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Original article

Clinical impact of adjuvant radiation therapy delay after neoadjuvant chemotherapy in locally advanced breast cancer

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ABSTRACT

Background: and Purpose: Post-operative radiation therapy (PORT) is usually indicated for patients with breast cancer (BC) after neoadjuvant chemotherapy (NAC) and surgery. However, the optimal timing to initiation of PORT is currently unknown.

Material and methods: We retrospectively evaluated data from patients with BC who received PORT after NAC and surgery at our institution from 2008 to 2014. Patients were categorized into three groups according to the time between surgery and PORT: <8 weeks, 8–16 weeks and >16 weeks.

Results: A total of 581 patients were included; 74% had clinical stage III. Forty-three patients started PORT within 8 weeks, 354 between 8 and 16 weeks and 184 beyond 16 weeks from surgery. With a median follow-up of 32 months, initiation of PORT up to 8 weeks after surgery was associated with better disease-free survival (DFS) (<8 weeks versus 8–16 weeks: HR 0.33; 95% CI 0.13–0.81; p = 0.02; <8 weeks versus >16 weeks: HR 0.38; 95% CI 0.15–0.96; p = 0.04) and better overall survival (OS) (<8 weeks versus 8–16 weeks: HR 0.22; 95% CI 0.05–0.90; p = 0.036; <8 weeks versus >16 weeks: HR 0.28; 95% CI 0.07–1.15; p = 0.08).

Conclusion: PORT started up to 8 weeks after surgery was associated with better DFS and OS in locally-advanced BC patients submitted to NAC. Our findings suggest that early initiation of PORT is critically important for these patients. However, the low numbers of patients and events in this study prevent us from drawing firm conclusions.

1. Introduction

Breast cancer (BC) leads in prevalence and death from cancer among females worldwide. However, the disease is diagnosed without metastatic disease in approximately 90% of cases [1]. In this scenario, cure is the ultimate goal, and a multidisciplinary approach is critical to achieve it [2]. This includes coordinated and timely administration of systemic therapy, surgery and post-operative radiation therapy (PORT).

PORT after breast conserving surgery (BCS) improves outcomes and has been established as an alternative to mastectomy [3,4]. While robust evidence supports PORT to women submitted to upfront mastectomy [5,6], it's use in patients treated with neo-adjuvant chemotherapy (NAC) and mastectomy is still guided by retrospective analyses of prospective trials. As expected, the approaches differ significantly across cancer centers, but PORT tends to be indicated for patients with clinical stage III or T3 tumors, and to

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those with pathologic residual lymph nodes, an unfavorable scenario in which this treatment is more likely to improve outcomes [7–11].

Due to financial restrictions and/or overloaded oncology services, timely initiation of cancer treatments has been a concern worldwide, particularly in developing economies [12–14]. Of note, it has been shown that time to start adjuvant chemotherapy significantly influences survival outcomes [15–17]. However, the clinical impact of delayed PORT remains unclear, as data have been inconclusive [18–25]. In particular, no studies specifically evaluated the neoadjuvant scenario, in which patients have high-risk disease, and also had a considerably long treatment-free interval before initiation of PORT, to allow for definitive surgery to be performed. In theory, these patients could be at even greater risk from delays, and could represent a unique population to test this hypothesis.

On that basis, we performed a retrospective analysis to evaluate the potential impact of the time to initiation of PORT in BC patients who underwent NAC followed by surgery.

2. Patients and methods

2.1. Patient population

We performed a retrospective analysis of all patients diagnosed with BC who received NAC followed by potentially curative surgery and PORT between 2008 and 2014.

We extracted data on relevant prognostic factors commonly associated with cancer recurrence. The electronic charts were reviewed by physicians (SBS, ARBM, JMSL, KMLBL, TBF, MCLAS, RGMVA, PAHV) who obtained information on age at diagnosis, clinical stage, histological grade [1–3], hormonal receptors status (positive or negative), HER-2 status (positive or negative), NAC schedule (anthracycline-based, anthracycline and taxane-based, or other), neoadjuvant and adjuvant trastuzumab if HER-2 positive (yes or no), adjuvant endocrine therapy if estrogen and/or progesterone receptor positive (yes or no), type of surgery (mastectomy or breast-conserving surgery[BCS]), axillary dissection (yes or no) and pathological complete response in both primary tumor and lymph nodes (pCR; yes or no).

2.2. Study endpoints

The primary endpoint was the comparison of the disease-free survival (DFS) among three groups defined by the time for initiation of PORT (<8 weeks, 8–16 weeks, >16 weeks). DFS was defined as the time from date of surgery to the date of recurrence at any site or death from any cause. Secondary endpoints included overall survival (OS), defined as the time from date of surgery to death from any cause; and subgroup analyses of DFS and OS, stratifying results according to molecular profile, clinical stage and pCR.

2.3. Statistical methods and considerations

Patients were categorized according to the time (in weeks) from definitive surgery to PORT into one of three groups: <8 weeks, 8–16 weeks, and >16 weeks. Demographics and baseline characteristics were summarized using descriptive statistics and compared using ANOVA, Kruskal–Wallis test for continuous variables and Fisher's exact test or χ^2-test for categorical variables, whenever appropriate. OS and DFS curves were estimated with the Kaplan-Meier method and compared them with the log-rank test adjusted for pCR. We used Cox proportional hazard regression models to estimate hazard ratios (HRs) and to investigate whether the effect of time to receive PORT was modified by adjustments for the following covariates (all of them well-known to be related to survival outcomes in breast cancer): age (as continuous variable), pCR, molecular profile, clinical stage and histological grade. We also planned to include any other variable which is unbalanced among groups. An exploratory analysis to estimate survivals in subgroups adjusting for confounders was performed using Multivariate Cox Proportional Hazards Model. Multivariate analysis was also carried out using the binary logistic regression model with the covariates aforementioned to calculate the adjusted odds ratios for recurrence. All tests were two-sided and a p value of <0.05 was considered statistically significant. SPSS software (version 20.0; SPSS, Chicago, IL, USA) was used for statistical analyses.

3. Results

3.1. Patients characteristics

A total of 581 patients were identified, with a median follow-up of 32 months (range: 2–82). Patients were properly staged according to institutional standards. Most patients had clinical stage III (74%) or IIB (18%). Almost all patients were treated with anthracycline and taxane-based NAC (95%), and the majority was treated with mastectomy (75%). All women with estrogen and/or progesterone receptor positive tumors received adjuvant endocrine therapy, and 96.3% of HER-2 positive patients received trastuzumab treatment. Patients who received breast-conserving surgery underwent PORT to the breast with or without nodal areas (supraclavicular in 87.1%; axillary levels II and III in 86.6%; axillary level I in 9.8% and internal mammary in 8.3%). Similarly, after mastectomy or adenomastectomy, all patients received PORT in the chest wall and most of them nodal areas were also included (supraclavicular in 95.1%; axillary levels II and III in 93.8%; axillary level I in 8.6% and internal mammary in 9.0%). Tumor and treatment characteristics were well balanced between the three groups (Table 1). Forty-three (7.4%) patients received PORT<8 weeks from surgery, 354 (60.9%) 8–16 weeks and 184 (31.7%) >16 weeks from surgery. The median time to start PORT was 3.2 months.

3.2. Analyses of disease-free and overall survival

At the cut-point, with a median follow-up of 32 months, 96 patients had died and 160 had experienced a recurrence event. Seven patients had isolated locoregional recurrence, 94 only distant recurrence, and 59 patients both locoregional and distant recurrence events. Starting PORT within 8 weeks from surgery was associated with better DFS when compared to both 8–16 weeks (HR 0.33; 95% CI 0.13–0.81, p = 0.02) and >16 weeks groups (HR 0.38; 95% CI 0.15–0.96; p = 0.04– Fig. 1). There was no difference between 8 and 16 and > 16 weeks groups (HR 1.16; 95% CI 0.83–1.61; p = 0.39). No recurrence events were reported in patients who had pCR and received PORT within 8 weeks of surgery (Supplementary Fig. 1). Starting PORT within 8 weeks also improved OS when compared to 8–16 weeks (HR 0.22; 95% CI 0.05–0.90; p = 0.36) and >16 weeks (HR 0.28; 95% CI 0.07–1.15; p = 0.08– Fig. 2), and, again, no difference between 8 and 16 and > 16 weeks was observed (HR = 1.25; 95% CI 0.80–1.92; p = 0.32). Due to the similarities between these two groups in terms of clinical outcomes, we combined them to allow for a comparison between <8weeks vs. > 8weeks, in which the benefit of starting PORT within 8 weeks was statistically significant both in terms of DFS (HR 0.34; 95% CI 0.14–0.84; p = 0.02) and OS (HR 0.24; 95% CI 0.06–0.97; p = 0.045).

3.3. Subgroup analyses

As exploratory analyses, we estimated HRs for survival endpoints (DFS and OS) by time to initiation of PORT according to the