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Research Article

Molecular and Immunophenotypic Modulation Induced by Radiotherapy in Breast Carcinoma

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Abstract

Breast cancer remains one of the most significant causes of morbidity and mortality among women worldwide. Beyond its therapeutic role, radiotherapy (RT) may induce biological alterations that modify hormonal receptor expression and HER2 amplification. This study evaluated 152 breast carcinomas diagnosed at the University Hospital Center 'Mother Teresa' (2023–2025), comparing pre and postradiotherapy profiles using IHC and SISH. Findings reveal marked immunophenotypic plasticity, including ER/PR downregulation and HER2 amplification. Molecular insights suggest that radiation induced oxidative stress, genomic instability, and epigenetic remodeling drive these changes. Understanding RT induced reprogramming is essential for optimizing post treatment therapeutic decisions.

Keywords: breast carcinoma; radiotherapy; hormone receptors; HER2; immunophenotypic modulation; epigenetics; oxidative stress

1. Introduction

Breast carcinoma is a biologically diverse disease characterized by significant heterogeneity in clinical behavior, therapeutic response, and prognosis. Molecular sub classification, based primarily on ER, PR, and HER2 expression, forms the foundation of treatment algorithms. Luminal tumors generally benefit from endocrine therapy, whereas HER2 positive tumors respond to HER2 targeted therapies. Triple-negative breast cancer (TNBC) remains therapeutically challenging due to the absence of actionable receptors.

Radiotherapy plays a central role in breast conserving surgery and loco regional control. However, emerging evidence suggests that RT is more than a local cytotoxic intervention. Ionizing radiation generates reactive oxygen species (ROS), induces

double-strand DNA breaks, and activates downstream stress response pathways. These changes can disrupt the expression of key oncogenes and tumor suppressors, leading to a shift in the tumor's molecular profile.

Experimental models indicate that RT modulates ESR1, PGR, and ERBB2 expression through both transcriptional and epigenetic mechanisms. Notably, radiation has been associated with downregulation of ER/PR and upregulation of HER2, possibly reflecting clonal selection or adaptive resistance. Such alterations may shift tumors from hormone sensitive to more aggressive phenotypes, complicating post treatment decisions.

The objective of this study is to characterize RT induced molecular and immunophenotypic modulation in 152 breast carcinoma cases, offering a detailed analysis of phenotype shifts and their implications for treatment.

2. Materials and Methods

This study included 152 patients diagnosed with breast carcinoma between 2023–2025 at the University Hospital Center 'Mother Teresa'. Paired biopsy samples obtained before and after radiotherapy were analyzed.

Immunohistochemistry was performed on FFPE tissue using Ventana BenchMark XT and UltraPlus systems. ER and PR were considered positive at ≥1% nuclear staining. HER2 was scored from 0 to 3+, with SISH used for equivocal 2+ cases to determine gene amplification with improved precision.

Statistical analysis employed SPSS v28. Receptor modulation was assessed using descriptive statistics and Pearson's χ^2 test to evaluate the significance of changes between pre and post treatment receptor status.

3. Results

RT induced receptor modulation was evident across multiple biomarkers. ER decreased in 9.2% of cases and increased in 0.7%. PR decreased in 26.3% and increased in 9.2%. HER2 negativization occurred in 17.8%, while HER2 positivization was found in 16.4%.

The χ^2 test ($\chi^2 = 5.86$; $p = 0.015$) confirmed a statistically significant association between RT exposure and receptor profile alteration, supporting the hypothesis that RT contributes to molecular phenotype switching.

4. Discussion

This analysis reinforces the multifaceted biological impact of RT on breast carcinoma. Ionizing radiation drives genomic instability through DNA double-strand breaks, which activate ATM/ATR signaling cascades, p53-mediated transcriptional changes, and chromatin remodeling. These processes collectively influence receptor gene expression.

RT also affects tumor cell metabolism, mitochondrial function, and homeostasis. Increased oxidative stress alters protein stability, receptor turnover, and intracellular signaling. HER2 upregulating post RT may reflect a survival advantage under oxidative pressure, consistent with HER2's known role in stress resistance and proliferation.

Epigenetic alterations represent another mechanism underlying receptor modulation. Studies suggest that methylation of ESR1 and PGR promoters increases after RT, leading to reduced ER/PR expression. Conversely, HER2 gene accessibility may increase through chromatin opening, enhancing transcription and protein expression.

Clinically, RT induced phenotypic shifts have significant implications. A tumor initially classified as luminal may transition toward HER2 positive or triple negative phenotype post treatment, altering therapeutic options. If receptor status is not reassessed, inappropriate endocrine or targeted therapy may be administered, reducing treatment efficacy.

This study aligns with previous findings by Michmerhuizen et al. (2022), Fenton et al. (2025), and Zhang et al. (2024), all of which emphasize RT's capacity to induce plasticity and select for resistant clones. Understanding this phenomenon is essential for precision oncology.

5. Limitations and Future Directions

Limitations include concomitant systemic therapies that may confound the molecular effects attributed solely to radiotherapy.

6. Conclusion

Radiotherapy induces significant molecular and immunophenotypic changes in breast carcinoma, influencing ER, PR, and HER2 expression patterns. Routine reassessment of receptor status after RT is essential for accurate molecular classification and optimal therapeutic planning. A deeper understanding of RT driven reprogramming will advance personalized oncology.

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