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Research Article

Dynamic Modulation of Immune Markers in Breast Cancer Following Radiotherapy

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Abstract

Purpose: To evaluate dynamic changes in systemic and tumour immune markers—neutrophil-to-lymphocyte ratio (NLR) and tumour-infiltrating lymphocytes (TILs)—before and after radiotherapy (RT) in breast cancer patients, and to assess their association with ipsilateral breast tumour recurrence (IBTR).

Materials and Methods: Thirty-five breast cancer patients were analysed for pre-RT and post-RT NLR and TIL levels. Paired t-tests were performed to assess changes induced by RT, and independent t-tests were used to compare these immune markers between patients with and without IBTR.

Results: RT induced significant immune modulation. NLR increased significantly after treatment (mean change = 0.59; $p < 0.0001$), while TILs decreased markedly ($p < 0.0001$). Pre-RT NLR showed a trend toward higher values among patients who developed IBTR ($p = 0.08$), whereas pre-RT TILs did not differ significantly ($p = 0.97$). Post-RT NLR and TILs showed no significant association with IBTR status. These findings suggest that pre-treatment NLR may have prognostic value in identifying patients at higher risk.

Conclusion: Radiotherapy significantly alters immune marker profiles in breast cancer, characterised by increased NLR and decreased TILs post-treatment. A higher pre-RT NLR may indicate an adverse immunologic milieu and could serve as a potential biomarker for patient stratification. Validation in larger, prospective cohorts is warranted to confirm these preliminary observations.

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1. INTRODUCTION

Breast cancer remains one of the most prevalent malignancies worldwide, with radiotherapy serving as a cornerstone of curative treatment, particularly for enhancing locoregional control following breast-conserving surgery. Over the past decade, breast cancer management has evolved substantially, yet radiotherapy continues to play a pivotal role not only through its direct cytotoxic effects but also via its ability to modulate the tumour microenvironment [1]. Emerging evidence highlights the immunomodulatory properties of radiotherapy, which can reshape both local and systemic immune responses, thereby influencing treatment outcomes and recurrence risk [2]. Neoadjuvant radiotherapy (RT) is gaining renewed attention in the management of early-stage and locally advanced breast cancer as an innovative approach to improve tumour response, enhance breast conservation, and modulate the tumour microenvironment before surgical resection. Beyond tumour cytoreduction, neoadjuvant RT can induce immunogenic cell death, promote the release of tumour-associated antigens, and stimulate both local and systemic immune activation—effectively transforming the irradiated tumour into an *in-situ* vaccine [3]. These effects have generated growing interest in combining RT with systemic or immune-targeted therapies in the neoadjuvant setting to harness synergistic antitumor activity and enable individualised treatment strategies [4]. Among the immune-related biomarkers under investigation, the neutrophil-to-lymphocyte ratio (NLR) and tumour-infiltrating lymphocytes (TILs) have emerged as promising indicators of prognosis and therapeutic response [5]. NLR, derived from routine peripheral blood counts, reflects the balance between tumour-promoting inflammation and anti-tumour immunity. An elevated NLR denotes a pro-inflammatory, immunosuppressive state and has been consistently associated with inferior survival outcomes across multiple malignancies, including breast cancer [1]. The radiosensitivity of lymphocytes further accentuates this effect, as radiotherapy-induced lymphopenia may compromise immune surveillance and facilitate tumour persistence [2]. Conversely, TILs represent the local immune response within the tumour microenvironment. High TIL density, particularly of cytotoxic $CD8^+$ T cells, correlates with improved prognosis and enhanced treatment response, most notably in biologically aggressive subtypes such as triple-negative and HER2-positive breast cancers [5]. Radiotherapy has been shown to alter TIL composition and activity, potentially influencing tumour control, treatment sensitivity, and recurrence dynamics. [3,4] Despite increasing recognition of NLR and TILs as clinically relevant biomarkers, the dynamic immunologic shifts induced by radiotherapy and their correlation with disease outcomes remain insufficiently characterised. Understanding these alterations may provide insight into mechanisms of radio resistance, enable risk-adapted treatment strategies, and identify immune biomarkers predictive of therapeutic efficacy. This study aims to evaluate pre- and post-radiotherapy alterations in NLR and TILs and to assess their association with ipsilateral breast tumour recurrence, thereby exploring their potential role as predictive biomarkers in breast cancer radiotherapy.

2. MATERIALS AND METHODS

Study Population

This prospective study included 35 female patients with histologically confirmed invasive breast carcinoma treated between 2020 and 2022 at a tertiary oncology centre. Eligible patients were aged ≥18 years and had undergone either breast-conserving surgery or mastectomy, in conjunction with pre-operative radiotherapy. Availability of complete clinical data, including pre- and post-radiotherapy immune marker assessments, was mandatory for inclusion. Patients with prior malignancies or those who had received neoadjuvant chemotherapy were excluded to avoid potential confounding effects on systemic immune parameters. Institutional ethics approval was obtained before study initiation, and all patients provided informed consent.

Radiotherapy Treatment

All patients received pre-operative radiotherapy according to institutional and international standards. Treatment planning was performed using Intensity-Modulated Radiotherapy (IMRT) following individualised CT-based simulation. The prescribed dose was 40 Gy in 15 fractions, delivered to the whole breast clinical target volume. A Simultaneous Integrated Boost (SIB) of 48 Gy in 15 fractions was delivered to the tumour bed. Dose constraints for organs at risk—including the heart, ipsilateral lung, and contralateral breast—followed standard ASTRO and RTOG protocol recommendations to ensure optimal safety and minimise toxicity.

Immune Marker Assessment

Peripheral venous blood samples were collected within one week before RT initiation (pre-RT) and within four weeks post-RT completion (post-RT) for complete blood count analysis. The neutrophil-to-lymphocyte ratio (NLR) was calculated as the ratio of absolute neutrophil count to absolute lymphocyte count using standardised automated haematology analyzers under rigorous internal quality control. Tumour-infiltrating lymphocytes (TILs) were evaluated on formalin-fixed, paraffin-embedded (FFPE) surgical specimens by two independent pathologists blinded to clinical outcomes. Stromal TILs were quantified as the percentage of mononuclear inflammatory cells within the stromal compartment of the invasive tumour area, in accordance with the International Immuno-Oncology Biomarker Working Group (2014) recommendations.

Clinical Endpoints and Follow-up

All patients were followed up at regular intervals after treatment completion. The median follow-up duration was 48 months (range: 44–52 months). The primary endpoint was ipsilateral breast tumour recurrence (IBTR), confirmed radiologically or histopathologically within the treated breast. Recurrence-free survival (RFS) was defined as the time from completion of radiotherapy to the first documented IBTR or the last clinical follow-up.

Statistical Analysis

Data normality was assessed using the Shapiro–Wilk test. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR) based on distribution, while categorical variables were presented as frequencies and percentages. Paired t-tests were employed to compare pre-RT and post-RT immune marker values. Independent sample t-tests evaluated differences in immune marker levels between patients with and without IBTR. Statistical significance was defined as a two-tailed *p*-value <0.05. All analyses were performed using IBM SPSS Statistics, version 25.0.

3. RESULTS

The study cohort included 35 female patients with a mean age of 55.6 ± 5 years (range: 47–64 years). Tumour subtype distribution comprised triple-negative breast cancer (TNBC) in 12 patients (34.3%), HER2-positive in 12 patients (34.3%), and luminal subtype in 11 patients (31.4%). A pathologic complete response (PCR) was achieved in 34.3% (12/35) of patients. During a median follow-up period of 48 months (range: 44–52 months), ipsilateral breast tumour recurrence (IBTR) was observed in 34.3% (12/35) of the cohort.

Table 1: Patient and Tumour Characteristics (n = 35)

Characteristic	Value	n (%)/Mean ± SD
Age (years)	Mean (Range)	55.6 ± 5 (47–64)
Histology	Invasive carcinoma	35 (100%)
Tumor subtype	Triple-negative	12 (34.3%)
	HER2-positive	12 (34.3%)
	Luminal	11 (31.4%)
Pathologic complete response (pCR)	Achieved	12 (34.3%)
Ipsilateral breast tumour recurrence (IBTR)	Yes	12 (34.3%)
	No	23 (65.7%)
Median follow-up (months)	Range	48 (44–52)

Table 1 summarises the baseline demographic and pathological characteristics of the study population. The cohort demonstrated a balanced distribution among molecular subtypes, with comparable representation of TNBC and HER2-positive cases.

Approximately one-third of patients achieved pCR, while a similar proportion experienced IBTR during the median follow-up period. Paired t-test analysis demonstrated statistically significant immunologic alterations. Following radiotherapy, underscoring the dynamic nature of systemic and tumour immune modulation. The neutrophil-to-lymphocyte ratio (NLR) increased significantly after treatment immune infiltration within the tumour microenvironment. These opposing trajectories—an increase in systemic inflammation (NLR) and a decrease in local lymphocytic density (TILs)—highlight the bidirectional immunologic effects of radiotherapy. While systemic inflammation appears to intensify, localised immune presence within the tumour stroma diminishes, reflecting a potential radiation-induced immune redistribution phenomenon. Independent t-test comparisons were performed to explore the relationship between baseline immune markers and subsequent local recurrence. Patients who developed ipsilateral breast tumour recurrence (IBTR) demonstrated a trend toward higher pre-RT NLR compared to those who remained recurrence-free (mean 2.12 vs. 1.88; t=1.80, p=0.08). Although this did not reach statistical significance, it suggests a possible prognostic inclination of elevated baseline systemic inflammation toward poorer local control. In contrast, pre-RT TIL levels were comparable between patients with and without IBTR (mean 31.3% vs. 30.6%; t=-0.04, *p*=0.97), indicating that pre-treatment stromal lymphocytic density alone may not sufficiently discriminate recurrence risk in this cohort. Post-radiotherapy immune marker evaluation revealed no statistically significant differences between patients with and without IBTR. Mean post-RT NLR values were similar between groups (IBTR: 3.10, non-IBTR: 3.05; t = 0.81, p=0.42), and post-RT TILs also showed no significant variation (IBTR: 26.7%, non-IBTR: 26.9%; t = -0.0016, p = 0.999). These findings suggest that, although radiotherapy induces measurable immune shifts, the post-treatment immune state may represent a transient adaptive phase rather than a sustained determinant of recurrence risk. The results collectively point to pre-treatment immune equilibrium—particularly systemic inflammatory status—as a more relevant marker of local disease behaviour than post-treatment immune profiles.

Table 2: Dynamic Changes in Immune Markers Pre- and Post-Radiotherapy

Immune Marker	Pre-RT (Mean± SD)	Post-RT (Mean± SD)	Mean Difference	t-value	*p*-value
NLR	1.97 ± 0.31	3.07 ± 0.30	+0.59	-15.04	< 0.0001
TILs (%)	30.86 ± 13.88	26.83 ± 12.48	-4.03	14.90	< 0.0001

Table 2 illustrates the paired comparison of immune markers before and after radiotherapy. Radiotherapy induced significant systemic inflammatory activation (increased NLR) and reduction in intratumoral lymphocytic infiltration (decreased TILs), demonstrating a bidirectional immune shift consistent with radiation-induced immunomodulation.

The patient cohort was subdivided into high and low groups based on the median cut-off values of pre-radiotherapy neutrophil-to-lymphocyte ratio (NLR) and tumour-infiltrating lymphocytes (TILs) to explore associations with clinicopathological parameters. For NLR stratification, significant associations were observed with hormone receptor status. A higher proportion of patients in the high NLR group were estrogen receptor (ER) and progesterone receptor (PR) positive (73.3%) compared to none in the low NLR group (*p*< 0.001). HER2 receptor status was comparable between groups. The presence of lymph node metastasis showed no significant

difference (p = 0.237). Breast cancer subtype distribution differed significantly ($p < 0.001$), with the luminal subtype predominating in the high NLR group, while triple-negative breast cancer (TNBC) was more frequent in the low NLR group. The use of regional nodal irradiation (RNI) was significantly higher in the high NLR group (73.3% vs. 0%, $p < 0.001$), whereas chemotherapy administration did not differ between the two groups. For TIL stratification, significant differences were primarily observed in hormone receptor status. All patients in the high TILs group were ER and PR negative, compared to 42.1% hormone receptor negativity in the low TILs group (p = 0.001). HER2 status was similar between groups. Breast cancer subtype distribution showed a strong association (p < 0.001), with TNBC predominating among patients with high TILs. The use of RNI was notably lower in the high TILs group (0% vs. 42.1%, p = 0.001). Age, lymph Node metastasis and chemotherapy use were comparable across TIL categories. These findings highlight the distinct clinicopathological correlates of systemic and local immune biomarkers in breast cancer. A higher NLR was associated with luminal subtypes and greater use of regional nodal irradiation, whereas elevated TILs were linked to triple-negative disease and absence of RNI. Collectively, these results underscore the divergent biological and treatment profiles associated with systemic (NLR) and intratumoral (TILs) immune parameters, supporting their potential utility in risk stratification and personalised therapeutic planning.

Table 3: Clinicopathological Characteristics by Pre-Radiotherapy NLR and TILs Stratification

Variable	NLR Low	NLR High	p-value	TILs Low	TILs High	p-value
Age (years)	55.2 ± 4.8	56.0 ± 5.2	0.521	55.3 ± 4.9	55.8 ± 5.1	0.744
ER/PR positivity	0 (0%)	11 (73.3%)	<0.001	10 (57.9%)	0 (0%)	0.001
HER2 positivity	6 (40.0%)	6 (40.0%)	1.000	6 (35.3%)	6 (40.0%)	0.820
Lymph node metastasis	5 (33.3%)	8 (53.3%)	0.237	7 (36.8%)	6 (40.0%)	0.812
Subtype distribution	TNBC predominant	Luminal predominant	<0.001	Luminal predominant	TNBC Predominant	<0.001
Regional nodal irradiation	0 (0%)	11 (73.3%)	<0.001	8 (42.1%)	0 (0%)	0.001
Chemotherapy use	12 (80.0%)	13 (86.7%)	0.624	14 (73.7%)	12 (80.0%)	0.662

Table 3 summarises clinicopathological characteristics according to pre-radiotherapy NLR and TILs stratification. Significant associations were observed between immune marker categories and hormone receptor status, molecular subtype, and use of regional nodal irradiation, underscoring distinct systemic versus intratumoral immune profiles.

4. DISCUSSION

This study provides a comprehensive evaluation of systemic and local immune biomarkers—namely the neutrophil-to-lymphocyte ratio (NLR) and tumour-infiltrating lymphocytes (TILs)—in breast cancer patients receiving radiotherapy (RT), highlighting their clinical associations and potential prognostic implications for ipsilateral breast tumour recurrence (IBTR). The findings reveal that RT induces distinct and opposing immunologic alterations: a significant post-treatment increase in NLR and a corresponding decrease in TILs. These results underscore the dual and dynamic nature of RT-induced immune modulation, reflecting the complex interplay between systemic inflammation and local immune suppression [6,7]. The observed elevation in NLR after RT likely reflects radiation-induced lymphopenia and compensatory neutrophil mobilisation, generating a systemic pro-inflammatory milieu that may contribute to tumour persistence or resistance [8]. In contrast, the decline in TILs post-treatment suggests depletion or functional exhaustion of effector lymphocytes within the tumor microenvironment (TME), potentially due to direct irradiation effects and altered cytokine signalling. Together, these trends illuminate the bidirectional immunologic consequences of radiotherapy, where systemic immune activation coexists with local immune attenuation, highlighting the importance of evaluating both systemic and tumour-specific immune dynamics when interpreting treatment response [9]. Stratification analyses revealed distinct clinicopathological profiles associated with systemic and local immune markers. Patients with elevated pre-RT NLR were more likely to exhibit hormone receptor positivity and luminal subtypes, features commonly associated with a less immunogenic tumor phenotype [7]. The association between high NLR and greater use of regional nodal irradiation suggests that systemic inflammation may correlate with higher-risk disease requiring more extensive treatment fields. Conversely, patients with high baseline TILs predominantly displayed hormone receptor-negative, triple-negative breast cancer (TNBC) profiles, aligning with existing literature describing TNBC as immunologically active and enriched for lymphocytic infiltration [10]. Moreover, reduced utilisation of nodal irradiation among high-TIL patients may reflect differences in disease biology or treatment planning based on a favorable immune contexture. Notably, neither NLR nor TILs correlated with nodal metastasis or chemotherapy use, reinforcing their independent value as immunologic indicators rather than reflections of traditional clinicopathologic variables. When correlated with IBTR, pre-RT NLR showed a non-significant trend toward higher values among patients who

developed recurrence, whereas TILs demonstrated no significant association. While this trend suggests that systemic inflammation may predispose to poorer local control, the lack of statistical significance could stem from the modest sample size or biological heterogeneity within the cohort. Previous reports have linked elevated NLR to inferior survival and recurrence outcomes [6,7], whereas higher TIL levels have been associated with a favourable prognosis, particularly in TNBC [10]. The current findings partially align with these trends, but the absence of robust associations underscores the complexity of immune-tumour interactions and the potential need to assess immune biomarkers in conjunction with temporal dynamics and additional parameters such as PD-L1 expression, T-cell clonality, and cytokine profiles [11]. Post-treatment immune marker analysis revealed no significant correlation with IBTR, suggesting that the immune alterations immediately following RT may represent a transient, adaptive state rather than a sustained determinant of recurrence risk. These findings integrate into the broader context of breast cancer immunobiology, where the immune system exerts dual roles in tumour control and progression. Radiotherapy has been shown to activate the cGAS-STING pathway, enhancing antigen presentation and priming of cytotoxic T cells, thereby potentiating anti-tumour immunity [8,9,12]. Conversely, radiation-induced lymphopenia and stromal remodelling may dampen immune surveillance and promote immune escape [12]. Understanding the temporal balance between these immune-stimulatory and suppressive effects is critical for optimising combined-modality approaches. In particular, the evolving synergy between radiotherapy and immunotherapy offers promising avenues for augmenting local control and systemic response, especially in aggressive subtypes such as TNBC, which are inherently more immunogenic [10,13]. The study's limitations include a relatively small sample size and a single-institution design, which may limit the generalizability of the findings. Dichotomizing continuous biomarkers such as NLR and TILs can also obscure subtle gradations and nonlinear relationships with outcomes. Nonetheless, the consistent trends observed provide a biologically plausible foundation for future research. Prospective multicenter studies incorporating larger cohorts and longitudinal immune profiling are warranted to validate these observations. Integration of advanced immune assays—including checkpoint molecule expression, T-cell repertoire analysis, and multiplex immunohistochemistry—could elucidate functional immune shifts in response to RT. Additionally, combining immune biomarkers with Radiogenomic and imaging signatures could enhance the precision of recurrence-risk prediction [8,11]. The emerging understanding of immune biomarkers such as NLR and TILs heralds a paradigm shift in personalized breast cancer management. Comprehensive immune profiling may enable more refined patient selection for treatment de-escalation or intensification strategies. Patients with favourable immune signatures, characterised by low systemic inflammation and robust intratumoral immunity, may be candidates for de-escalation approaches such as omission of regional nodal irradiation or partial breast irradiation, minimising treatment-related toxicity without compromising oncologic outcomes [10,13]. Conversely, patients with unfavourable immune profiles—high NLR and low TILs—may benefit from intensified systemic therapy or incorporation of immunomodulatory agents, including immune checkpoint inhibitors or radiosensitizers, to overcome immune suppression and enhance RT efficacy [8,9]. Dynamic monitoring of NLR and TILs throughout treatment could further guide adaptive therapy modification, aligning with the principles of response-adaptive radiotherapy. Ultimately, integrating immune biomarkers into breast cancer care pathways has the potential to refine risk stratification, personalise radiotherapy delivery, and improve long-term outcomes, advancing biologically informed precision oncology [13].

5. CONCLUSION

This study highlights the dynamic immunologic modulation induced by radiotherapy in breast cancer, characterised by a significant post-treatment increase in systemic inflammation, reflected by elevated neutrophil-to-lymphocyte ratio (NLR), and a concomitant reduction in local immune activity, evidenced by decreased tumour-infiltrating lymphocytes (TILs). The distinct associations of high pre-treatment NLR with hormone receptor–positive luminal subtypes and increased regional nodal irradiation, alongside elevated TILs in hormone receptor–negative, triple-negative tumours, underscore the heterogeneity of tumour–immune interactions that shape therapeutic responses. Although neither pre-radiotherapy NLR nor TILs achieved statistical significance in predicting ipsilateral breast tumor recurrence, their consistent biological trends and contextual relevance suggest complementary value in immune-based risk stratification. Integrating these markers with molecular and genomic classifiers could refine patient selection for adaptive treatment strategies—enabling radiotherapy de-escalation in immunologically favorable profiles or immunotherapy augmentation in immunosuppressed phenotypes. Prospective validation through multi-institutional studies with longitudinal immune monitoring is warranted to establish NLR and TILs as clinically actionable biomarkers, guiding personalised radiotherapy planning and advancing precision oncology in breast cancer care.

Statements

Statement of Ethics: This study protocol was reviewed and approved by the Institutional Ethics Committee, Kidwai Memorial Institute of Oncology, Bengaluru, India (Approval No: KMIO/MEC/2023/04/PG/RO/46).

Consent to participate statement: Written informed consent was obtained from all participants before inclusion in the study.

Conflict of Interest: The author declares no conflict of interest.

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Author Contributions

Rahul Thirugnanam: Conceptualisation, methodology, data collection, data analysis, manuscript drafting, and final approval.
Gomathi Meenashki: Clinical supervision, surgical data acquisition, manuscript review.
V. Nandhini: Clinical inputs, surgical data acquisition, critical revision of the manuscript.
Priya Darshini: Data curation, statistical assistance, manuscript editing.
Vijayath B. R.: Supervision, interpretation of findings, manuscript review and final approval. All authors have read and approved the final version of the manuscript.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request. Due to patient confidentiality and institutional policy, the datasets are not publicly available.

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REFERENCES

1. Ethier JL, Desautels D, Templeton A, Shah PS, Amir E. Prognostic role of neutrophil-to-lymphocyte ratio in breast cancer: a systematic review and meta-analysis. *Breast Cancer Res*. 2017;19(1):5. doi:10.1186/s13058-016-0794-1
2. De Caluwé A, Bellal S, Cao K, Peignaux K. Adapting radiation therapy to immunotherapy: delineation and treatment planning of pre-operative immune-modulating breast iSBRT in 151 patients treated in the randomized phase II Neo-CheckRay trial. *Radiother Oncol*. 2025;166:110836. doi:10.1016/j.radonc.2025.110836
3. Gunster JLB, Groen EJ, Salgado R. Tumor-infiltrating lymphocytes and preoperative partial breast irradiation in early-stage breast cancer: insights from the prospective PAPBI cohort. *Int J Radiat Oncol Biol Phys*. 2025;[Epub ahead of print]. doi:10.1016/j.ijrobp.2025.08.058
4. Galluzzi L, Bolini L, Shulman RM. Radiation therapy as a biological modifier of the breast cancer immune microenvironment. *npj Breast Cancer*. 2025;11:84. doi:10.1038/s41523-025-00801-3
5. Finkelman BS, Zhang H, Hicks DG, Rimm DL, Turner BM. Tumor infiltrating lymphocytes in breast cancer: a narrative review with focus on analytic validity, clinical validity, and clinical utility. *Hum Pathol*. 2025;162:105866. doi:10.1016/j.humpath.2025.105866
6. Huang Z, Fu Z, Huang W, Huang K. Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: a meta-analysis. *Am J Emerg Med*. 2020;38(3):641–7. doi:10.4266/acc.003576
7. Colangelo NW, Gerber NK, Vatner RE, Cooper BT. Harnessing the cGAS-STING pathway to potentiate radiation therapy: current approaches and future directions. *Front Pharmacol*. 2024;15:10.3389/fphar.2024.1383000. doi:10.3389/fphar.2024.1383000
8. Kho VM, Mekers VE, Span PN, Bussink J, Adema GJ. Radiotherapy and cGAS/STING signaling: impact on MDSCs in the tumor microenvironment. *Cell Immunol*. 2021;362:104298. doi:10.1016/j.cellimm.2021.104298
9. Fenton M, Yoneyama M, Wennerberg E, Lund T, Tutt A, Melcher A. The untapped potential of radiation and immunotherapy for hormone receptor-positive breast cancer. *npj Breast Cancer*. 2025;11:24. doi:10.1038/s41523-025-00796-x
10. Zhang J, Yu S, Peng Q, Wang P, Fang L. Emerging mechanisms and implications of cGAS-STING signaling in cancer immunotherapy strategies. *Cancer Biol Med*. 2024;21(1):1–20.
11. Storozynsky Q, Hitt MM. The impact of radiation-induced DNA damage on cGAS-STING-mediated immune responses to cancer. *Int J Mol Sci*. 2020;21:8877. doi:10.3390/ijms21228877
12. Heshmat-Ghahdarijani K, Sarmadi V, Heidari A, Marvasti AF, Neshat S, Raeisi S. The neutrophil-to-lymphocyte ratio as a new prognostic factor in cancers: a narrative review. *Front Oncol*. 2023;13:1228076. doi:10.3389/fonc.2023.1228076
13. McGuinness C, Britt KL. Estrogen receptor regulation of the immune microenvironment in breast cancer. *J Steroid Biochem Mol Biol*. 2024;240:106517. doi:10.1016/j.jsbmb.2024.106517

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