (OS), (**b**) distant metastasis-free survival (DMFS), (**c**) regional recurrence-free survival (RFS), and (**d**) local recurrence-free survival (LFS) based on the presence or absence of nonmass lesions (NMLs).

causes that might explain the observed disparities in outcomes between patients who underwent upfront surgery with mastectomy and those who received neoadjuvant chemotherapy followed by mastectomy. One of the critical factors in deciding on neoadjuvant chemotherapy and subsequent adjuvant therapy is the clinical T stage, which is determined using ultrasound, mammography, and MRI. This process includes measuring the longest dimension of the malignant mass, including the surrounding NMLs, for accurate clinical T staging, indicating a potential impact of NMLs on PMRT. Based on previous researches, PMRT is administered in patients with clinical stage T3 (> 5 cm) or above[16–25]. According to these criteria, among the mastectomy patients, 71.1% of the patients who received PMRT with a tumor + NML > 5 cm on initial MR imaging were in the group that underwent neoadjuvant chemotherapy, and 12.3% were in the group that underwent upfront surgery. Therefore, in the upfront surgery group, although the initial MRI showed a tumor + NML > 5 cm, the actual tumor size was less than 5 cm upon mastectomy, resulting in a decreased proportion of patients receiving PMRT. Both groups received treatment according to the NCCN guidelines. However, as previously described, in patients receiving neoadjuvant chemotherapy, those with NMLs may have been staged as clinical T3 instead of what would have been pathologic T2 if they had undergone upfront surgery. Therefore, it can be inferred that the patients who were deemed suitable for receiving PMRT owing to an initial MRI finding of tumor + NML > 5 cm but subsequently receiving neoadjuvant chemotherapy did include those whose actual tumor size was less than 5 cm. This difference in clinical staging could potentially explain the improved overall survival in patients with NMLs due to more active treatment.

Variables	OS	
	HR (95% CI)	*P* value
NML (no vs. yes)	0.47 (0.25–0.90)	0.022
Age	1.02 (1.00–1.03)	0.107
Breast surgery (mastectomy vs. BCS)	0.71 (0.42–1.21)	0.205
Pathologic tumor size	1.11 (1.06–1.24)	0.001
Pathologic node metastasis	1.05 (1.02–1.07)	0.050
Nuclear grade (1,2 vs. 3)	1.13 (0.72–1.78)	0.606
Lymphovascular invasion (neg. vs. pos.)	1.66 (1.03–2.68)	0.037
Estrogen receptor (neg. vs. pos.)	0.46 (0.25–0.82)	0.009
Progesterone receptor (neg. vs. pos.)	0.27 (0.13–0.56)	< 0.001
HER2 status (neg. vs. pos.)	0.27 (0.13–0.50)	< 0.001
KI-67 (20 < vs. 20≥)	1.96 (1.15–3.33)	0.013
Radiation therapy (no vs. yes)	0.45 (0.28–0.71)	0.001
Neoadjuvant chemotherapy (no vs. yes)	3.94 (2.45–6.36)	< 0.001
Adjuvant chemotherapy (no vs. yes)	0.60 (0.27–1.32)	0.207
Endocrine therapy (no vs. yes)	0.67 (0.28–1.57)	0.352

Table 2. Multivariate Cox regression analysis for overall survival in patients with breast cancer. All the data are expressed as numbers (percentages). NML, nonmass lesion; HER2, human epidermal growth factor receptor 2; BCS, breast conserving surgery; OS, overall survival; HR, hazard ratio; CI, confidence interval.

A previous retrospective study examined 443 CNBs for NMLs on breast MRI in 411 patients[2]; most biopsies (68.0%) were found to be benign, while 11.5 and 20.5% were atypical and malignant, respectively. Similar results were observed in another study in which the majority (61.5%) of the "worst" lesions identified in NMLs were benign alterations or lesions[13]. However, 22.3% (29 out of 130 patients) were diagnosed with ductal carcinoma in situ (DCIS) or invasive carcinoma, with invasive cancer being the primary lesion in only 5.4% (7 out of 130 patients). Conversely, some studies have reported a higher incidence of malignancy in biopsy results of NMLs. In a previous study by Jansen et al.[5], the majority of NMLs (81.2%, 212 of 261) correlated with malignant lesions. Additionally, in a study by Bartella et al., among the 94 patients exhibiting NMLs, histological analysis revealed invasive ductal carcinoma in 42 patients (44.7%) and DCIS in 15 patients (16.0%)[26]. Therefore, MRI reveals that NMLs are associated with a wide range of histological outcomes, from benign lesions to malignant lesions, as determined by a combination of previous and current findings.

Essentially, this further supports and implies that individuals who would have been classified as T2 instead of T3 if they had undergone upfront surgery are included in the cohort that received PMRT. This discrepancy is believed to explain why various survival indicators were more favorable in the group with NMLs. It can be concluded that PMRT may be beneficial for some high-risk patients even in clinical stage T2 patients. Previously, PMRT was primarily recommended for patients with N2 or above[27]. However, through extensive research and clinical studies, its application has been extended to include N1 high-risk patients[21]. Moreover, another study has shown that in some patients diagnosed with pathologic T1-2N0 disease following upfront mastectomy, particularly those in the high-risk group, PMRT has been effective at reducing locoregional recurrence, distant recurrence, and breast cancer mortality[28]. This increase in treatment guidelines reflects a growing understanding of the benefits of PMRT across different stages and risk profiles. The potential impact of NMLs on treatment planning, especially in the context of PMRT, necessitates a re-evaluation of the existing criteria and guidelines to ensure optimal therapeutic outcomes for patients with breast cancer. Future studies should focus on identifying the molecular and biological characteristics of NMLs, which might provide a way to develop more individualized and precision-based therapeutic approaches for the management of breast cancer.

This study has several limitations. First, this study was retrospective in nature and conducted at a single institution. Inevitably, it incorporated possible biases, making it less reliable than a prospective design. Future research, ideally multicenter and prospective in design, will be necessary to further validate these conclusions. Second, although our data indicate an association between the presence of NMLs and favorable survival outcomes in patients who underwent neoadjuvant chemotherapy followed by mastectomy, we were unable to provide statistical evidence that PMRT had a direct impact on these results. Third, because of the retrospective nature of the study, it was not feasible to include a suitable control group to demonstrate that PMRT improved survival outcomes for patients who, although clinically classified as T3, were at high risk (T2) with neoadjuvant chemotherapy and mastectomy. Fourth, as the study focused on patients who received neoadjuvant chemotherapy, we could not predict the pathological stage when upfront surgery was initially performed. Fifth, we could not conclusively confirm the differential effect of ipsilateral NMLs based on PMRT administration, although we did identify a trend in this direction. This limitation highlights the need for caution when interpreting our results and emphasizes the significance of additional prospective research to support our findings. Sixth, while different types and grades of NMLs could theoretically affect the histologic results, if biopsies were conducted solely on NMLs, this study did not differentiate between them. Instead, we focused on the overall prognosis in patients diagnosed with breast cancer accompanied by NMLs on MRI, regardless of these variations. Finally, during the

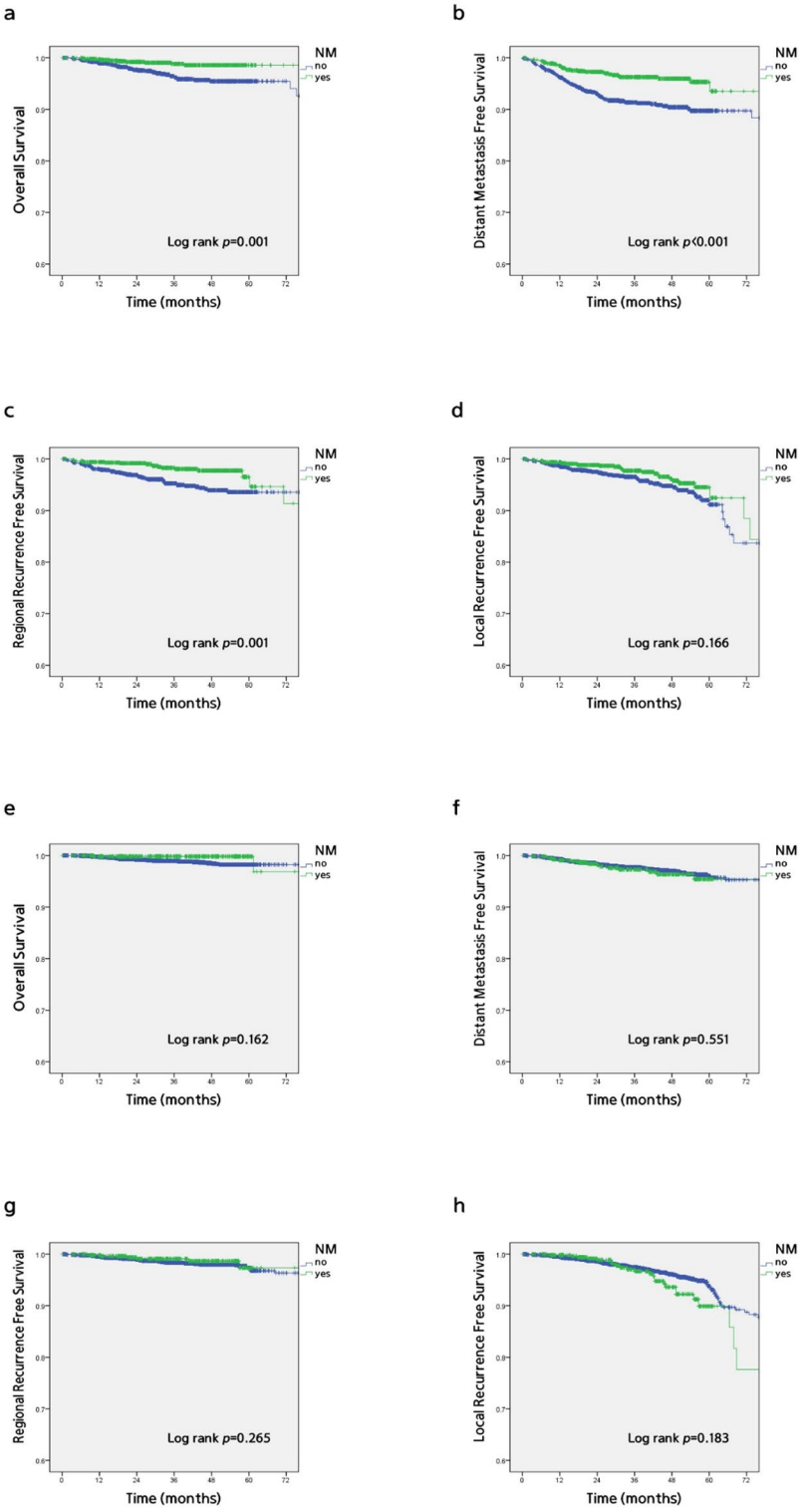

Fig. 3. Kaplan–Meier curves for the mastectomy and BCS groups. (**a**) OS, (**b**) distant metastasis-free survival (DMFS), (**c**) regional recurrence-free survival (RFS), and (**d**) local recurrence-free survival (LFS) for the mastectomy group; (**e**) OS, (**f**) DMFS, (**g**) RFS, and (**h**) LFS for the BCS group; based on the presence or absence of nonmass lesions (NMLs).

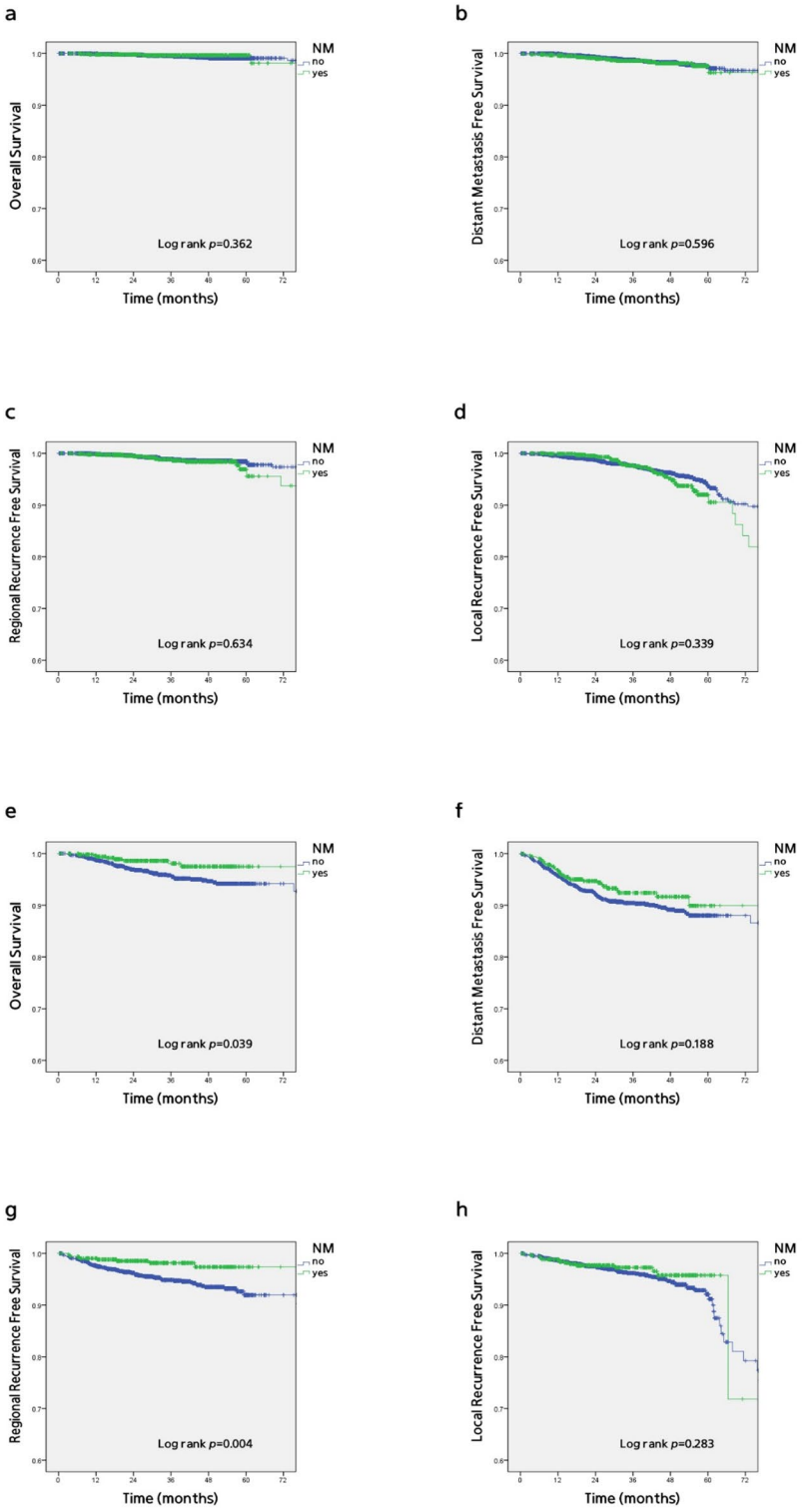

Fig. 4. Kaplan–Meier curves for the upfront surgery and neoadjuvant chemotherapy groups. (**a**) OS, (**b**) distant metastasis-free survival (DMFS), (**c**) regional recurrence-free survival (RFS), and (**d**) local recurrence-free survival (LFS) for the upfront surgery group; (**e**) OS, (**f**) DMFS, (**g**) RFS, and (**h**) LFS for the neoadjuvant chemotherapy group; based on the presence or absence of nonmass lesions (NMLs).

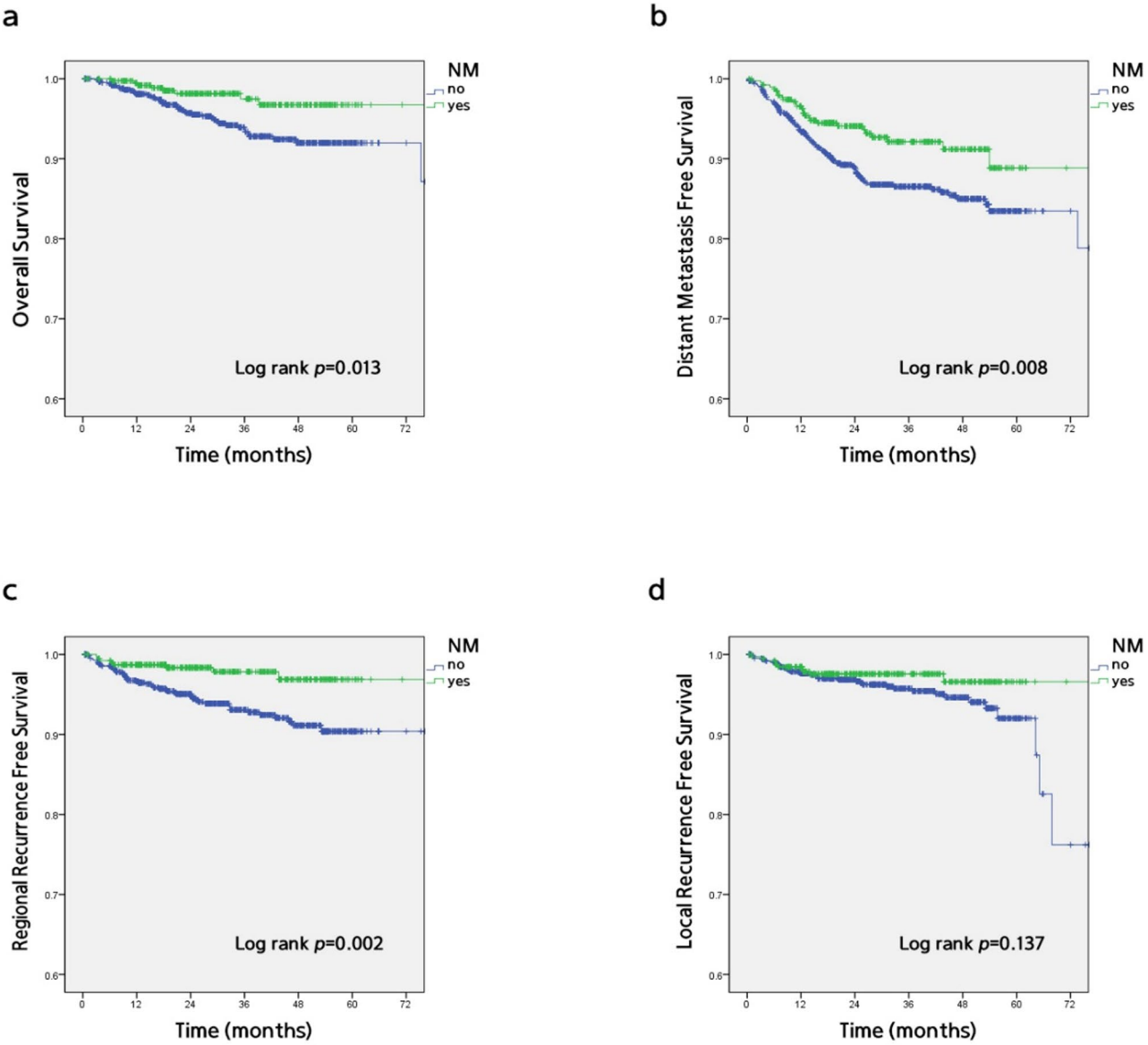

Fig. 5. Kaplan–Meier curves for patients who underwent mastectomy following neoadjuvant chemotherapy. (**a**) Overall survival (OS), (**b**) distant metastasis-free survival (DMFS), (**c**) regional recurrence-free survival (RFS), and (**d**) local recurrence-free survival (LFS) based on the presence or absence of nonmass lesions (NMLs).

		Neoadjuvant Chemotherapy				Upfront Surgery			
		≤5 cm	>5 cm	Total	*P* value	≤5 cm	>5 cm	Total	*P* value
All breast surgery					0.099				<0.001
Adjuvant RT	Yes	131 (69.3%)	276 (75.8%)	407 (73.6%)		369 (61.4%)	128 (27.6%)	497 (46.7%)	
	No	58 (30.7%)	88 (24.2%)	146 (26.4%)		232 (38.6%)	335 (72.4%)	567 (53.3%)	
Mastectomy					<0.001				0.577
Adjuvant RT	Yes	49 (45.8%)	214 (71.1%)	263 (64.5%)		26 (10.8%)	46 (12.3%)	72 (11.7%)	
	No	58 (54.2%)	87 (28.9%)	145 (35.5%)		215 (89.2%)	329 (87.7%)	544 (88.3%)	

Table 3. Proportion of nonmass lesion (NML) (+) patients receiving adjuvant radiation therapy in the neoadjuvant chemotherapy and upfront surgery groups stratified by combined tumor and NML size (>5 cm vs. ≤5 cm) as a criterion for postmastectomy radiation therapy. All data are expressed as numbers (percentages). NML, nonmass lesion; RT, radiation therapy.

analysis, different neoadjuvant therapies were not categorized independently, making it difficult to determine the respective effects of various neoadjuvant therapies.

This study is the first to investigate NMLs as prognostic factors. Previous research on NMLs has focused primarily on analyzing the enhancement patterns observed via MRI to determine their correlation with cancer or on assessing the proportion of malignant lesions in tissue samples taken from NMLs.

Conclusion

Our research offers an advanced perspective on the prognostic value of NMLs in breast cancer, especially when they are found on preoperative MRI. The results demonstrated a direct relationship between improved OS and NML presence, establishing the NML as a possible independent prognostic factor. Furthermore, the findings of the present study suggested that PMRT, which is traditionally recommended for patients with stage T3 or higher breast cancer, may also potentially benefit certain high-risk patients with stage T2 disease. This indicates a possible need to re-evaluate the current treatment guidelines.

Data availability

The datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

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References

1. Giaquinto, A. N. et al. Breast cancer statistics 2024. *CA Cancer J. Clin.* **74** (6), 477–495 (2024).
2. Bartels, A. K., Fadare, O., Hasteh, F. & Zare, S. Y. Nonmass enhancement lesions of the breast on core needle biopsy: outcomes, frequency of malignancy, and pathologic findings. *Hum. Pathol.* **111**, 92–97 (2021).
3. Liberman, L. et al. Breast lesions detected on MR imaging: features and positive predictive value. *AJR Am. J. Roentgenol.* **179** (1), 171–178 (2002).
4. Jiang, L. et al. Is there different correlation with prognostic factors between non-mass and mass type invasive ductal breast cancers? *Eur. J. Radiol.* **82** (9), 1404–1409 (2013).
5. Jansen, S. A. et al. The diverse pathology and kinetics of mass, nonmass, and focus enhancement on MR imaging of the breast. *J. Magn. Reson. Imaging.* **33** (6), 1382–1389 (2011).
6. Goto, M. et al. The role of breast MR imaging in pre-operative determination of invasive disease for ductal carcinoma in situ diagnosed by needle biopsy. *Eur. Radiol.* **22** (6), 1255–1264 (2012).
7. Jirarayapong, J., Chikarmane, S. A., Portnow, L. H., Farah, S. & Gombos, E. C. Discriminative factors of malignancy of ipsilateral nonmass enhancement in women with newly diagnosed breast Cancer on initial staging breast MRI. *J. Magn. Reson. Imaging* (2023).
8. Machida, Y. et al. Descriptors of malignant Non-mass enhancement of breast MRI: their correlation to the presence of invasion. *Acad. Radiol.* **23** (6), 687–695 (2016).
9. Jun, S. et al. Significance of non-mass enhancement in the subareolar region on preoperative breast magnetic resonance imaging for Nipple-Sparing mastectomy. *Clin. Breast Cancer*. **20** (4), e458–e68 (2020).
10. Yoon, G. Y. et al. The role of MRI and clinicopathologic features in predicting the invasive component of biopsy-confirmed ductal carcinoma in situ. *BMC Med. Imaging*. **20** (1), 95 (2020).
11. Aydin, H. The MRI characteristics of non-mass enhancement lesions of the breast: associations with malignancy. *Br. J. Radiol.* **92** (1096), 20180464 (2019).
12. Liu, G., Li, Y., Chen, S. L. & Chen, Q. Non-mass enhancement breast lesions: MRI findings and associations with malignancy. *Ann. Transl. Med.* **10** (6), 357 (2022).
13. Torous, V. F. et al. Histopathologic correlates of nonmass enhancement detected by breast magnetic resonance imaging. *Arch. Pathol. Lab. Med.* **145** (10), 1264–1269 (2021).
14. Shin, S. U. et al. Neoadjuvant chemotherapy and surgery for breast cancer: preoperative MRI features associated with local recurrence. *Radiology* **289** (1), 30–38 (2018).
15. Bae, S. J. et al. Resolution of nonmass enhancement extension to the nipple at breast MRI after neoadjuvant chemotherapy: pathologic response and feasibility for nipple-sparing mastectomy. *Radiology*. **307** (2), e221777 (2023).
16. Mamounas, E. P. et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National surgical adjuvant breast and bowel project B-18 and B-27. *J. Clin. Oncol.* **30** (32), 3960–3966 (2012).
17. Taghian, A. G. et al. Low locoregional recurrence rate among node-negative breast cancer patients with tumors 5 cm or larger treated by mastectomy, with or without adjuvant systemic therapy and without radiotherapy: results from five National surgical adjuvant breast and bowel project randomized clinical trials. *J. Clin. Oncol.* **24** (24), 3927–3932 (2006).
18. Overgaard, M. et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish breast Cancer cooperative group 82b trial. *N. Engl. J. Med.* **337** (14), 949–955 (1997).
19. Ragaz, J. et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. *J. Natl. Cancer Inst.* **97** (2), 116–126 (2005).
20. Poortmans, P. M. et al. Internal mammary and medial supraclavicular irradiation in breast Cancer. *N Engl. J. Med.* **373** (4), 317–327 (2015).
21. McGale, P. et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* **383** (9935), 2127–2135 (2014).
22. Clarke, M. et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* **366** (9503), 2087–2106 (2005).
23. Recht, A. et al. Postmastectomy radiotherapy: an American society of clinical oncology, American society for radiation oncology, and society of surgical oncology focused guideline update. *Pract. Radiat. Oncol.* **6** (6), e219–e34 (2016).
24. Mukesh, M. B. et al. The Cambridge post-mastectomy radiotherapy (C-PMRT) index: a practical tool for patient selection. *Radiother. Oncol.* **110** (3), 461–466 (2014).
25. Overgaard, M. et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant Tamoxifen: Danish breast Cancer cooperative group DBCG 82c randomised trial. *Lancet* **353** (9165), 1641–1648 (1999).
26. Ballesio, L. et al. Non mass-like enhancement categories detected by breast MRI and histological findings. *Eur. Rev. Med. Pharmacol. Sci.* **18** (6), 910–917 (2014).
27. Goldhirsch, A. et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen international expert consensus on the primary therapy of early breast Cancer 2013. *Ann. Oncol.* **24** (9), 2206–2223 (2013).

28. Luo, C. et al. The effect of postmastectomy radiation therapy on high-risk patients with T1-2N0 breast cancer. *Breast*. **60**, 1–5 (2021).

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Author contributions
T.K.Y. and J.K. prepared figures. I.Y.C. and B.S.K. prepared tables. H.J.K., J.W.L. and B.H.S. interpreted the data. S.B.L. contributed to the conception and reviewed the manuscript. J.S.M. wrote the main manuscript text.

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Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent
Informed consent was waived because the study was based on retrospective clinical data.

Additional information
Correspondence and requests for materials should be addressed to S.B.L.