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*Original Research Article*

# Evaluating Early Versus Delayed Radiotherapy Initiation and Its Impact on Recurrence Risk in TNBC Patients

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***Abstract***: ***Background:*** Triple-negative breast cancer (TNBC) is a high-risk subtype that has a high probability of early recurrence. Although adjuvant radiotherapy is known to minimize local recurrence, it is unclear when adjuvant radiotherapy should be administered. ***Objective:*** To compare the effect of early and delayed radiotherapy on recurrence risk and recurrence-free survival in TNBC patients. ***Methods:*** This was a retrospective comparative study in which the medical records of 200 TNBC patients who underwent surgery and then adjuvant radiotherapy were reviewed from 1st January 2022 to 1st January 2025. Patients were divided into early (<8 weeks) and delayed (9 weeks and above) radiotherapy groups. The baseline demographics, tumor characteristics, treatment details, and outcomes of recurrence were obtained. Data analysis was done using SPSS 25.0. Chi-square and t-tests were used to compare them. Kaplan-Meier analysis and log-rank test were used to determine recurrence-free survival, and Cox proportional hazards regression was conducted to determine independent predictors of recurrence. ***Results:*** Among 200 patients, a delay in radiotherapy indicated a much increased overall recurrence rate ($p = 0.004$) and shorter recurrence-free time ($p = 0.012$). On multivariate analysis, delayed radiotherapy ($p = 0.013$) and Stage III disease ($p = 0.022$) was independent predictive factors of recurrence. ***Findings:*** Timely radiotherapy is crucial since the late introduction of radiotherapy in TNBC leads to high chances of recurrence. Priorities should be placed on early radiotherapy to enhance the oncologic outcomes.

*Keywords*: Triple-negative breast cancer, Radiotherapy timing, Recurrence, Recurrence-free survival, Retrospective cohort

## INTRODUCTION

Triple negative breast cancer (TNBC) refers to a unique and aggressive molecular phenotype of breast cancer that is characterized by the lack of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2)

 

expression.[1, 2] TNBC, which is present in about 10-15% of all invasive breast cancer cases, is overrepresented in young women and is characterized by high histologic grade and rapid proliferation, and a lack of target treatment therapy (in comparison to other types, such as hormone receptor positive or HER2 positive).[3]

TNBC is clinically associated with an increased risk of early recurrence and the reduction in the long-term outcome.[4] The recurrence rate of TNBC is the highest in the first 2-3 years after diagnosis, with distant metastasis and locoregional relapses being earlier and more frequent than in other breast cancer subtypes.[5] Although there is progress in systemic therapies, such as using combinations of chemotherapy and immune checkpoint inhibitors, locoregional control is an important element of multimodal therapy. Postoperative radiotherapy (either breast conserving surgery or mastectomy) is a normative procedure aimed at eliminating residual microscopic disease and decreasing the risk of recurrence, especially in high-risk disease.[6]

It has been demonstrated that the timing of treatment in TNBC affects outcomes.[7] Although the period between adjuvant chemotherapy and radiotherapy is the most studied area of the literature, which has shown that the delay in adjuvant radiotherapy initiation correlates with poorer survival and increased risk of relapse, especially in higher-grade subtypes, such as TNBC, the sequence of adjuvant radiotherapy and timing relative to other modalities is less clearly defined.[8, 9] In the case of chemotherapy, retrospective analyses show that waiting more than 30-60 days after surgery is associated with a higher recurrence and reduced survival of TNBC patients.[10] Equally, there is evidence to indicate that long intervals to radiotherapy can minimise local control, but the data regarding survival effects are inconsistent and difficult to produce in a randomised study due to ethical considerations.[8, 11]

TNBC is a very aggressive form of breast cancer with a proven tendency to recur at an early stage and have low survival rates.[5] Although radiotherapy achieves great success in the localization of the disease, its time of initiation is yet to be established, especially in the scenario of invasive tumors such as TNBC. Radiotherapy started early has a chance of eliminating residual microscopic disease before it will have time to expand and treatment delayed may permit tumors to repopulate and raise the risk of recurrence. Although its clinical significance is acknowledged, there is a lack of strong evidence to specifically refer to the timing of radiotherapy in TNBC. This research thus aims to address this knowledge gap of high priority as it will examine whether early or delayed radiotherapy has any significant value in terms of recurrence risk, which can serve as a possible clue to sequence the treatment strictly and enhance the survival rates among high-risk patient populations. The purpose of the current study was to determine the difference in recurrence risk between patients with triple-negative breast cancer (TNBC) when they start radiotherapy early or late.

## Methods

A retrospective comparative study design was used in this study. The research was conducted in the Department of Oncology at the Hospital. The reviews of the medical records of patients with the histologically proven triple-negative breast cancer (TNBC) surgery followed by adjuvant radiotherapy were examined. This was done to include patients who were treated between 1st January 2022 and 1st January 2025 so that the follow-up period would be at least 3 years to ascertain the outcomes of recurrence. The study received an ethical approval by the Institutional Review Board of _____.

The institutional administration gave permission to access the hospital records. The confidentiality of the patients was preserved, and all the data were anonymized. The study required the use of records as it was a retrospective review, therefore informed consent was not required according to the institutional policy.

Eligible records that were accessible within the study period were used and the minimum requirement of about 200 patients was achieved. A non-probability consecutive method was employed. All TNBC patients meeting the inclusion criteria and with full treatment and follow-up records were enlisted. The inclusion criteria were as follows: females aged 18 years or older; history of triple-negative breast cancer (ER-negative, PR-negative, and HER2-negative); breast-conserving surgery or mastectomy; adjuvant radiotherapy; and 2 years or longer follow-up. The exclusion criteria were: metastatic disease on initial presentation, a history of other malignancy, radiotherapy to the chest wall or breast, incomplete treatment record or absence of follow-up data or loss to follow-up within 1 year of radiotherapy.

Hospital tumor registry files, oncology clinic files, radiotherapy department files, and follow-up charts were surveyed through a structured data extraction form to gather information and data. Demographic information (age, residence), tumor information (tumor size, nodal status, stage, grade), the type of surgery, the use of neoadjuvant or adjuvant chemotherapy, and the radiotherapy information were documented. It was the time interval between surgery to the start of radiotherapy and this was determined in weeks, and the patients were divided into early radiotherapy and delayed radiotherapy groups based on the pre-determined cut-offs based on the prior literature. Results of recurrence, such as

locoregional recurrence, distant metastasis, and time to recurrence, were obtained during follow-up visits, imaging, and oncology reports.

Data analysis was done through SPSS version 25 (IBM Corp., Armonk, NY). The descriptive statistics were performed, summarizing quantitative variables in the form of mean ± standard deviation and categorical variables in the form of frequencies and percentages. Chi-square test or independent t-test was used to compare baseline characteristics of early and late radiotherapy groups. The Kaplan-Meier survival analysis was used to evaluate recurrence-free survival, and the log-rank test was used to evaluate differences between groups. To determine the hazard ratios with a 95% confidence interval, Cox proportional hazards regression analysis was conducted by including possible confounders such as age, tumor stage, nodal status, type of surgery, and chemotherapy. A 0.05 p-value was regarded as statistically significant.

## RESULTS

This involved 200 patients with triple-negative breast cancer, where 100 had undergone early radiotherapy, and 100 had undergone delayed radiotherapy. The average age of the population under study was 48.6 ± 9.2 years, with no significant difference between populations. The majority of patients lived in the urban regions (64%), and the status of residence was not different between the groups. The incidence of Stage I-II was much higher in the early radiotherapy group than the delayed group ($p = 0.041$). Patients who were getting delayed radiotherapy were more likely to get node-positive disease, but this was not statistically significant. Most patients had a mastectomy (54%), and there was high uptake of chemotherapy in both arms of treatment, with no significant difference. These results demonstrate that the two groups were mostly similar at baseline with minor differences in the distribution of tumor stages (Table 1).

**Table 1. Baseline demographic and clinical characteristics of study participants (N = 200)**

| Variable | Total n (%) | Early RT n = 100 | Delayed RT n = 100 | p-value |
|---|---|---|---|---|
| **Age (years), mean ± SD** | 48.6 ± 9.2 | 47.9 ± 8.8 | 49.3 ± 9.6 | 0.312 |
| **Residence** | | | | |
| Urban | 128 (64.0%) | 66 (66.0%) | 62 (62.0%) | 0.569 |
| Rural | 72 (36.0%) | 34 (34.0%) | 38 (38.0%) | |
| **Tumor Stage** | | | | |
| Stage I–II | 122 (61.0%) | 68 (68.0%) | 54 (54.0%) | 0.041* |
| Stage III | 78 (39.0%) | 32 (32.0%) | 46 (46.0%) | |
| **Nodal Status** | | | | |
| Node-negative | 84 (42.0%) | 48 (48.0%) | 36 (36.0%) | 0.084 |
| Node-positive | 116 (58.0%) | 52 (52.0%) | 64 (64.0%) | |
| **Type of Surgery** | | | | |
| Breast-conserving | 92 (46.0%) | 50 (50.0%) | 42 (42.0%) | 0.248 |
| Mastectomy | 108 (54.0%) | 50 (50.0%) | 58 (58.0%) | |
| **Chemotherapy Received** | 178 (89.0%) | 92 (92.0%) | 86 (86.0%) | 0.182 |

The average period of postoperative time to radiotherapy therapy was found to be 6.2 ± 1.4 weeks in the early radiotherapy group and 12.7 ± 3.1 weeks in the delayed radiotherapy group, and the difference was very significant ($p < 0.001$). The design ensured that all the patients in the early radiotherapy group started treatment in eight weeks of surgery, and all the patients in the delayed group started radiotherapy after nine weeks or later. This categorical division of the timing categories permitted the effective comparison of the results of the two exposure groups (Table 2).

**Table 2. Radiotherapy timing characteristics**

| Variable | Early RT n = 100 | Delayed RT n = 100 | p-value |
|---|---|---|---|
| **Interval from surgery to RT (weeks), mean ± SD** | 6.2 ± 1.4 | 12.7 ± 3.1 | <0.001* |
| **RT within ≤8 weeks** | 100 (100%) | 0 (0%) | |
| **RT ≥9 weeks** | 0 (0) | 100 (100%) | |

At the follow-up period, the outcomes of recurrence were significantly different across groups. There was an overall recurrence of 12% of patients who received early radiotherapy as opposed to 28% of those who received delayed radiotherapy (p = 0.004). The locoregional recurrence and distant metastasis were more common in the delayed radiotherapy group (14% each) than in the early radiotherapy group (6% each), and the differences were statistically significant (p = 0.049 in both cases). The proportion of patients who never recurred was higher in the early radiotherapy group (88% vs. 72%), implying that their protective value of timely initiation of treatment was of clinical significance (Table 3).

**Table 3. Recurrence outcomes during follow-up**

| Outcome | Early RT n = 100 | Delayed RT n = 100 | p-value |
|---|---|---|---|
| **No recurrence** | 88 (88.0%) | 72 (72.0%) | 0.006* |
| **Locoregional recurrence** | 6 (6.0%) | 14 (14.0%) | 0.049* |
| **Distant metastasis** | 6 (6.0%) | 14 (14.0%) | 0.049* |
| **Overall recurrence (any)** | 12 (12.0%) | 28 (28.0%) | 0.004* |

The Kaplan-Meier survival analysis revealed that patients who underwent early radiotherapy had a better recurrence-free survival rate than those who had delayed radiotherapy. The early radiotherapy group had a mean recurrence-free survival time of 31.8 ± 4.6 months, while the delayed radiotherapy group had a mean recurrence-free survival time of 27.2 ± 6.1 months. The log-rank test revealed the difference between the survival curves to be statistically significant (p = 0.012), which implies that the later the radiotherapy commenced, the higher the cumulative incidence of recurrence with time. (Table 4)

**Table 4. Kaplan–Meier recurrence-free survival comparison**

| Group | Mean RFS (months) ± SD | Recurrence events n (%) | Log-rank p-value |
|---|---|---|---|
| **Early RT** | 31.8 ± 4.6 | 12 (12.0%) | |
| **Delayed RT** | 27.2 ± 6.1 | 28 (28.0%) | **0.012*** |

The multivariate Cox proportional hazards regression analysis found delayed radiotherapy to be an independent predictor of recurrence. The recurrence risk in patients who received radiotherapy after nine weeks or later was more than twofold higher than in those who received it earlier, after adjusting for age, tumor stage, nodal status, type of surgery, and the use of chemotherapy (p = 0.013). The Stage III disease was also found to be highly correlated with a higher risk of recurrence (p=.022). Other characteristics, such as age 50 years and above, nodal status, type of surgery, and receiving chemotherapy, were not statistically significant predictors in the adjusted model. These results highlight the prognostic effect of radiotherapy timing on recurrence among TNBC patients (Table 5).

**Table 5. Cox proportional hazards regression for predictors of recurrence**

| Variable | Adjusted HR (95% CI) | p-value |
|---|---|---|
| **Delayed RT (≥9 weeks)** | **2.18 (1.18–4.01)** | **0.013*** |
| Age ≥50 years | 1.24 (0.69–2.21) | 0.466 |
| Stage III disease | 1.96 (1.10–3.47) | 0.022* |
| Node-positive | 1.58 (0.91–2.74) | 0.102 |
| Mastectomy vs BCS | 1.12 (0.62–2.01) | 0.708 |
| Chemotherapy received | 0.72 (0.34–1.51) | 0.384 |

## DISCUSSION

Delayed radiotherapy initiation was found to be linked with a significantly increased risk of recurrence and worse recurrence-free survival than early radiotherapy with respect to patients with TNBC, which in turn supports the paramount importance of treatment in this aggressive form. These results coincide with a comprehensive range of evidence, which argues that adjuvant treatment is timely and can impact oncologic outcomes in TNBC and in general breast cancer conditions.

Even though most of the timing research has been done on chemotherapy as opposed to radiotherapy, parallels may be made. An extensive real-life cohort study reported that timing of administration of chemotherapy, especially neoadjuvant versus adjuvant therapy, had an impact on survival, with neoadjuvant therapy demonstrating some activity in patients who attained pathologic complete response (pCR). Timing is important even in local treatment options.[12]

The influence of radiotherapy in TNBC beyond timing itself has been studied in a number of studies. A meta-analysis on more than 5,000 TNBC patients that assessed the impact of adjuvant radiotherapy showed a major decrease in locoregional recurrence, although the overall survival benefits were inconsistent with respect to the stage and age group.[13] Other studies also elaborated that T and N stages and proliferative indexes such as Ki-67 were

notable predictors of survival following postoperative radiotherapy, supporting the fact that biologic and clinical state influences the outcome even when timing is alone.[14-17]

In particular, it has been reported that the timing of radiotherapy can be influential. In a high-risk breast cancer post-hoc analysis, it was found that greater delays between surgery/chemotherapy and radiotherapy were associated with inferior distant metastasis, disease-free, and overall survival, which further supports the clinical significance of minimizing delays in high-risk patient groups.[18] On the other hand, however, some observational evidence also indicates that the relationship between radiotherapy timings and radiation outcomes is not linear, with the earliest and latest timelines of radiotherapy showing very uneven success in predicting better outcomes across the broad range of clinical conditions, claiming that radiotherapy timelines may not be the critical factors in all clinical environments.[19]

Notably, the vast majority of the radiotherapy-timing literature is older than 2021; however, there is a consistent trend: the delay in adjuvant local or systemic therapy is usually associated with poorer recurrence outcomes, which is also true in the case of TNBC. Indicatively, retrospective TNBC cohort analyses have revealed that adjuvant chemotherapy initiation delay of more than 60 days was associated with a large relative risk at relapse (HR of about 2.4), which reflects the general concept that prompt initiation of definitive therapy by TNBC is more effective in disease control than delayed initiation.[20] This chemotherapy-based evidence is not specifically regarding radiotherapy, but it will contribute to the biological argument that aggressive tumor biology in TNBC cannot afford the long treatment lapse without the risk of recurrence.

Other cohort and registry studies introduce subtle insights concerning the timing of treatment. An example of timing and prognosis interaction is work that has been conducted regarding the timing of post-mastectomy radiotherapy after chemotherapy, which found that the interval greater than 42 days was linked to poorer distant metastasis and survival.[18] Interestingly, a few studies conducted on timing beyond the TNBC population have indicated that early radiotherapy might not necessarily offer better results, and therefore, the ideal time frame could be subject to a particular clinical situation.[19]

In addition to timing, recent innovations in the methods of radiotherapy, including protocols of hypofractionated or accelerated radiotherapy, were meant to balance between the treatment delivery optimization and the oncologic control. Although these methods are not specifically timing-related, they indicate changing attitudes toward making radiotherapy more effective, without increasing the risk of recurrence, and represent a more comprehensive clinical perspective of how to enhance the quality and timeliness of treatment. Altogether, our results of finding that delayed radiotherapy correlates with an increased probability of recurrence in TNBC are consistent with the biological aggressiveness of this subtype and prior literature concerning the timing of systemic therapy as well as local therapy. All of this evidence contributes to the importance of reducing treatment delays where feasible, personalizing timing decisions according to patient and tumor characteristics, and further study of the best sequencing of prospective studies.

**Limitations**

There are a few limitations to be considered in this study. It has a retrospective design, which is vulnerable to documentation bias, missing records, and unmeasured confounding factors, including comorbidity, socioeconomic status, or delayed treatment because of patient or system-related problems. Differences in surgical procedures, chemotherapy, and radiotherapy measures might have had effects, and recurrence measures were based on institutional records and were not centralized in terms of review, which may have underestimated subclinical events. Also, it is a single-center study, which restricts the generalizability, and molecular heterogeneity of TNBC, such as BRCA status and proliferative index, was not considered. Although the sample size is satisfactory, prospective multicenter trials are required to confirm such results and optimize the best timing of radiotherapy in TNBC.

## Conclusion

In this research, a late onset of radiotherapy among TNBC patients was diagnosed with a substantially increased chance of recurrence and reduced chances of survival without recurrence, highlighting the crucial role of administering radiotherapy in such a severe subtype. These results indicate that early radiotherapy is an important component of multidisciplinary care, which healthcare systems should prioritize and reduce the presence of barriers that lead to delays in treatment. These findings reinforce the international data that even small delays in adjuvant treatment can influence the outcome negatively, and, therefore, there is a necessity for simplified care mechanisms. The prospective multicenter trials in the future that involve molecular profiling and real-life treatment factors are vital in maximizing the individualized radiotherapy timing and enhancing survival rates among TNBC patients.

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