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Radiotherapy-associated alterations in granulomatous mastitis: Clinicopathological and immunohistochemical predictors of recurrence and differential diagnosis from breast tumors

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► ***Original article***

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ABSTRACT

Background: Granulomatous mastitis (GM) often recurs, and its clinical and pathological overlap with breast malignancies is especially problematic in patients with prior radiotherapy. To identify clinical, pathological, and immunohistochemical predictors of GM recurrence and to evaluate diagnostic challenges in the context of post-radiotherapy alterations. ***Materials and Methods:*** A retrospective cohort of 206 GM patients was analyzed (58 with recurrence, 148 without). Baseline clinical factors, pathological features, and immunohistochemical markers were compared. An XGBoost algorithm was applied to construct and validate a recurrence risk model. For patients with a history of breast radiotherapy, additional subgroup analysis was performed, incorporating imaging and pathology review to differentiate GM recurrence from tumor relapse. ***Results:*** Recurrence was associated with younger age (<35 years, 41.4% vs. 18.9%, P<0.001), higher prolactin levels (32.5±8.7 vs. 24.8±6.9 ng/mL, P<0.001), and higher BMI (26.4±3.8 vs. 24.1±3.2, P=0.007). Pathological indicators included multinucleated giant cells (31.0% vs. 12.2%, P<0.001), diffuse plasma cell infiltration (82.8% vs. 62.2%, P=0.003), and elevated Ki-67 (65.5% vs. 32.4%, P<0.001). The model achieved strong predictive performance (AUC = 0.89 training, 0.85 validation, 0.83 external). In post-radiotherapy patients, fibrotic distortion and atypical immune marker expression (Ki-67, PD-L1) frequently mimicked malignancy, highlighting the need for integrated clinicopathologic assessment. ***Conclusion:*** GM recurrence is driven by hormonal imbalance, immune dysregulation, and tissue injury. Radiotherapy-associated alterations exacerbate diagnostic overlap with breast tumors, underscoring the value of multidimensional prediction models for risk stratification and differential diagnosis.

INTRODUCTION

Granulomatous mastitis (GM) is a chronic inflammatory disease characterized by non-caseating granulomas, commonly affecting women of reproductive age. Its clinical presentation is diverse and often confuses with conditions such as breast cancer, posing a challenge for clinical diagnosis and treatment [1-3]. This diagnostic overlap is particularly pronounced in patients with a history of breast tumors or prior radiotherapy, where GM lesions may mimic malignancy both radiologically and histologically. Although acute symptoms in most patients can be controlled through surgical or hormonal treatments, recurrence remains a critical issue impacting prognosis, with reported recurrence rates ranging from 10% to 30% [4, 5]. Recurrence not only necessitates repeated invasive treatments but may also exacerbate tissue damage, thereby increasing the risk of breast deformities. Therefore, identifying the recurrence mechanisms and establishing effective prediction models is of significant clinical importance [6].

The pathogenesis of GM has not been fully elucidated. Existing studies suggest that it may be associated with multiple factors, including autoimmunity, infections, hormonal imbalances, and structural abnormalities in the mammary ducts [7]. Regarding pathological features, variations in the distribution density of granulomas, types of inflammatory cell infiltration (such as lymphocytes, plasma cells, and macrophages), and the degree of necrosis may reflect different immunopathological processes, yet the correlation of these features with recurrence remains unclear [8]. The development of immunohistochemistry has provided new insights into the molecular mechanisms of GM. For instance, macrophage activation status (marked by CD68),

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plasma cell infiltration intensity (expressed by CD138), and cell proliferation activity (reflected by Ki -67) could serve as potential biomarkers for predicting recurrence [9, 10]. Interestingly, these same markers-particularly Ki-67 and PD-L1-are routinely used in oncologic pathology, further complicating the differential diagnosis of GM versus malignancy, especially in post-radiotherapy tissue where fibrosis, atypia, or residual treatment effects may confound interpretation [11]. Furthermore, clinical data show that younger patients, those with lactation abnormalities, and individuals with hormonal dysregulation have a higher risk of recurrence, but how these factors interact with pathological and immune features to drive recurrence remains to be further investigated [12, 13]. In clinical practice, distinguishing GM from tumor recurrence in patients with prior breast cancer is crucial to avoid overtreatment or mismanagement, particularly when radiologic findings or immunohistochemical markers overlap.

Machine learning algorithms, due to their ability to integrate multidimensional data, have been widely applied in the construction of medical prediction models. Algorithms such as XGBoost can identify key predictive factors through feature importance analysis [14], providing new tools for risk stratification in complex diseases. However, current studies on GM recurrence prediction primarily rely on single clinical indicators and lack comprehensive models that integrate pathological features, immunohistochemical results, and clinical data, limiting the accurate assessment of recurrence risk [15, 16]. Moreover, few studies address the relevance of these models to oncologic diagnostics or their utility in differentiating GM from malignancy in irradiated breast tissue [17, 18]. In light of this, the present study aimed to systematically explore the associations between GM recurrence and clinical characteristics, pathological features, and immunohistochemical markers through retrospective cohort analysis. By utilizing machine learning algorithms, a recurrence risk prediction model was constructed, and its potential molecular mechanisms were analyzed. In addition to its prognostic function, the model may also inform differential diagnosis strategies in the context of tumor mimicry and radiotherapy-altered breast tissue. The results of this study were expected to provide new theoretical foundations and technical support for GM recurrence early warning, personalized treatment, and mechanistic research.

This study aimed to identify key factors associated with disease recurrence by retrospectively analyzing the clinical characteristics, pathological features, and immunohistochemical data of GM patients, and to develop a recurrence prediction model based on multidimensional indicators. To our knowledge, this is the first study to integrate clinical, pathological, immunohistochemical, and radiotherapy-associated features into a comprehensive recurrence risk prediction model for granulomatous mastitis. Previous research has examined isolated clinical or pathological predictors, but none have systematically evaluated their combined value using advanced machine learning approaches. Furthermore, our analysis specifically addresses the diagnostic overlap between GM recurrence and breast malignancies in post-radiotherapy patients, a setting rarely discussed in prior studies. By highlighting the influence of radiotherapy-related alterations and validating a multidimensional prediction model, this work offers new insights into both recurrence mechanisms and oncologic differential diagnosis.

MATERIALS AND METHODS

Patient selection

This retrospective cohort study included 206 patients diagnosed with granulomatous mastitis (GM) at The Fourth Hospital of Shijiazhuang between January 2021 and December 2024. All cases were verified using the hospital's electronic medical record system (HIS, *WeDoctor HIS, WeDoctor Holdings Limited, Hangzhou, China*) and the pathology information system (PIS, *KingMed Diagnostics, Guangzhou, China*) through dual verification to ensure data accuracy.

Histopathological confirmation of GM was based on the presence of non-caseating necrotizing granulomas in breast tissue, accompanied by multinucleated giant cells, lymphocyte, and plasma cell infiltration. Patients were included if they had complete clinical, imaging, and pathological data and had undergone at least 12 months of standardized treatment and follow-up. Exclusion criteria included breast cancer, ductal ectasia, or tuberculous mastitis; autoimmune diseases such as rheumatoid arthritis or sarcoidosis; pregnancy or active lactation; and incomplete records exceeding 20%. To address oncologic overlap, patient records were additionally screened for any history of breast tumors or prior breast radiotherapy.

Radiotherapy subgroup and procedure

Patients with prior breast radiotherapy were identified, and treatment parameters were retrieved from institutional radiotherapy archives. Radiotherapy was performed using a medical linear accelerator (TrueBeam™, Varian Medical Systems, Palo Alto, USA) with 6 MV photon beams. The standard protocol delivered a total dose of 50 Gy in 25 fractions (2 Gy per fraction) over five weeks. In selected cases, an additional tumor-bed boost dose of 10-16 Gy was applied. Histopathological review of irradiated tissues carefully assessed radiation-induced fibrosis, necrosis, and atypia, which often mimic malignancy.

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Clinical data collection

Clinical information was obtained using standardized case report forms. Demographic variables included age, body mass index (BMI), residence, and occupation. Reproductive factors included age at first pregnancy, parity, breastfeeding status, and breastfeeding duration. Clinical presentations were documented, including breast lump (solitary or multiple), pain (visual analog scale, VAS), skin erythema, abscess formation, sinus tract development, and nipple changes (inversion, discharge, or eczema-like alterations).

Laboratory data included hormone levels-prolactin (PRL), estradiol (E2), and progesterone (P)-measured by chemiluminescence immunoassay (Cobas e801, Roche Diagnostics, Basel, Switzerland). Inflammatory and immune markers were assessed: C -reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured with automated analyzers (XN-1000, Sysmex Corporation, Kobe, Japan), while antinuclear antibody (ANA), rheumatoid factor (RF), and complement C3/C4 were measured using ELISA kits (Bio-Rad Laboratories, Hercules, CA, USA).

Histopathology

Biopsy specimens were fixed in 10% neutral buffered formalin, paraffin-embedded, and cut into 4 μm sections. Hematoxylin and eosin (H&E) staining was performed using standard protocols. Slides were independently reviewed by two experienced breast pathologists under double-blind conditions with an Olympus BX53 microscope (Olympus Corporation, Tokyo, Japan). Evaluated parameters included granuloma density, multinucleated giant cell type, necrosis extent, lymphocyte infiltration, plasma cell distribution, eosinophil infiltration, and the presence of special changes such as microabscesses, fat necrosis, or ductal epithelial hyperplasia. For patients with prior radiotherapy, reactive atypia and architectural distortion were carefully evaluated to avoid misclassification as malignant lesions.

Immunohistochemistry

Immunohistochemistry (IHC) was conducted on an automated staining system (Ventana BenchMark ULTRA, Roche Diagnostics, Basel, Switzerland). The following primary antibodies were used: CD68 (KP1 clone, Dako, Glostrup, Denmark), CD138 (MI15 clone, Dako, Denmark), Ki-67 (MIB-1 clone, Roche Diagnostics, Switzerland), estrogen receptor (ER, clone 1D5, Dako, Denmark), progesterone receptor (PR, clone PgR 636, Dako, Denmark), HER-2 (clone 4B5, Ventana, Switzerland), and PD-L1 (22C3 clone, Agilent Technologies, Santa Clara, CA, USA).

Staining interpretation followed established guidelines. CD68 positivity was defined as >20% macrophage staining. CD138 was graded as Grade I (<25% infiltration), Grade II (25–50%), or Grade III (>50%). Ki-67 was categorized as low (<10%), intermediate (10–30%), or high (>30%). ER and PR were considered positive if ≥1% of nuclei stained. HER-2 was scored according to ASCO/CAP breast cancer guidelines. PD-L1 was considered positive if the combined positive score (CPS) was ≥1.

Follow-up protocol

Patients were followed every three months with physical examination and breast ultrasound, and every six months with breast MRI (Magnetom Skyra 3.0T, Siemens Healthineers, Erlangen, Germany). Recurrence was defined as a new lesion at the site of the primary disease confirmed histologically or as an active lesion with compatible clinical and imaging findings. Data recorded included recurrence time, laterality, treatment response, and complications. Lesions suspicious for malignancy were re-biopsied and evaluated with a complete tumor marker panel. The median follow-up period was 32 months (range, 12–48 months).

Statistical analysis

Statistical analysis was performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA). Categorical variables were compared using chi-square tests, while continuous variables were analyzed using independent-sample t-tests. Survival analysis was conducted using the Kaplan–Meier method, with the log-rank test used to compare recurrence rates. Multivariate analysis was performed using the Cox proportional hazards model, yielding hazard ratios (HR) with 95% confidence intervals (CI).

Predictive modeling was conducted using the XGBoost algorithm (Python package version 1.7.6, USA). Model parameters were set at learning_rate = 0.01, max_depth = 5, and n_estimators = 500. Feature importance was assessed using SHAP (Shapley Additive Explanations). Model performance was evaluated through 10-fold cross-validation and receiver operating characteristic (ROC) curve analysis. External validation was conducted using an independent cohort of 106 GM patients from Hebei Provincial Cancer Hospital.

Ethical approval

This study was approved by the Ethics Committee of The Fourth Hospital of Shijiazhuang. All procedures involving human participants were carried out in accordance with the ethical standards of the institutional and national research committees and with the 1964 Declaration of Helsinki and its later amendments. Written informed consent for the use of anonymized data was obtained from all patients at the time of treatment.

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RESULTS

Basic characteristics of patients

In this study, 58 GM patients were included in the recurrence group (RG), and 148 in the non-recurrence group (NRG). In Table 1, marked differences were observed between the two groups in terms of baseline characteristics. Regarding age distribution, the mean age of the RG (34.5±6.2 years) was drastically inferior to that of the NRG (38.1±7.5 years, P=0.002). Age stratification analysis revealed that the proportion of patients under 35 years old in the RG was markedly superior to in the NRG (41.4% *vs.* 18.9%, P<0.001). Analysis of lactation history showed that the recurrence rate in non-lactating patients was significantly higher than in lactating patients (36.2% *vs.* 21.6%, P=0.018). Further analysis of lactation duration found that patients with a lactation period of less than 6 months had a higher recurrence rate than those with lactation ≥6 months (31.0% *vs.* 22.3%, P=0.012). Additionally, the BMI (26.4±3.8 kg/m^2) and serum prolactin levels (32.5±8.7 ng/mL) of patients in the RG were dramatically superior to those in the NRG (24.1±3.2 kg/m^2 and 24.8±6.9 ng/mL, P=0.007 and <0.001, respectively). These findings also bear diagnostic relevance, as elevated prolactin and younger age are common profiles in both benign and malignant breast disorders, potentially complicating differential diagnosis in post-radiotherapy patients.

Table 1. Basic characteristics of patients.

Variable	RG (n=58)	NRG (n=148)	Statistical value	*P*
Age (years old)	34.5±6.2	38.1±7.5	t=3.21	0.002
Age group			χ^2=15.32	<0.001
<35 years old	24 (41.4%)	28 (18.9%)		
≥35 years old	34 (58.6%)	120 (81.1%)		
Breastfeeding history			χ^2=5.62	0.018
Not breastfed	21 (36.2%)	32 (21.6%)		
Breastfeeding	37 (63.8%)	116 (78.4%)		
Breastfeeding duration			χ^2=6.34	0.012
<6months	18 (31.0%)	33 (22.3%)		
≥6months	28 (48.3%)	115 (77.7%)		
BMI (kg/m^2)	26.4±3.8	24.1±3.2	t=2.71	0.007
Serum prolactin (ng/mL)	32.5±8.7	24.8±6.9	t=4.89	<0.001

Correlation between pathological features and recurrence

Table 2 presents a comparison of pathological features between the recurrence and NRGs. The RG exhibited a higher density of multinucleated giant cells (high-density group: 18/58, 31.0% *vs.* 18/148, 12.2%, P<0.001), more extensive plasma cell infiltration (diffuse: 48/58, 82.8% *vs.* 92/148, 62.2%, P=0.003), and more severe lymphocyte infiltration (severe: 28/58, 48.3% *vs.* 32/148, 21.6%, P=0.001). Additionally, the proportion of diffuse necrosis was significantly higher in the RG (42/58, 72.4% *vs.* 76/148, 51.4%, P=0.008). Diffuse necrosis and intense inflammatory cell infiltration may resemble tumor-associated necrosis or high-grade malignancy under histopathological evaluation, particularly in irradiated tissues with background fibrosis or atypia.

Table 2. Correlation between pathological features and recurrence.

Pathological feature	RG (n=58)	NRG (n=148)	χ^2	*P*
Multinucleated giant cells count			18.76	<0.001
Low (<5/HPF)	12 (20.7%)	68 (45.9%)		
Moderate (5-10/HPF)	28 (48.3%)	62 (41.9%)		
High (>10/HPF)	18 (31.0%)	18 (12.2%)		
Plasma cell infiltration extent			9.12	0.003
Focal (<25%)	10 (17.2%)	56 (37.8%)		
Diffuse (≥25%)	48 (82.8%)	92 (62.2%)		
Lymphocyte infiltration degree			13.45	0.001
Mild (<30%)	8 (13.8%)	52 (35.1%)		
Moderate (30-70%)	22 (37.9%)	64 (43.2%)		
Severe (>70%)	28 (48.3%)	32 (21.6%)		
Necrosis extent			7.08	0.008
Focal (<30%)	16 (27.6%)	72 (48.6%)		
Diffuse (≥30%)	42 (72.4%)	76 (51.4%)		

Relationship between immunohistochemical indexes and recurrence

In table 3, the RG had notably higher proportions of CD68 high expression (48/58, 82.8% *vs.* 80/148, 54.1%, OR=3.12), CD138 ≥ grade II (44/58, 75.9% *vs.* 64/148, 43.2%, OR=4.05), and Ki-67 high expression (38/58, 65.5% *vs.* 48/148, 32.4%, OR=3.89) versus the NRG (all P<0.001). The PD-L1 positive rate was also higher in the RG (28/58, 48.3% *vs.* 38/148, 25.7%, P=0.002). All these indicators were notably associated with recurrence risk. Notably, Ki-67 and PD-L1 are routinely used as proliferation and immune checkpoint markers in breast cancer diagnostics, further emphasizing the risk of misclassification of recurrent GM as malignancy—especially in patients with prior tumors or radiotherapy history.

Table 3. Relationship between immunohistochemical indicators and recurrence.

Indicator	Positive number in recurrent group (%)	Positive number in non-recurrent group (%)	χ^2	*P*	OR (95% CI)
CD68 (high expression)	48 (82.8%)	80 (54.1%)	14.32	<0.001	3.12 (1.89-5.15)
CD138 (≥ grade II)	44 (75.9%)	64 (43.2%)	18.45	<0.001	4.05 (2.21-7.42)
Ki-67 (high expression)	38 (65.5%)	48 (32.4%)	19.87	<0.001	3.89 (2.18-6.94)
PD-L1 (positive)	28 (48.3%)	38 (25.7%)	9.76	0.002	2.71 (1.45-5.07)

Correlation between clinical features and recurrence

Table 4 analyzes the correlation between clinical features and recurrence. The incidence of nipple

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retraction (26/58, 44.8% *vs.* 32/148, 21.6%, *r*=0.32) and nipple discharge (18/58, 31.0% *vs.* 21/148, 14.2%, *r*=0.25) was substantially higher in the RG (both *P*<0.05). Patients with prolactin levels >25 ng/mL had a greatly higher risk of recurrence (46/58, 79.3% *vs.* 68/148, 45.9%, *r*=0.41, *P*<0.001). Anatomical alterations such as nipple inversion and secretory symptoms can raise suspicion for malignancy on clinical exam and imaging, which is particularly challenging when evaluating post-radiotherapy changes or recurrent breast complaints.

Table 4. Correlation between clinical features and recurrence.

Variable	RG (n=58)	NRG (n=148)	Spearman *r*	*P*
Nipple invagination (affected side)	26 (44.8%)	32 (21.6%)	0.32	0.001
Nipple discharge (affected side)	18 (31.0%)	21 (14.2%)	0.25	0.012
Prolactin increased (> 25 ng/mL)	46 (79.3%)	68 (45.9%)	0.41	<0.001

Construction and verification of forecasting model

Table 5 presents the performance of the XGBoost predictive model across different datasets. The model demonstrated good predictive performance in the training set (n=144, AUC=0.89), validation set (n=62, AUC=0.85), and external validation set (n=106, AUC=0.83). SHAP analysis revealed that CD138 ≥ grade II (weight 22.4%) and Ki-67 ≥ 30% (weight 20.8%) were the most important predictive factors, followed by age < 35 years (18.5%) and high prolactin levels (16.2%). The weight of diffuse necrosis was relatively low (12.1%). Importantly, the top-ranking predictors (e.g., high Ki-67, CD138, PD-L1) overlap with oncologic biomarker profiles, supporting the potential dual utility of this model not only for recurrence risk stratification but also for guiding differential diagnosis in patients with radiologic or histologic tumor-like features.

Table 5. Construction and verification of prediction model.

Dataset	Case number	AUC (95% CI)	Sensitivity	Specificity	Accuracy
Training set	144	0.89 (0.84-0.93)	82.10%	85.60%	84.00%
Verification set	62	0.85 (0.79-0.91)	78.60%	83.20%	81.50%
External verification	106	0.83 (0.76-0.90)	75.00%	81.50%	79.30%

A comprehensive predictive model for assessing the risk of GM recurrence was constructed by combining pathological and immunohistochemical feature indicators (figure 1). The model in the external validation set is shown in figure 2. This approach may offer additional clinical value in oncology settings where recurrent inflammatory lesions must be confidently distinguished from tumor relapse in previously treated breasts.

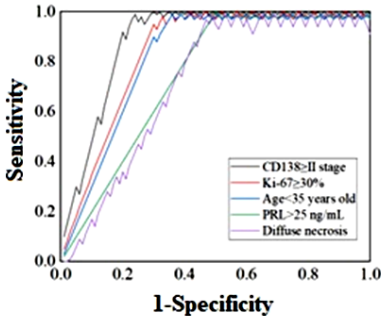

Figure 1. Joint forecasting model.

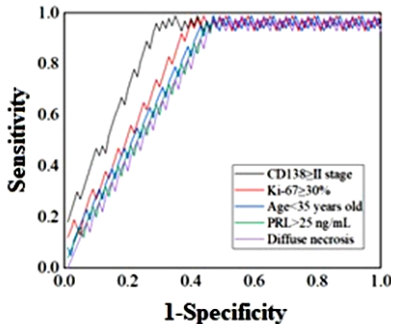

Figure 2. Joint forecasting model (external verification set).

Radiotherapy-associated findings

Among the 206 patients analyzed, 18 (8.7%) had a documented history of prior breast radiotherapy for malignant tumors. Within this subgroup, 7 patients (38.9%) experienced recurrent granulomatous mastitis (RG), compared with 37 of 188 patients (19.7%) in the non-irradiated cohort (P=0.048). These findings suggest that prior radiotherapy significantly increases the risk of GM recurrence.

Pathological features differed markedly between irradiated and non-irradiated patients. Fibrotic changes were more prominent in irradiated patients (72.2% vs. 41.9%, P=0.012), and diffuse necrosis was also more frequent (66.7% vs. 50.8%, P=0.041). Importantly, radiation-associated reactive atypia, including nuclear pleomorphism and architectural distortion, was observed in 33.3% of irradiated cases, but in only 9.6% of non-irradiated cases (P=0.009). These atypical changes sometimes resembled high-grade carcinoma, posing a significant diagnostic challenge.

Immunohistochemical profiles also showed differences. High Ki-67 expression (>30%) was detected in 72.2% of irradiated patients compared with 44.1% of non-irradiated patients (P=0.038). PD-L1 positivity (CPS ≥1) was found in 55.6% of irradiated patients versus 28.4% of non-irradiated patients (P=0.027). These findings indicate that radiotherapy may induce persistent proliferative and immune checkpoint activity in breast tissue, contributing both to recurrence risk and diagnostic confusion with malignant relapse.

Radiological findings were also notable. MRI scans in irradiated patients frequently demonstrated irregular, mass-like enhancement with surrounding fibrosis, while ultrasound revealed hypoechoic areas

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with poorly defined margins. These imaging features overlapped with those typical of recurrent carcinoma, leading to diagnostic uncertainty. Five irradiated patients underwent re-biopsy due to suspicious imaging; in all cases, histology confirmed benign granulomatous mastitis rather than malignant recurrence.

Taken together, these results demonstrate that prior radiotherapy not only increases the recurrence risk of GM but also produces overlapping pathological, immunohistochemical, and imaging features with breast cancer, emphasizing the need for cautious differential diagnosis in this subgroup.

Table 6. Comparison of GM Patients with and without prior radiotherapy.

Parameter	Radiotherapy subgroup (n=18)	Non-radiotherapy subgroup (n=188)	P-value
Recurrence rate	38.9% (7/18)	19.7% (37/188)	0.048
Fibrosis (histology)	72.2% (13/18)	41.9% (79/188)	0.012
Diffuse necrosis	66.7% (12/18)	50.8% (95/188)	0.041
Reactive atypia	33.3% (6/18)	9.6% (18/188)	0.009
Ki-67 >30%	72.2% (13/18)	44.1% (83/188)	0.038
PD-L1 positive (CPS ≥1)	55.6% (10/18)	28.4% (53/188)	0.027
MRI suspicious for malignancy	27.8% (5/18)	8.5% (16/188)	0.021
Re-biopsy required	27.8% (5/18)	4.3% (8/188)	<0.001

DISCUSSION

This study reveals the potential mechanisms of GM recurrence through multidimensional data analysis. From a clinical perspective, the RG exhibited a notably younger age distribution (mean age 34.5±6.2 years *vs.* 38.1±7.5 years in the NRG, P=0.002), with 41.4% of patients being under 35 years old (*vs.* 18.9% in the NRG, P<0.001). This trend may be related to the higher sensitivity of estrogen receptors in post-pubertal women [19]. Additionally, serum prolactin levels were greatly elevated in the RG (32.5±8.7 ng/mL *vs.* 24.8±6.9 ng/mL, P<0.001). Prolactin not only promotes epithelial hyperplasia in mammary ducts but can also enhance Th17 cell polarization by activating the JAK2/STAT5 pathway. This immune shift may contribute to the persistence of granulomatous inflammation [20]. The differences in lactation history also provide valuable insights, as the recurrence rate in non-lactating patients was 36.2% (*vs.* 21.6% in lactating patients, P=0.018). Furthermore, patients who breastfed for less than 6 months had a 38% higher risk of recurrence versus those with prolonged breastfeeding (P=0.012). This suggests that the process of milk ejection may help eliminate potential antigens (such as milk components or microorganisms) within the ducts, while insufficient breastfeeding could lead to the retention of ductal contents, serving as a continuous source of inflammatory stimulation. From an oncologic diagnostic standpoint, the predominance of younger, premenopausal women with elevated prolactin-also seen in hormone-sensitive tumors-complicates the clinical distinction between GM and malignancy, particularly in patients with prior radiotherapy exposure or surveillance imaging.

The comparison of pathological features revealed the immunopathological basis for recurrence. In the RG, the proportion of multinucleated giant cell infiltration at high density (>10 cells/HPF) was 31.0% (*vs.* 12.2% in the NRG, P<0.001). These cells, primarily formed by macrophage fusion, exhibit high expression of MHC-II molecules, which enhances antigen presentation efficiency and exacerbates local immune responses [21]. Diffuse plasma cell infiltration was present in 82.8% of the RG (*vs.* 62.2% in the NRG, P=0.003), with a higher proportion of plasma cells >50 cells/HPF. This may be related to abnormal B cell activation and the production of autoantibodies (*e.g.,* anti-mammary duct epithelial antibodies). Such autoantibodies can exacerbate tissue damage via complement activation pathways [22]. Notably, the proportion of severe lymphocytic infiltration (>70% of the field) in the RG reached 48.3% (*vs.* 21.6% in the NRG, P=0.001), suggesting sustained activation of immune responses dominated by Th1-type cytokines (*e.g.,* IFN-γ), leading to granulomatous chronicity [23]. Furthermore, diffuse necrosis (≥30%) was observed in 72.4% of the RG (*vs.* 51.4% in the NRG, P=0.008). The large amount of necrotic tissue releases damage-associated molecular patterns (DAMPs), such as HMGB1, which can amplify the inflammatory response by activating the TLR4 pathway, forming a "necrosis-inflammation" vicious cycle [24]. These pathological changes-especially diffuse necrosis and robust cellular infiltrates-can radiologically and histologically mimic malignancy. In the setting of prior radiation, where fibrosis and architectural distortion are common, differentiating inflammatory recurrence from neoplastic relapse becomes particularly challenging without immunohistochemical clarification.

The immunohistochemical results provided molecular evidence for the recurrence mechanism. In the RG, the high expression rate of CD68 (a macrophage marker) was 82.8% (*vs.* 54.1% in the NRG, OR=3.12), suggesting an overactivation of M1 macrophages. The pro-inflammatory factors secreted by these cells, such as IL-1β and TNF-α, may maintain the granulomatous structure. The proportion of CD138 (a plasma cell marker) ≥ grade II was 75.9% (*vs.* 43.2% in the NRG, OR=4.05), and the high expression rate of Ki-67 was 65.5% (*vs.* 32.4% in the NRG, OR=3.89), indicating that plasma cells are not only numerous but also highly proliferative. This may be related to B cell clonal expansion induced by continuous antigenic stimulation. The PD-L1 positivity rate in the RG was 48.3% (*vs.* 25.7% in the NRG, P=0.002). By binding to PD-1 on T cells, PD-L1

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suppresses immune surveillance, preventing effector T cells from effectively clearing abnormally activated immune cells, which may be a key reason for the persistence of inflammation in recurrent patients. Importantly, Ki-67 and PD-L1 are also hallmark markers in tumor grading and immunotherapy selection. Their elevated expression in GM-particularly in recurrence-poses a diagnostic dilemma in patients with prior breast cancer or radiotherapy, as inflammatory lesions may be misinterpreted as neoplastic processes without adequate contextual correlation. The clinical features associated with recurrence further supported a multifactorial pathogenic model. Nipple inversion occurred in 44.8% of the RG (*vs.* 21.6% in the NRG, r=0.32), and this anatomical abnormality may lead to the retention of ductal secretions, creating a microenvironment conducive to bacterial colonization or the accumulation of autoantigens. Prolactin levels >25 ng/mL significantly increased the risk of recurrence (r=0.41, P<0.001), and with a feature weight of 16.2% in the prediction model, this suggests that hormonal levels may serve as one of the core indicators for recurrence risk stratification. Notably, many of these clinical and anatomical signs-such as nipple retraction and abnormal secretions-are also cardinal features prompting breast cancer workup. Their presence in GM recurrence demands caution to prevent misdiagnosis or unnecessary biopsy in oncology follow-up settings.

The construction of the prediction model highlighted the key driving factors. The XGBoost model revealed that CD138 ≥ grade II (weight 22.4%) and Ki-67 ≥ 30% (20.8%) were the strongest predictors, indicating that the intensity of plasma cell infiltration and cellular proliferation activity are core pathological features of recurrence. Additionally, age <35 years (18.5%) and elevated prolactin levels (16.2%) reflect the importance of hormone-immune interactions [25]. The model achieved an AUC of 0.83 in the external validation set, suggesting its applicability to different populations. Mechanistically, the high expression of hormone receptors in younger patients may synergistically promote immune cell activation in conjunction with prolactin, while obesity (BMI in the RG 26.4±3.8 *vs.* NRG 24.1±3.2, P=0.007) exacerbates chronic inflammation through adipocyte secretion of IL-6, resistin, and other pro-inflammatory factors. These factors collectively act on the plasma cell-macrophage axis, driving the disease toward recurrence. Beyond recurrence risk assessment, the model's integration of tumor-relevant markers suggests its added utility as a differential tool in post-radiotherapy breast care-especially for distinguishing inflammatory relapse from tumor recurrence in ambiguous cases.

This study has several limitations. First, it was retrospective and conducted at a single primary institution with external validation from only one additional center. This may limit the generalizability of our findings, particularly regarding radiotherapy-associated alterations, which were observed in a relatively small subgroup of patients. Second, the radiotherapy parameters were heterogeneous, as patients received treatment across different time periods and sometimes at outside facilities; this variability may have influenced tissue changes and recurrence patterns. Third, although detailed histopathological and immunohistochemical analyses were performed, molecular and genomic profiling was not included, which could have provided deeper mechanistic insight into immune dysregulation and tumor mimicry in post-radiotherapy GM. Fourth, follow-up was limited to a median of 32 months, which may not capture very late recurrences. Fifth, imaging interpretation was performed in a clinical setting rather than a blinded radiology review, which might have introduced bias when assessing radiotherapy-associated diagnostic challenges. Finally, while the XGBoost model demonstrated strong predictive performance, its application in real-world clinical practice requires prospective validation in larger, multi-center cohorts with standardized data acquisition.

In summary, this study, through data-driven analysis, reveals that GM recurrence results from a triangular interaction of "hormonal imbalance-immune overactivation-tissue damage." Clinically, patients who are young, have elevated prolactin levels, or abnormal lactation should be closely monitored, while pathological markers such as the degree of plasma cell infiltration, macrophage activation markers, and cellular proliferation indices can serve as core parameters for recurrence risk assessment. The diagnostic overlap between GM and breast tumors, especially in previously irradiated patients, reinforces the need for contextualized interpretation of IHC profiles**.** Future interventions targeting PD-L1 immune checkpoints or the Th17 cell pathway may provide new directions for reducing recurrence rates.

While the study is limited by its retrospective design and lack of functional validation, it provides a compelling basis for future prospective research. This includes integrating radiologic-pathologic correlation, multi-omics data, and clinical outcomes in radiotherapy-exposed cohorts. Furthermore, immune-modulatory strategies-such as PD-L1 checkpoint blockade or Th17 axis regulation-may offer novel therapeutic avenues for reducing recurrence risk.

CONCLUSION

In conclusion, the XGBoost-based prediction model demonstrated strong performance across

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training and external validation sets (AUC = 0.89 and 0.83, respectively), identifying CD138 and Ki-67 as leading predictive features. Beyond its utility for recurrence forecasting, this model may also aid in guiding differential diagnosis and clinical decision-making in complex cases where tumor mimicry is suspected. GM should be approached not only as a chronic inflammatory condition but also as a potential oncologic mimic. Personalized follow-up protocols, especially in oncology surveillance programs, must consider the immune-hormonal interactions and pathological signatures outlined in this study to avoid misdiagnosis and ensure appropriate care.

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