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Original article

The impact on clinical outcomes of post-operative radiation therapy delay after neoadjuvant chemotherapy in patients with breast cancer: A multicentric international study

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ABSTRACT

Introduction: Radiation therapy (RT) is frequently used for post-operative treatment in breast cancer (BC) patients who received preoperative systemic therapy (PST) and surgery. Nevertheless, the optimal timing to start RT is unclear.

Material and methods: Data from BC patients who underwent chemotherapy as PST, breast surgery and RT at 3 Institutions in Brazil and Canada from 2008 to 2014 were evaluated. Patients were classified into three groups regarding to the time to initiation of RT after surgery: <8 weeks, 8–16 weeks and >16 weeks.

Results: A total of 1029 women were included, most of them (59.1%; N = 608) had clinical stage III. One hundred and forty-one patients initiated RT within 8 weeks, 663 between 8 and 16 weeks and 225 beyond 16 weeks from surgery. With a median follow-up of 32 months, no differences in disease-free survival (DFS), overall survival and locoregional recurrence-free survival (LRRFS) were observed of time to indicated RT (<8 weeks versus 8–16 weeks versus >16 weeks). However, in luminal subtype patients (46.5%; N = 478), initiation of RT up to 8 weeks after surgery was associated with better LRRFS (<8 weeks versus >16 weeks: HR 0.22; 95%CI 0.05–0.86; p = 0.03), with a tendency to a better DFS (<8 weeks versus >16 weeks: HR 0.50; 95%CI 0.25–1.00).

Conclusion: RT initiated up to 8 weeks after surgery was related to better LRRFS in luminal BC patients who underwent PST. Our results suggest that early start of RT is important for these patients.

1. Introduction

Worldwide, breast cancer (BC) is one of the most prevalent tumors among women [1]. A multidisciplinary management is essential to achieve the curative treatment [2]. This comprises synchronized and timely approach of breast surgery, systemic therapy, and post-operative radiation therapy (RT).

Based on phase III trials, RT after both mastectomy and breast conserving surgery (BCS) improves local control and survival rates for most patients with BC. Nonetheless, none of these trials comprised patients that received chemotherapy as preoperative systemic therapy (PST) [3–5]. The role of RT in BC patients treated with PST has been established mostly based on retrospective data. These studies showed a solid rationale for the use of RT to the breast/chest wall and regional nodes for locally advanced BC women. Moreover, in a subgroup of stage II disease with high-risk for loco-regional relapse, RT was associated with better clinical outcomes [6–15].

In clinical practice, the indication of RT in BC patients treated

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with PST is normally guided by pre-PST tumors' and patients' characteristics, the type of surgery performed, as well as the response of the tumor to treatment [16–18]. '

Timely initiation of oncology treatments has been a problem due to economic limitations and/or overloaded medical centers, especially in developing countries and in welfare states with public health systems [19–21]. Of note, it has been demonstrated that time to initiation post-operative chemotherapy significantly impact on survival rates [22,23]. Nevertheless, the clinical influence of delayed RT is uncertain, as previous reports generated conflicting results [24–27].

We have previously reported on our experience which suggested that delayed administration of RT after PST was associated with worse clinical outcomes. However, the sample employed in that study had a potential bias which was the small number of patients treated with RT within 8 weeks from surgery, resulting in a large confidence intervals [24].

The aim of this study was to assess the potential impact of the time to start of RT in patients with BC who received PST and breast surgery in a larger and more diversified (multinational cohort) patient population.

1.1. Patients and methods

This is a multicentric retrospective study that included BC patients who underwent chemotherapy as PST followed by breast surgery and RT at Instituto do Câncer do Estado de São Paulo (ICESP) – a public Institution from Brazil, Hospital Sírio-Libanês – a private Institution from Brazil, and McGill University Health Center (MUHC) – Canada. Data were consecutively collected in the 3 hospitals from 2008 to 2014. The electronic charts were assessed to obtain data on demographic, tumor and treatment features of all patients. All patients received RT in the breast or chest wall with or without regional nodal irradiation.

Patients were classified into three groups regarding to the time to initiation of RT after surgery: <8 weeks, 8–16 weeks and >16 weeks.

The primary endpoint was disease-free survival (DFS) defined as

Table 1
Patient and clinical features.

Characteristics	<8 weeks (N = 141)		8–16 weeks (N = 663)		>16 weeks (N = 225)		
	N	%	N	%	N	%	
Clinical stage*							
I	6	4,3%	14	2,1%	3	1,3%	p < 0.001
II	64	45,4%	262	39,5%	60	26,7%	
III	68	48,2%	380	57,3%	160	71,1%	
Missing	3	2,1%	7	1,1%	2	0,9%	
Hitological grade							
1	14	9,9%	33	5,0%	14	6,2%	p = 0.2
2	56	39,7%	287	43,3%	103	45,8%	
3	65	46,1%	334	50,4%	105	46,7%	
Missing	6	4,3%	5	0,8%	0	0,0%	
Hormonal and Her2 status							
HRpos Her2 neg (luminal)	76	53,9%	297	44,8%	105	46,7%	p = 0.08
HR pos Her2 pos	29	20,6%	128	19,3%	35	15,6%	
HRneg Her2 pos	11	7,8%	40	6,0%	9	4,0%	
HRneg Her2 neg (triple negative)	22	15,6%	189	28,5%	75	33,3%	
Missing	3	2,1%	9	1,4%	1	0,4%	
Primary systemic therapy							
Anthracycline-taxane	126	89,4%	606	91,4%	205	91,1%	p = 0.72
Others	13	9,2%	50	7,5%	19	8,4%	
Missing	2	1,4%	7	1,1%	1	0,4%	
Trastuzumab in Her2 + (N = 252)	**(N = 40)**		**(N = 168)**		**(N = 44)**		
Yes	39	97,5%	163	97,0%	41	93,2%	p = 0.42
No	1	2,5%	2	1,2%	2	4,5%	
Missing	0	0,0%	3	1,8%	1	2,3%	
Pertuzumab in Her2 + (N = 252)	**(N = 40)**		**(N = 168)**		**(N = 44)**		
Yes	4	10,0%	1	0,6%	1	2,3%	p = 0.02
No	36	90,0%	165	98,2%	42	95,5%	
Missing	0	0,0%	2	1,2%	1	2,3%	
Endocrine therapy in HR-positive (N = 680)	**(N = 106)**		**(N = 433)**		**(N = 141)**		
Yes	99	93,4%	415	95,8%	137	97,2%	p = 0.67
No	5	4,7%	13	3,0%	3	2,1%	
Missing	2	1,9%	5	1,2%	1	0,7%	
Surgery							
Mastectomy	76	53,9%	441	66,5%	179	79,6%	p < 0.001
BCS	65	46,1%	221	33,3%	46	20,4%	
Missing	0	0,0%	1	0,2%	0	0,0%	
Axillary dissection							
Yes	103	73,0%	516	77,8%	200	88,9%	p < 0.001
No	38	27,0%	144	21,7%	23	10,2%	
Missing	0	0,0%	3	0,5%	2	0,9%	
pCR							
Yes	28	19,9%	142	21,4%	38	16,9%	p = 0.35
No	113	80,1%	520	78,4%	187	83,1%	
Missing	0	0,0%	1	0,2%	0	0,0%	

Note: HR, hormone receptor; HER2, human epidermal growth factor receptor 2; pCR, pathologic complete response; BCS, breast conserving surgery; pos, positive; neg, negative *clinical stage according to AJCC 2010.

the time from date of surgery to the date of relapse at any site or death from any cause. Secondary endpoints were overall survival (OS), defined as the time from date of surgery to death from any cause, locoregional recurrence-free survival (LRRFS), defined as the time from date of surgery to local and/or regional recurrence, and distant-recurrence free survival, defined as the time from date of surgery to distant recurrence.

Pathological complete response (pCR) is defined as the absence of residual invasive carcinoma (ypT0pN0 or ypTispN0).

The patients' follow-up was performed by history and physical examination: every 3–4 months for 1–2 years, then every 6 months for 5 years, and then annually. Bilateral breast mammograms were performed annually. In the presence of clinical signs and symptoms suggestive of recurrent disease, additional exams (laboratory and/or imaging studies) for screening were performed.

1.2. Statistical methods

Patients were categorized according to the time (in weeks) from definitive surgery to RT 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 c2-test for categorical variables, whenever appropriate. OS and DFS curves were estimated with the Kaplan-Meier method and compared them with the log-rank. We used Cox proportional hazard regression models to estimate hazard ratios (HRs) and to investigate whether the effect of time to receive RT was modified by adjustments for the following covariates: age (as continuous variable), subtype, type of surgery, pCR, and institution.

2. Results

2.1. Patients characteristics

A total of 1029 patients were included, with a median follow-up of 32 months (range: 1–124). A total of 581 patients (56.5%) were from ICESP, 376 (36.5%) from HSL and 72 (7%) from the MUHC. Although most patients (59.8%; N = 615) had locally advance clinical stage III disease, the groups were unbalanced in terms of

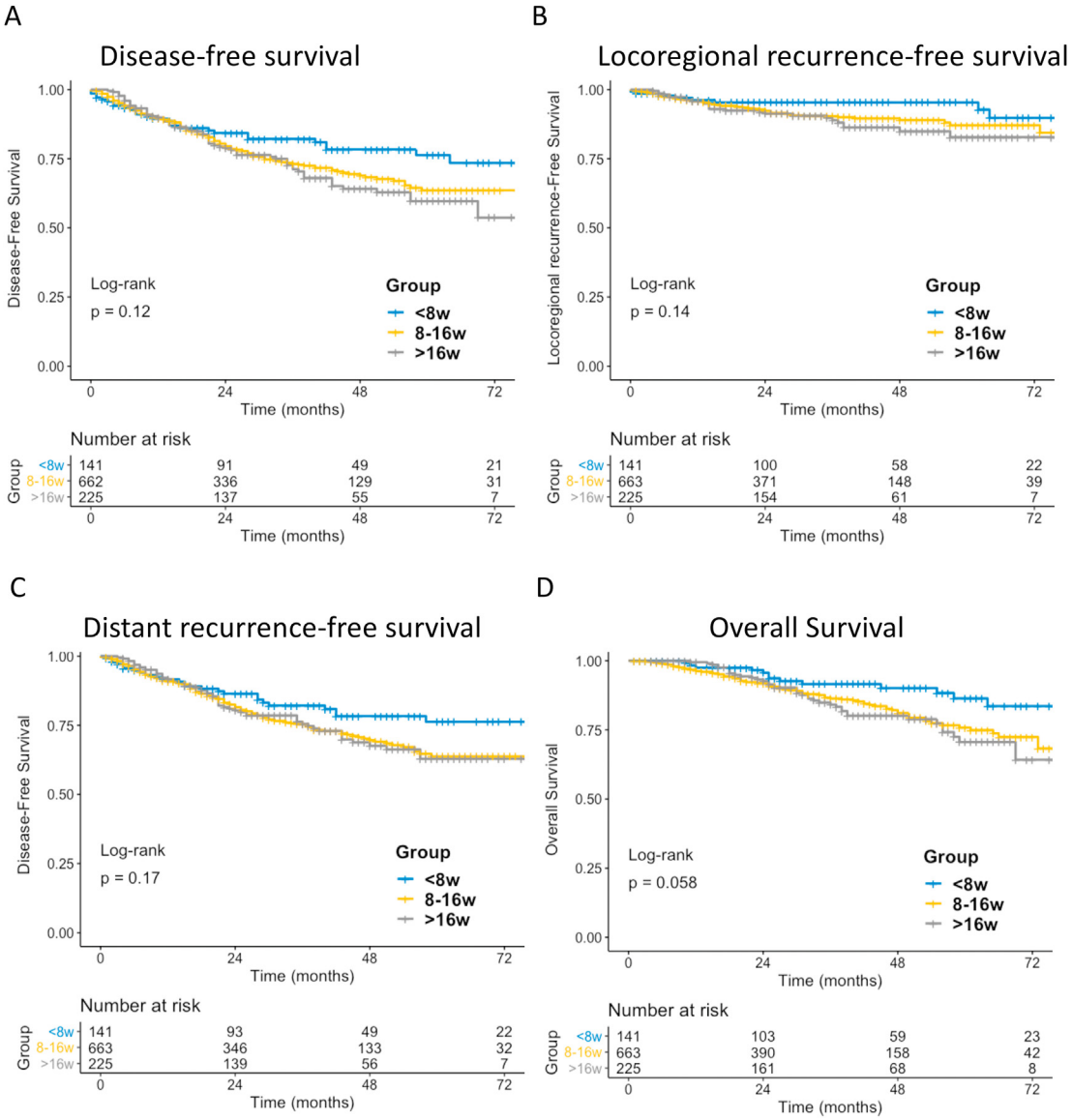

Fig. 1. Survival outcomes.

disease stage, with a higher proportion of stage III patients in the >16-week group (Table 1). Anthracycline and taxane-based PST was used for most patients (91.1%; N = 937), and the majority were treated with a mastectomy (67.6%; N = 696). Almost all estrogen and/or progesterone receptor positive patients received endocrine therapy (96.9%; N = 651) in adjuvant setting, and almost all (96.4%; N = 243) HER-2 positive patients received trastuzumab with or without pertuzumab in both neoadjuvant and adjuvant settings (Table 1).

The most usual RT schedule was the conventional 50Gy–50.4Gy in 25–28 fractions (82.3%; N = 847). Hypofractionated irradiation with doses of 40.05Gy–42.5Gy delivered in 15–16 fractions was used in 17.7% of patients. Boost was used in 42% of patients. Most patients received regional nodal irradiation (81.6% to the supraclavicular fossa; 76.0% to the axillary levels 2 and 3; 43.8% to the axillary level 1; 13.7% to the internal mammary).

The median time to initiation of RT was 11 weeks. One hundred and forty-one (13.7%) patients received RT < 8 weeks from surgery, 663 (64.4%) 8–16 weeks and 225 (21.9%) >16 weeks from surgery.

2.2. Survival outcomes

A total of 92 (8.9%) patients had locoregional recurrence, 232 (22.5%) distant recurrence, and 252 (24.5%) locoregional and/or distant recurrence events.

In the overall patient population, no differences in terms of DFS, OS and LRRFS were observed according to the time of initiation of RT (<8 weeks versus 8–16 weeks versus >16 weeks) - Fig. 1.

Fig. 2 depicts DFS rates for the various molecular sub-types (luminal, triple positive, Her-2 pure and triple negative) according to time of initiation of RT. For luminal sub-type patients (46.5%; N = 478), starting RT within 8 weeks significantly improved DFS (log-rank p 0.037- Fig. 2).

Moreover, for this group of patients, LRRFS and distant disease-free survival (DDFS) were also improved in patients who started RT within 8 weeks, though with no differences in OS rates (Fig. 3).

As an exploratory analysis, we estimated adjusted HRs for survival endpoints (DFS, LRRFS and DDFS) for luminal patients by time to initiation of RT according to the following subgroups: pCR, institution, age, type of surgery and stage. The results after adjusting for confounders are presented in supplement 1. Comparing to patients who started RT after 8 weeks from surgery, a better LRRFS and DDFS favoring treatment within 8 weeks was found.

3. Discussion

This multicentric, multinational study is the largest so far

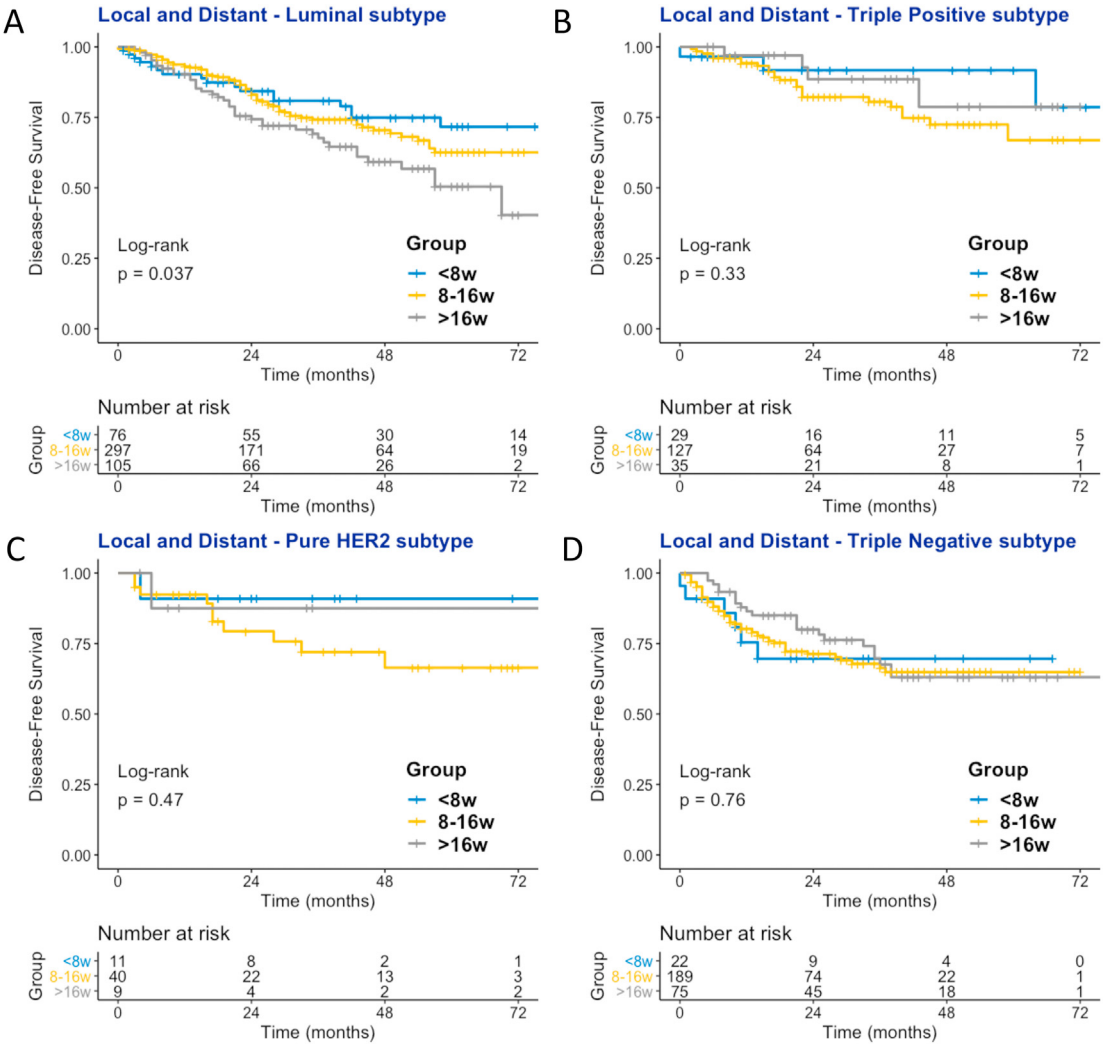

Fig. 2. Survival outcomes according to tumor sub-type characteristics.

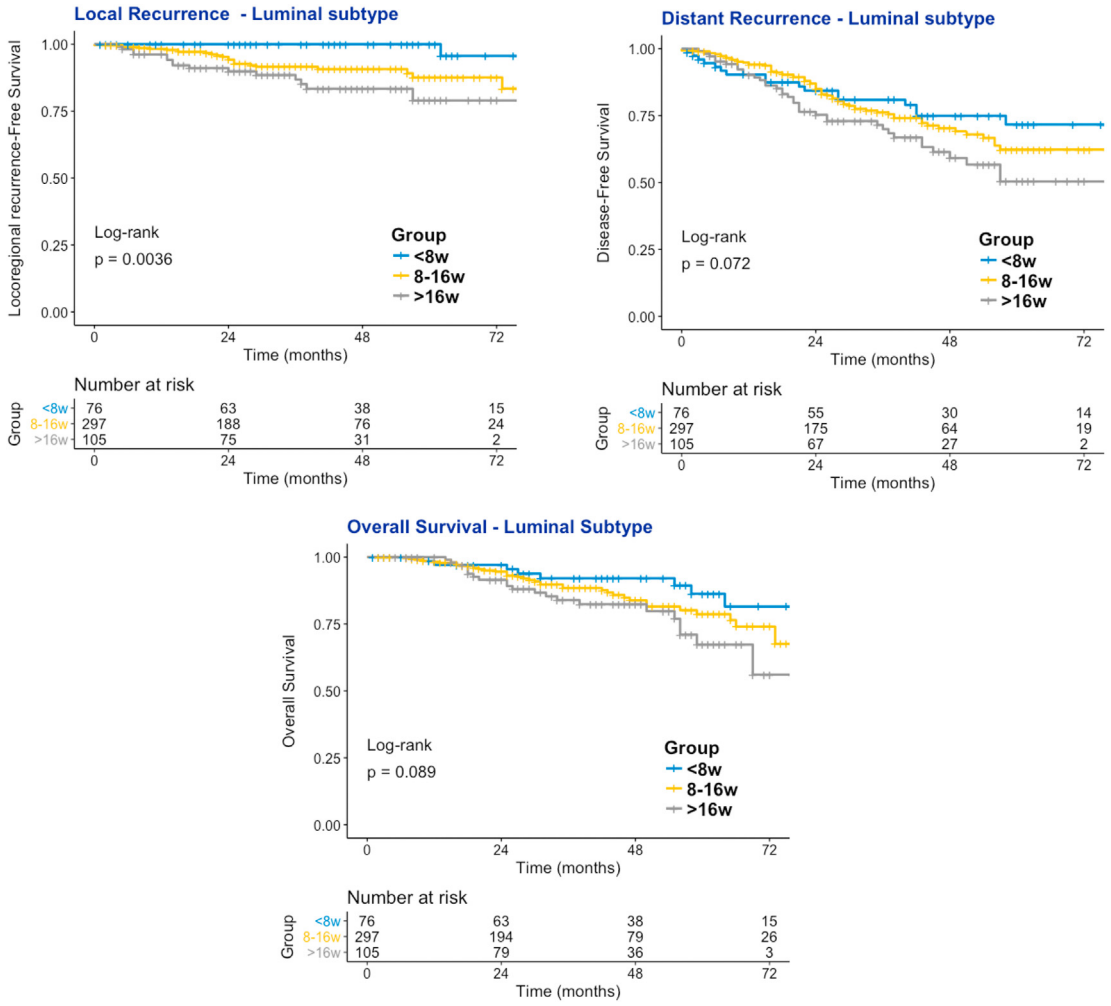

Fig. 3. Survival outcomes for luminal patients.

addressing the clinical impact of timing to start RT in BC patients treated with PST and surgery. Our cohort comprised mostly of patients with locally advance disease who were homogeneously treated with standard systemic therapy. In this context, in which RT is recognized to be related to improved local and survival rates [3,4], our results suggest that RT started >8 weeks from surgery was not related to poorer clinical outcomes in the overall study population.

Previous reports [25,26,28] evaluated timing of RT in early BC patients who underwent breast conservative surgery with adjuvant systemic therapy (which might have worked as a protector effect between RT and, hypothetically decreasing any deleterious consequence of delaying RT treatment). The first report of our group that included data from one single Brazilian Public Center showed a statically significant benefit in OS and DFS to initiate RT < 8 weeks [24]. However, as previously noted, this group was very small and potentially not well representative of the full population. To minimize to possible bias of the single center analyzes, we performed the present study comprising date from three Oncology Centers (Brazil – Public Center; Brazil – Private Center; Canada). We assessed the timing of RT initiation in a homogeneous group of patients, be likely to harbor more advanced disease, theoretically assigning them at higher risk from RT delays. After an evaluation of more than 1000 patients, we found no clear relationship between the time to start RT and oncological outcomes. Similarly with our findings, a retrospective study reported on 248 patients across different time-points who underwent RT, did not find significant differences in locoregional outcome among the three groups of patients [8 weeks vs. >8 weeks ($p = 0.634$, $\leq$12 vs > 12 weeks ($p = 0.332$), or $\leq$16 vs > 16 weeks ($p = 0.549$)], suppporting the theory that RT should be offered regardless of the time elapsed since the last treatment [27]. However, in our study, in the subgroup of luminal patients, the early start of RT was associated with improvement in DFS, LRRFS and DDFS. This result can be potentially explained by the fact that luminal tumors are the group that least responds to systemic treatment, implying that the more chemosensitive Her2+ and TN patients were better "protected" by chemotherapy ± anti-Her2 therapy against loco-regional failure making the clinical impact of delaying RT less relevant in these subgroups. Despite the better overall prognosis of luminal breast cancer compared to the other molecular subtypes (Her +, triple negative) [29], it is possible to infer that shorter time of RT may benefit luminal BC patients.

Our study has limitations which may have influenced the results. First, it is retrospective in nature, making it more be vulnerable to errors such as selection bias. Second, the short median follow-up time, which is a problem particularly for luminal BC patients, who are more likely to present late tumor relapse. Thus, these limitations represent weaknesses within the study that may influence outcomes and conclusions of the research, being a fact

that may restrict the application of the study findings in clinical practice.

They are the constraints on generalizability, applications to practice, and/or utility of findings that are the result of the ways in which you initially chose to design the study or the method used to establish internal and external validity or the result of unanticipated challenges that emerged during the study.

In conclusion, RT initiated up to 8 weeks after surgery was related to better LRRFS in luminal BC patients who underwent PST. Our results suggest that early start of RT, within 8 weeks of surgery, is important for these patients.

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Declaration of competing interest

All authors declare that they have no conflicts of interest in relation to the authorship or publication of this contribution.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2020.08.013.

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