REVIEW ARTICLE

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The Impact of Chemoradiation Therapy on Serum Biomarkers in Breast Cancer Patients: A Review of Prognostic and Predictive Dynamics

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Abstract

Background: Chemoradiation therapy (CRT) is fundamental for treating locally advanced and high-risk breast cancer. Although effective, it significantly impacts systemic physiology, which can be tracked through fluctuations in serum biomarkers. This review consolidates existing research on how CRT affects circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), inflammatory cytokines, and tissue injury markers, assessing their value for predicting outcomes and guiding treatment.

Methods:A systematic search of PubMed, Embase, Scopus, and Web of Science was conducted for studies to 2025. Keywords included "breast cancer," "chemoradiation," "serum biomarker," "ctDNA," "CTC," and related terms. Eligible studies reported serum biomarker levels in breast cancer patients before, during, or after CRT and linked them to clinical results.

Results: Analysis of studies indicates that CRT causes a predictable but individualized alteration in serum biomarkers. A swift decrease in CTCs and ctDNA levels during neoadjuvant or definitive CRT strongly correlates with pathological complete response (pCR) and better survival. In contrast, detectable ctDNA after treatment is a powerful indicator of minimal residual disease (MRD) and impending relapse. Inflammatory markers such as IL-6 and CRP generally increase during therapy; prolonged elevation is linked to poorer prognosis and greater toxicity. Additionally, biomarkers like high-sensitivity Troponin I and TGF-β1 enable early identification of subclinical cardiotoxicity and radiation-induced skin damage, respectively.

Conclusion: Serum biomarkers offer a real-time, dynamic reflection of tumor response and host toxicity during CRT. Incorporating liquid biopsy components (CTCs, ctDNA) and host-response markers into clinical practice shows great potential for personalizing treatment, facilitating early intervention, and enhancing long-term results. Prospective studies are urgently required to standardize testing methods and confirm their clinical utility in guiding treatment strategies.

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Introduction

The management of breast cancer has increasingly shifted toward a multimodal and personalized strategy [1]. For individuals with locally advanced disease, inflammatory presentations, or high-risk postoperative features, combined chemotherapy and radiotherapy—administered sequentially or concurrently as chemoradiation therapy (CRT)—forms a treatment cornerstone [2,3]. The synergistic effect of cytotoxic drugs (e.g., anthracyclines, taxanes) and radiation improves local tumor control and eliminates micrometastases, leading to better survival outcomes [4,5].

However, this potent combination has effects that reach beyond the primary tumor site. CRT triggers a complex cascade involving tumor cell death, changes in the tumor microenvironment (TME), and a systemic inflammatory and immune reaction [6,7]. Traditionally, treatment response has been evaluated using anatomical imaging (e.g., MRI, CT) and post-surgical pathology [8]. While crucial, these approaches are limited by their static nature, invasiveness, inability to reflect real-time biological changes, and low sensitivity for detecting early treatment failure or MRD [9]. Analyzing serum biomarkers provides a transformative, minimally invasive "liquid biopsy" of this intricate process [10]. Blood-based markers can be monitored sequentially to give a comprehensive, dynamic picture of:

- **Tumor Burden and Genomics:** Through ctDNA and CTCs [11,12].
- **Systemic Inflammation and Immune Response:** Through cytokines (e.g., IL-6, TNF-α) and acute-phase proteins (e.g., CRP) [13,14].
- **Normal Tissue Toxicity:** Through specific indicators of cardiac (Troponins, BNP), skin (TGF-β1), and blood-related injury [15,16].

This review aims to systematically summarize and critically assess current evidence regarding the influence of CRT on these diverse serum biomarker categories in breast cancer patients. It explores their roles in predicting treatment effectiveness, monitoring therapeutic response, forecasting recurrence, and managing treatment-related side effects, thereby outlining a path toward more personalized and predictive oncology.

Methods

Search Strategy and Selection Criteria

A literature review was performed according to PRISMA guidelines [17]. PubMed, Embase, Scopus, and Web of Science were searched for relevant studies published from 2025. The search used a mix of Medical Subject Headings (MeSH) terms and keywords . Inclusion was based on PICOS criteria: Adult patients with confirmed breast cancer,Concurrent or sequential CRT.

- **Outcomes:** Quantitative serum biomarker measurements correlated with cancer outcomes or toxicity.
- **Study Design:** Prospective or retrospective cohort studies, clinical trials.

Reviews, case reports, editorials, and studies lacking original data or clear CRT correlation were excluded (18).

Results

Dynamics of Tumor-Derived Biomarkers

- **Circulating Tumor DNA (ctDNA):** The prognostic value of ctDNA is well-established. A key study by Garcia-Murillas et al. showed that detecting ctDNA after CRT and surgery was the strongest predictor of relapse, preceding clinical recurrence by up to 11 months [19], a finding repeatedly confirmed [20,21]. The speed of ctDNA clearance is also predictive; for example, the rate of clearance after the first neoadjuvant chemotherapy cycle independently predicted pCR [22]. In definitive CRT for locally advanced breast cancer, a >50% reduction in ctDNA levels by mid-treatment correlates with better local control [23].
- **Circulating Tumor Cells (CTCs):** The presence of CTCs before starting CRT is consistently linked to worse disease-free and overall survival [24,25]. A meta-analysis confirmed a pooled hazard ratio of 2.15 for reduced disease-free survival [26]. Dynamic changes matter significantly; patients who clear CTCs after neoadjuvant chemotherapy have markedly better 3-year disease-free survival compared to those with persistent CTCs [27]. Phenotypic analysis of CTCs, such as the appearance of PD-L1 positive cells during CRT, is being studied as a dynamic marker of adaptive immune resistance [28,29].

Modulation of Inflammatory and Immune Biomarkers

- **Cytokines and Acute-Phase Proteins:** A consistent, notable increase in pro-inflammatory cytokines like IL-6, TNF-α, and IL-1β occurs during CRT [30,31]. A prospective study linked a >5-fold rise in IL-6 during radiotherapy with severe fatigue and reduced quality of life [32]. Elevated pre-treatment CRP is an independent negative prognostic factor for overall survival in patients receiving adjuvant CRT [33]. The CRP-to-albumin ratio is also emerging as a composite marker of inflammation and nutrition, with higher ratios predicting poorer outcomes [34].

- **Soluble Immune Checkpoints and Exosomes:** Soluble PD-L1 levels increase during radiotherapy, possibly reflecting a radiation-induced immune escape mechanism [35]. Recent research suggests high post-CRT soluble PD-L1 may identify triple-negative breast cancer patients who could benefit from added immunotherapy [36]. Additionally, tumor-derived exosomes with immunosuppressive content increase during CRT and may contribute to treatment resistance [37].

Biomarkers of Treatment-Induced Toxicity

- **Cardiotoxicity:** Monitoring high-sensitivity cardiac Troponin I and B-type Natriuretic Peptide is vital for early detection [38]. A pivotal study found early rises in Troponin I during anthracycline-based chemotherapy predicted subsequent heart dysfunction in patients, many of whom also received radiotherapy [39]. The combination of left-sided radiotherapy and certain chemotherapies creates high risk, warranting serial Troponin monitoring [40].
- **Radiation Dermatitis and Fibrosis:** Beyond clinical assessment, serum Transforming Growth Factor-beta 1 levels have predictive value. Patients with a >50% increase in TGF-β1 by the third radiotherapy week had a significantly higher rate of significant skin reactions and subsequent breast fibrosis [41]. Other markers like IL-37 and MMP-9 are also under investigation [42,43].
- **Hematological and Hepatic Toxicity:** While blood counts monitor bone marrow toxicity, markers like serum amyloid A have been associated with myelosuppression severity [44]. Liver enzymes are routinely tracked; glutathione S-transferase is being explored as a more sensitive marker for hepatic radiation injury [45].

Discussion

This review assembles strong evidence that CRT causes a highly dynamic and clinically informative change in the serum biomarker profile of breast cancer patients. Shifting from static, anatomical evaluations to dynamic, molecular monitoring represents a major change in oncology, providing a "real-time snapshot" of the disease and the body's treatment response [46]. The most significant progress lies in liquid biopsy. The capacity of ctDNA to identify MRD and predict recurrence well in advance offers a unique chance for early intervention in trials [47,48]. Similarly, real-time tracking of ctDNA and CTCs during therapy could guide treatment adjustments, allowing for therapy intensification in poor responders or reduction in rapid responders to avoid unnecessary toxicity [49,50]. Furthermore, incorporating host-response biomarkers adds a crucial layer for personalizing quality-of-life and long-term health management. Proactively identifying patients at high risk for cardiotoxicity or severe skin reactions using serum Troponins or TGF-β1 enables preventive measures like closer heart monitoring, cardioprotective medications, or advanced skin protectants [51,52]. This shifts supportive care from reactive to proactive.

Despite promise, several obstacles remain before widespread clinical use. Lack of assay standardization is a major barrier; ctDNA detection methods and positivity thresholds vary widely [53,54]. Cost and access also limit implementation, especially in resource-limited settings [55]. Biological complexity is another challenge; distinguishing tumor signals from treatment-related clonal hematopoiesis or inflammation requires advanced bioinformatics [56].

Future investigations should prioritize:

1. **Large, Prospective Validation:** Multi-center trials to validate biomarker-guided treatment decisions [57,58].
2. **Assay Standardization:** Consensus guidelines for liquid biopsy processing and reporting [59].
3. **Integration with Multi-Omics:** Combining serum biomarkers with radiomics and tissue-based data for comprehensive predictive models [60,61].
4. **Exploring Novel Biomarkers:** Investigating other markers like circulating microRNAs, platelet-bound RNA, and the microbiome in CRT response and toxicity [62,63].
5. **Focus on Health Disparities:** Ensuring biomarker research and application are equitable across diverse populations [64].

Conclusion

The array of serum biomarkers in breast cancer patients undergoing CRT is rich with prognostic and predictive information. Interpreting tumor-derived (ctDNA, CTCs) and host-derived (cytokines, tissue damage markers) signals together provides a holistic, real-time view of the interaction between treatment, tumor, and patient. As these tools are refined and validated in prospective trials, the future of breast cancer management will involve using this dynamic molecular feedback to personalize chemoradiation truly, maximizing effectiveness while protecting patient well-being and quality of life.

AI Use Declaration

Artificial intelligence tools were used minimally (~15%) during manuscript editing to enhance language clarity. All content generation, data analysis, interpretation, and writing were performed by the authors. AI was not used to create content, analyze data, or interpret results

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The authors contributed to the data analysis. Drafting, revising and approving the article, responsible for all aspects of this work.

Conflict of Interest

None

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