**Original Article**
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# Association of Postoperative Radiotherapy Delay with Relapse and Metastasis in Women with Breast Cancer Using Penalized Cox Regression

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## Abstract

**Background:** The impact of initiation time of radiotherapy after breast surgery on disease-free status of patient is a controversial issue. We assessed the relationship between the delay in adjuvant radiotherapy and surgery and relapse or metastasis-free survival in women with breast cancer taking heavy censoring into account.

**Method:** This was a historical cohort study on 284 patients with breast cancer, who underwent surgery between 2001 and 2007 and followed up until March 2017. The association of the duration between radiotherapy and surgery, as well as other demographic and clinical factors with occurrence of local relapse or metastasis of breast cancer was examined through penalized Cox regression modeling. The obtained data were analyzed using R 3.6.3.

**Results:** A total of 284 women with the mean age of 47.2 ± 11.3 years met the inclusion criteria. The maximum follow-up time was 11.1 years and the time between surgery and radiotherapy was 168 ± 84.3 days. About 10% of the patients experienced local relapse and 19% had metastasis. In multiple analysis of factors related to disease-free survival, the stage of disease was significant, while surgery to radiotherapy interval (≤180 days vs >180 days) did not have any significant impact on hazard of failure. Analysis of 3, 4, or 5 months of delay in radiation therapy did not imply any significant affects.

**Conclusion:** In the studied patients, the delay in radiotherapy initiation after surgery did not lead into outcomes of local relapse or metastasis.

***Keywords:*** Penalized Cox Regression, Breast neoplasm, Radiotherapy delay, Local relapse, Metastasis

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## Introduction

Worldwide, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death among females. About 2.1 million newly diagnosed female breast cancer cases were detected in 2018, which consisted almost 25% of all cancer cases. Furthermore, the major malignancy and the most frequent cause of cancer death in Iranian women is breast cancer; the number of new cases in 2018 was 13776 patients.[1] One of the specific characteristics of Iranian breast cancer patients is that they are one decade younger than their western counterparts.[2, 3] The results of randomized clinical trials showed that radiotherapy(RT) following breast-conserving surgery in breast cancer patients is associated with a significantly lower rate of local relapse.[4] There is a consensus on reducing the effectiveness of radiotherapy with an increasing number of clonogenic cancer cells. Such treatment should begin as soon after surgery as is practical.[5] On the other hand, the maximum safe time period between breast cancer surgery and the start of radiotherapy has not yet been established. Moreover, there are various reports on the impacts of timeliness of radiotherapy on the survival in breast cancer patients.[6-10] Survival modeling is an important approach to detect the risk factors in cancer studies. However, the use of routine methods such as the Cox regression model in the survival modeling of cancer datasets depends on the number of events.[11,12] It has been recommended that the number of events per variable (EPV) be between 10 to 20, as the number of EPV decreased, the regression coefficients become more biased.[13] When the number of EPV is less than 10, penalized regression methods, such as lasso, have been suggested for modeling the data.[14,15]

To the best of our knowledge, there are no studies on the timing of RT following breast surgery in Iranian breast cancer patients. Assessing the true impact of lag in RT following breast surgery is thus of paramount significance in terms of therapeutic decision-making, patient referral patterns, and patient counseling. Based on our findings, one of the characteristics of breast cancer was that the EPV was less than 10 for both the local relapse and distance relapse as an event of interest. Therefore, in this study, we aimed to assess the impact of delay in the initiation of RT on the local relapse and distance relapse-free survival of Iranian breast cancer patients via a lasso approach and comparing the results to a traditional Cox Regression model.

## Materials and Methods

This was a historical cohort study on females with definitive diagnosis of breast cancer, who underwent their first treatment at Ghaem Hospital or Omid Hospital of Mashhad University of Medical Sciences between 2001 to 2007 and were followed up to March 2017. The informed consent was obtained from all the participants. The dataset had no confidential information; however, the study protocol was approved by the Ethics Committee of the Mashhad University of Medical Sciences (IR.MUMS.REC.1398.096).

Herein, about 1000 women with early stage and locally advanced breast cancer were evaluated for adequate standard treatment, including chemotherapy, RT, hormone therapy, and targeted therapy. The patients were assessed depending on the type of surgery, stage of the disease, and hormonal receptors status.

Adjuvant chemotherapy indications in this study were determined as tumors larger than 0.5 to 1 cm in size or positive regional lymph nodes. The following regimens were considered for standard chemotherapy: 1.CMF (CTX, MTX,5FU) for six cycles; 2.AC (Doxorubicin, CTX) for four cycles in a very early stage of the disease; 3. AC (Doxorubicin, CTX) for four cycles followed by four cycles of taxanes; 4.TC (Docetaxel, CTX) for four cycles.

Patients with the following conditions became candidates for RT: 1. those with breast conserving surgery (BCS); 2. those with mastectomy with a tumor size of 5 cm or larger; 3. patients with regional lymph node metastasis with any kinds of surgery; 4. those with positive surgical margin. The standard dose of RT for the patients with BCS was 60 Gy (including 50 Gy to the whole breast with or without regional lymph nodes and

10 Gy for boost) and 50 Gy for whom with negative margin in mastectomy. The dose of RT in cases with positive margin were considered to be 60 to 66 Gy.

The subjects were included if they received adjuvant RT. If their dose of RT was unknown, they were excluded.

Totally, 284 patients, whose treatments were completed, entered the study. The patients were visited every 3 months in the first post-surgery year. Between the second and fifth year following the surgery, they were visited every 6 months and from the fifth year until the end of the follow-up, they were checked annually.

The dataset comprised demographic and clinical variables and all the information was extracted from the medical records of the subjects. Time to RT was defined as the interval between the surgery and the date of RT initiation. The patients were categorized based on the timing of RT initiation as equal or less than 6 months and more than 6 months. Other variables included in the analysis were the age at diagnosis, clinical stage of cancer (based on TNM system of the American Joint Committee on Cancer classification), time interval between the surgery to RT (classified as less or greater than 6 months), body mass index (BMI) (calculated through weight and height), diagnosis and hormone receptor status (estrogen and progesterone receptors (ER and PR)).

Two endpoints of interest were local relapse and distant metastasis. The time between the date of surgery to local relapse or distant metastasis were recorded. If a patient experienced neither of the above-mentioned events, their status would be considered as censored and the time of the last visit was recorded.

The analysis consisted of three parts in terms of local relapse, distant metastasis, and either of these two endpoints as event. In each part, we fitted both traditional Cox models as well as penalized Cox models, taking the heavy censoring into account.

### *Statistical analysis*

Since the number of events is much less than that of the censored data, we conducted the least absolute shrinkage and selection operator (LASSO) regression analysis.

**Table 1.** Patient and tumor characteristics

| Variable | Frequency(%) |
|---|---|
| **Age (years)** | |
| ≤ 45 | 137(48.2) |
| > 45 | 147(51.8) |
| **BMI (kg/m$^2$)** | |
| ≤ 30 | 191(67.3) |
| > 30 | 93(32.7) |
| **Clinical stage** | |
| I / II | 240(84.5) |
| III / IV | 44(15.5) |
| **Estrogen receptor** | |
| negative | 130(45.8) |
| positive | 154(54.2) |
| **Progesterone receptor** | |
| negative | 143(50.4) |
| positive | 141(49.6) |
| **Operation** | |
| BCS | 29(10.2) |
| MRM | 255(89.8) |
| **Time between surgery to radiotherapy** | |
| ≤ 180 days | 175(61.6) |
| > 180 days | 109(38.4) |

BMI: Body mass index, BCS: Breast-conserving surgery, MRM: Modified radical mastectomy

The traditional proportional-hazards model (Cox model) for the survival data assumed that:

$$h(t|\boldsymbol{x}) = h_0(x)\exp\left(\sum_j x_j\beta_j\right) \quad j = 1, \ldots, K$$

, where K is the number of covariates and h(t|x) is the hazard of event at time "t" given "j"$^{th}$ predictor and $\beta j$ is "$j$"$^{th}$ regression coefficient, while penalized regression methods that shrink the regression coefficients towards 0 are an option in a rare event setting, which effectively increase the EPV.[15]

The lasso algorithm minimizes the log partial likelihood subject to the sum of the absolute values of the parameters being bounded by a constant. This means if l(β) is the log partial likelihood function of a regression coefficient vector β for the risk factors under investigation, the idea of penalized regression is to modify the log-likelihood by adding a penalization term to estimate the coefficients.

**Table 2.** Analysis of the factors associated with disease-free survival using Cox and penalized Cox models

| | Cox | | | Penalized Cox | | |
|---|---|---|---|---|---|---|
| | **Beta (SE)** | **HR** | **95 % CI** | **Beta (SE)** | **HR** | **95 % CI** |
| **Clinical stage** | | | | | | |
| I/II | Reference | - | - | - | - | - |
| III/IV | 0.61 (0.27) | 1.85 | (1.08-2.96) | 032 (0.14) | 1.38 | (1.16-2.86) |
| **Surgery** | | | | | | |
| ≤ 180 days | -0.04(0.24) | 0.96 | (0.60-1.82) | 0 | - | - |
| >180 days | Reference | - | - | - | - | - |
| **Age** | | | | | | |
| ≤ 45 years | Reference | - | - | - | - | - |
| >45 years | -0.22(0.23) | 0.80 | (0.51-1.67) | 0 | - | - |
| **BMI** | | | | | | |
| ≤ 30 (kg/m$^2$) | Reference | - | - | - | - | - |
| >30 (kg/m$^2$) | 0.12 (0.25) | 1.13 | (0.69-2.00) | 0 | - | - |
| **ER** | | | | | | |
| Positive | Reference | - | - | - | - | - |
| Negative | -0.10 (0.29) | 0.90 | (0.51-1.67) | 0 | - | - |
| **PR** | | | | | | |
| Positive | Reference | - | - | - | - | - |
| Negative | 0.28(0.29) | 1.32 | (0.75-2.12) | 0 | - | - |

SE: Standard error, HR: Hazard ratio, CI: Confidence interval; BMI: Body mass index, ER: Estrogen receptor, PR: Progesterone receptor

$$\hat{\beta} = argmin\ l(\beta), \quad subject\ to \sum |\beta_j| \leq \lambda$$

As the tuning parameter λ≥0 increases, the increase in $\beta_j$ becomes more "costly" and while λ tends to infinity, the coefficients shrink towards 0.16

Choice of lambda was done via cross-validation in the penalized Cox proportional hazards regression analysis.[17] More precisely, the predictive ability of different values of the tuning parameter was evaluated by means of cross-validated log partial likelihood. We used 100-fold cross-validation in which the allocation of the subjects to the folds is random. In K-fold cross-validation, the dataset is divided into k equal subsets. Each time, one of the subsets would be regarded as the validation data and the error would be obtained based on other subsets which are

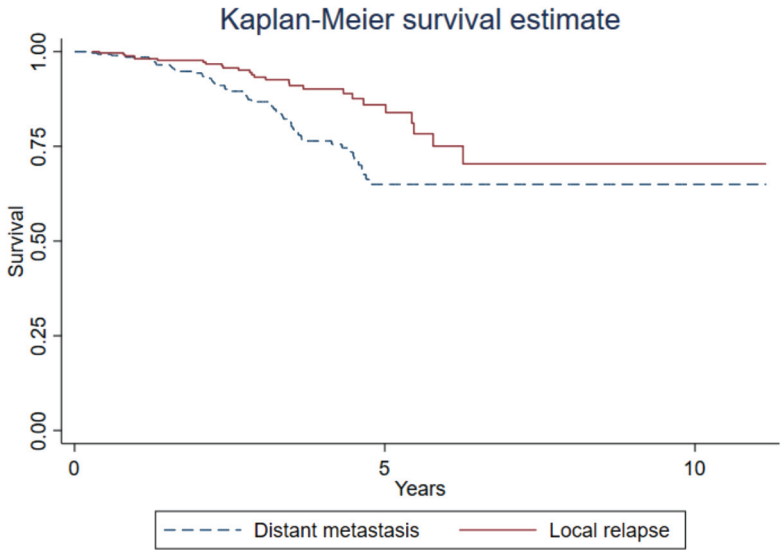


**Figure 1.** This figure shows the Kaplan-Meier survival considering local relapse or distant metastasis as the event.

**Table 3.** Analysis of the factors associated with local relapse using Cox and penalized Cox models

| | Cox | | | Penalized Cox | | |
|---|---|---|---|---|---|---|
| | **Beta (SE)** | **HR** | **95 % CI for HR** | **Beta (SE)** | **HR** | **95 % CI for HR** |
| **Clinical stage** | | | | | | |
| I/II | Reference | - | - | - | - | - |
| III/IV | 0.52 (0.50) | 1.69 | (0.62-1.86) | 0 | - | - |
| **Surgery** | | | | | | |
| ≤ 180 days | -0.26(0.43) | 0.76 | (0.32-1.39) | 0 | - | - |
| >180 days | Reference | - | - | - | - | - |
| **Age** | | | | | | |
| ≤ 45 years | Reference | - | - | - | - | - |
| >45 years | -0.03(0.40) | 0.97 | (0.44-1.55) | 0 | - | - |
| **BMI** | | | | | | |
| ≤ 30 (kg/m$^2$) | Reference | - | - | - | - | - |
| >30 (kg/m$^2$) | 0.68 (0.41) | 1.97 | (0.89-2.43) | 0 | - | - |
| **ER** | | | | | | |
| Positive | Reference | - | - | - | - | - |
| Negative | 0.20 (0.51) | 1.22 | (0.45-1.56) | 0 | - | - |
| **PR** | | | | | | |
| Positive | Reference | - | - | - | - | - |
| Negative | 0.19(0.51) | 1.32 | (0.45-1.57) | 0 | - | - |

SE: Standard error, HR: Hazard ratio, CI: Confidence interval; BMI: Body mass Iindex, ER: Estrogen receptor, PR: Progesterone receptor

called training datasets. This procedure will be repeated until all the subsets are used once as the validation dataset. The value of λ, for which the error becomes minimum, is chosen as the optimal tuning parameter.

This procedure makes variables interpretable and cuts the computation time. Moreover, the final model would be more stable than that given

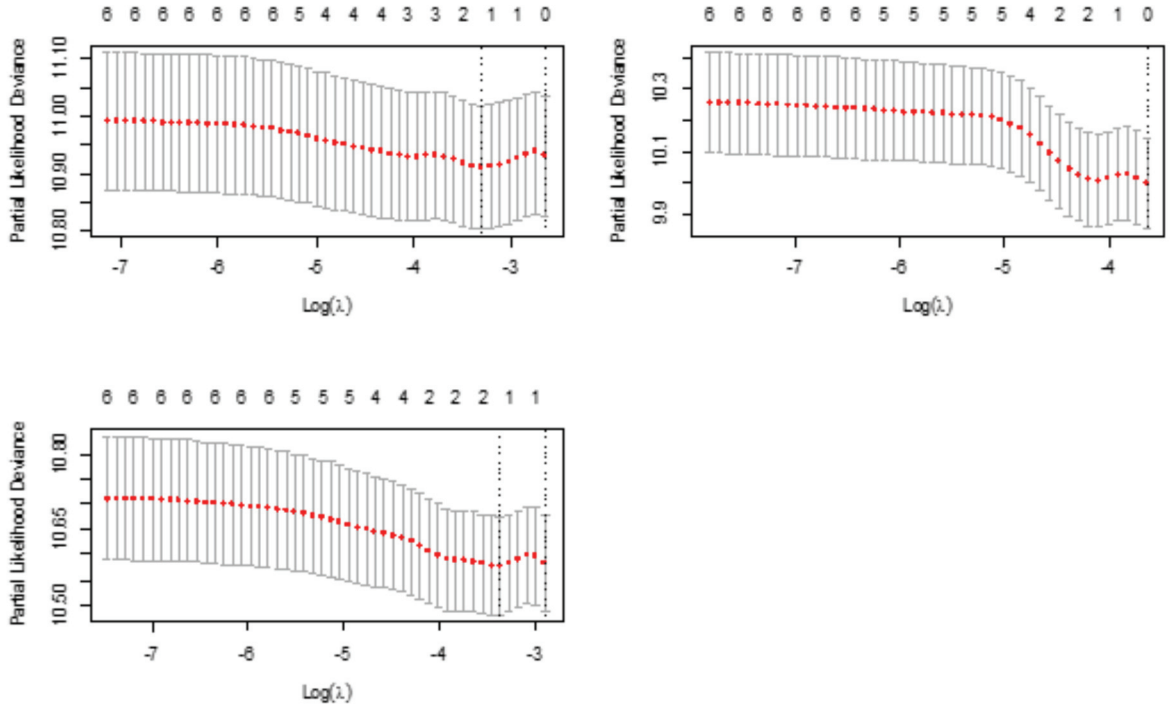


**Figure 2.** This figure shows the partial likelihood deviance against the logarithm of lambda for disease-free status (Top left), local relapse (Top right), distant metastasis (Bottom).
(Log(λ): Logarithm of lambda= tuning parameter)

**Table 4.** Analysis of the factors associated with distant metastasis using Cox and lasso-Cox models

| | Cox | | | Penalized Cox | | |
|---|---|---|---|---|---|---|
| | **Beta (SE)** | **HR for HR** | **95 % CI** | **Beta (SE)** | **HR for HR** | **95 % CI** |
| **Clinical stage** | | | | | | |
| I/II | Reference | - | - | - | - | - |
| III/IV | 0.66 (0.32) | 1.85 | (1.04-2.82) | 0.34(0.21) | 1.40 | (1.14-3.41) |
| **Surgery** | | | | | | |
| ≤ 180 days | -0.06(0.29) | 0.96 | (0.60-1.82) | 0 | - | - |
| >180 days | Reference | - | - | - | - | - |
| **Age** | | | | | | |
| ≤ 45 years | Reference | - | - | - | - | - |
| >45 years | -0.29(1.06) | 0.80 | (0.43-1.54) | 0 | - | - |
| **BMI** | | | | | | |
| ≤ 30 (kg/m$^2$) | Reference | - | - | - | - | - |
| >30 (kg/m$^2$) | 0.17 (0.32) | 1.13 | (0.44-1.56) | 0 | - | - |
| **ER** | | | | | | |
| Positive | Reference | - | - | - | - | - |
| Negative | -0.23 (0.35) | 0.90 | (0.39-1.49) | 0 | - | - |
| **PR** | | | | | | |
| Positive | Reference | - | - | - | - | - |
| Negative | 0.32(0.35) | 1.32 | (0.70-2.00) | 0 | - | - |

SE: Standard error, HR: Hazard ratio, CI: Confidence interval; BMI: Body mass index, ER: Estrogen receptor, PR: Progesterone receptor

by stepwise or best subset selection.[18]

The standard errors of lasso parameters were computed with bootstrap method – a nonparametric resampling Monte Carlo method. For this purpose, 1000 samples of length 284 (number of observations) with replacement were generated for each lasso-cox model. For each sample, the lasso-cox model was executed, parameter estimates were obtained, and the bootstrap standard errors were computed. The (1-α) % confidence intervals were based on Percentile intervals method in which we used the α/2 and (1- α)/2 quantiles of the bootstrap sample as lower and upper bound.[19] Afterwards, the confidence intervals (CI) would be exponentiated to get the (1-α) % confidence intervals of hazard ratios (HR).

Finally, the relative efficiency of the two models (cox versus penalized cox) was estimated through sum of square of coefficients standard error obtained from Cox proportional hazard model versus penalized cox model.[20]

Analysis was performed employing R 3.6.3 using survival, glmnet, and penalized packages.[21] The variables for which the 95% CI of HR included 1 were considered to be statistically significant.

## Result

The mean age of the 284 studied patients at diagnosis was 47.2 ± 11.3 years and 48.2% of them were under the age of 45. Most of the patients were not obese (BMI of ≤30 Kg/m$^2$), while 32.7 % were in the range of obesity. Totally, 10.2% of the subjects underwent BCS and the rest were treated with modified radical mastectomy. All the patients had received adjuvant radiation and chemotherapy and 182 (64.1%) used hormone therapy as well. Moreover, 5.6% underwent neoadjuvant chemotherapy as the first therapeutic action. The majority of the patients were at stage II or III of the disease at the time of the first visit (84.5%). 54.2% of them were with positive ER and 49.6% were with positive PR status (Table 1).

The maximum time of follow-up was 11.1 years. Those who were lost to follow-up within the study period were considered as censored cases and the time of their last visit was considered as their survival time. The mean time between the surgery to the last follow-up was 1188.4 ± 707.6 days (3.2 years) and the mean disease-free survival time was 3.4 years. The time interval between the surgery and RT was 168 ± 84.3 days

(median of 167 days). Furthermore, 26 patients (9.2%) had local relapse and 54 (19 %) experienced distant metastasis. The Kaplan Meier survival estimates are illustrated in figure 1.

To assess the relation of covariates and disease-free survival time (disease due to any of the two events of local relapse or distant metastasis), two models of Cox and penalized Cox were implemented. Table 2 depicts the detailed results. The optimal lambda for fitting the lasso-cox model was based on minimizing partial deviance 0.036 (log λ=-3.3) (Figure 2). The results indicated that using lasso-cox method led to shrink the coefficient of 5 variables with low effects toward zero. The Cox method also has retained 1 variable in the model. In both models, the stage of disease was found to be associated with higher risk of relapse or metastasis. The hazard of event in the patients who were in stages of III/IV were 1.85 (Cox model) or 1.38 (lasso-Cox model) times higher than those in women in stages of I/II. Moreover, the time interval between surgery and RT had no relationships with local relapse or metastasis (Table 2). The relative efficiency of lasso-Cox method compared with the Cox proportional hazard method was calculated as 3.7, which is indicative of the lasso method being 3.7 times more efficient.

Subsequently, we considered local relapse as event and evaluated the effects of age, BMI, ER, PR, stage of cancer, and delay in RT on time to relapse. The obtained tuning parameter for lasso-Cox was 0.026 (log λ=-3.6) (Figure 2). None of the mentioned covariates were statistically significant in neither of the models (Table 3).

For the third part of analysis, the distant metastasis was assumed as the target event. The optimal lasso-Cox model chose 1 active covariate based on lambda of 0.031 (log λ=-3.5) (Figure 2). Similar to disease-free survival, the stage of cancer at the first diagnosis was statistically significant in the occurrence of metastasis. According to table 4, the patients in stage III or IV were more likely to experience failure (distant metastasis) earlier than those in stage of I. Again, the delay in the RT after surgery had no impacts on metastasis (Table 4). The relatively higher efficiency of lasso-Cox method compared with Cox method was 2.3, which means the penalized Cox model was 2.3 times more efficient.

It should be noted that the time interval between the surgery and radiation therapy was dichotomized based on the cut point of 180 days, which was based on median. However, we set other cut points (90, 120 and 150 days) and in neither of the cases, the delay in RT affected the hazard of failure (relapse or metastasis).

## Discussion

With the increasingly important role of adjuvant RT after breast surgery, determination of the optimal time between the surgery and the first adjuvant RT and its influence on the disease-free status has become critically important. Despite several studies, the impacts of timeliness of RT on survival in breast cancer patients still remain unclear and various findings have been reported.

In the present historical cohort study, two different methods, Cox and penalized regression, were utilized for examining the effect of delay in the initiation of RT on the local relapse and distance metastasis -free survival along with demographic and clinical variables in Iranian breast cancer patients. Based on the timing of RT initiation (≤6 months, >6 months), the participants were classified into two groups. Our findings, based on Cox regression and lasso approach, revealed that the delay in RT could not influence the survival outcomes (local relapse, distant metastasis, local relapse, or distant metastasis). According to both models, the stage factor was found to be an influential factor for the disease-free survival and distant metastasis; meanwhile, none of the factors was found significant for the local relapse on both Cox and lasso approach.

Some studies have shown that the timing of RT was not an influential factor in survival.[8,9,22-24] In 2018, Zhang et al. reported their findings on 340 women who received chemotherapy and post-mastectomy RT. They divided the patients into three groups according to the starting time of RT (≤4 vs. >4 months, ≤5 vs. >5 months, ≤6 vs. >6 months). They observed no significant associations between timing of RT and local

recurrence-free survival, distant metastasis-free survival, disease-free survival, and overall survival.[22]

Alkis et al., in a retrospective study on 402 breast cancer cases, aimed to determine the optimal time of starting adjuvant treatment. Initially, they divide their subjects into five groups (shorter than 14 days, between days 15-29, between days 30-44, between days 45-59, and more than 59 days). Secondly, they were divided into two groups (≤44 days, >44 days). In both divisions, there were no differences concerning disease-free survival between the groups, but in the second grouping, the overall survival was significantly higher in the group receiving adjuvant treatment earlier.[23]

Balcázar et al., after examining 1000 patients in a cohort study, divided them into five groups based on the starting time of RT (≤30 days, 31 to 60 days,61 to 90 days, 91 to 120 days, and >120 days). They reported that delays in starting RT were not significant in early breast cancer patients, yet in locally advanced patients, they observed a significant decrease in disease-specific survival.[9] Livi et al., after examining 4820 patients with breast cancer, reported that delay in postoperative RT could not influence the local recurrence.[24] A cohort study on 1393 breast cancer patients treated with and without chemotherapy found that delay in RT was not associated with decreased local control or overall survival.[8] Our conclusions regarding the timing of RT are in line with the aforementioned studies.

In contrast to the above-mentioned studies, there are some other studies indicating the significant impact of delay in radiation therapy on survival.[25-27] In a study, a delay in starting the first adjuvant treatment for more than 4 months was found influential on the overall survival.[25] A retrospective data evaluation on breast cancer patients who underwent postoperative radiation therapy recommended that adjuvant RT before 8 weeks following the surgery could increase disease-free survival and overall survival.[26] A systematic review, based on the studies that characterized the relationship of timing RT and local control, metastasis, and survival, found that a delay longer than 8 weeks after surgery statistically developed 5-year local recurrence.[27]

## Conclusion

In conclusion, our study suggested that the delay in RT initiation after surgery does not compromise the outcomes of local relapse or metastasis.

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## Conflict of Interest

None declared.

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