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Determinants of delayed postoperative radiation therapy in breast cancer patients undergoing neoadjuvant chemotherapy: A subanalysis of the AMAZONA III prospective cohort

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ABSTRACT

Background: Delays in starting postoperative radiation therapy (PORT) in breast cancer patients may be associated with poorer clinical outcomes. This analysis aimed to identify factors contributing to delayed PORT in patients with breast cancer who underwent neoadjuvant chemotherapy followed by surgery and PORT in a Brazilian cohort.

Methods: Participants were categorized based on the interval from surgery to the initiation of PORT into two groups: ≤ 8 weeks and > 8 weeks. Socioeconomic and clinicopathological factors were analyzed for associations with delayed PORT. Univariable and multivariable regressions were performed.

Results: Factors significantly associated with delayed PORT included low educational level (RR: 1.50; 95 % CI: 1.05–2.14; $p = 0.0276$), public health insurance (RR: 3.29; 95 % CI: 1.76–6.12; $p = 0.0002$) and having a Luminal A or Luminal B-HER2-negative subtype (RR: 1.92; 95 % CI: 1.14–3.23; $p = 0.0153$) compared to the Triple Negative subtype. The absence of adjuvant endocrine therapy was associated with a lower risk of delayed PORT (RR: 0.67; 95 % CI: 0.46–0.99; $p = 0.0338$). In the multivariate analysis, public health insurance remained the sole independent predictor of delayed PORT (RR: 2.98; 95 % CI: 1.60–5.55; $p = 0.0006$).

Conclusion: In this cohort, reliance on public health insurance emerged as the primary independent predictor of delayed initiation of PORT in breast cancer patients who received neoadjuvant chemotherapy. Lower educational levels and household income also contributed to delays, highlighting disparities within the healthcare system. Addressing these barriers is essential for improving timely access to PORT and potentially enhancing clinical outcomes in this population.

Introduction

Breast cancer is the most frequently diagnosed malignancy and remains the leading cause of cancer-related mortality among women worldwide. Significant disparities in incidence rates are observed across different geographical regions, with the highest frequencies reported in low and middle incomes countries (LMIC) [1]. In Brazil, projections for the 2023–2025 triennial period estimate 73,610 new cases, translating to an incidence rate of 66.54 per 100,000 women [2].

The management of breast cancer involves a multidisciplinary approach that integrates local treatments, such as surgery and radiation therapy (RT), with systemic therapies, including chemotherapy, hormone therapy, and biological agents. The combined use of these treatment modalities has led to substantial improvements in patient outcomes, enhancing both disease-free and overall survival rates [3,4].

RT is frequently used as a postoperative treatment for breast cancer and is applicable to patients who have undergone either conservative surgery or mastectomy. Studies have demonstrated the efficacy of RT following surgery, showing a decrease in recurrence rates over a decade and a reduction in disease-related mortality within 15 years [5,6].

The survival outcomes for women diagnosed with breast cancer are significantly influenced by various risk factors, encompassing tumor characteristics, socioeconomic status, and treatment strategies. Delays in the initiation of therapeutic interventions may adversely affect patient prognosis and overall outcomes [7].

The timely initiation of cancer therapies remains a critical global issue, particularly in emerging nations, due to financial constraints and overburdened oncology services. Socioeconomic disparities have been associated with prolonged intervals between initial medical consultations and the commencement of breast cancer treatment. In Brazil, evidence indicates that women facing higher social vulnerability experience significant delays in accessing healthcare. Delays exceeding three months from initial symptom recognition to the start of breast cancer treatment have been shown to negatively impact survival rates [8].

The high prevalence of delays in the initiation of RT raises significant concerns. These delays are likely attributable to inadequate healthcare resources dedicated to cancer care in numerous developing, and even some developed, countries, further exacerbated by patients' financial limitations. Although the existence of these factors is recognized, there is a notable knowledge gap regarding their combined impact in LMIC, with few studies thoroughly exploring this issue. This study, therefore, seeks to elucidate the factors associated with delayed initiation of postoperative RT (PORT) among breast cancer patients in Brazil. Identifying these determinants is crucial, as it can inform the development of targeted and effective strategies to enhance timely access to treatment.

Patients and methods

Patient population

The AMAZONA III study is a multicenter prospective cohort conducted across 23 urban hospitals in Brazil, comprising 9 sites in the South, 7 in the Southeast, 4 in the Northeast, 2 in the Center-West, and 1 in the North region. Eligible participants were women aged 18 years or older with histologically confirmed invasive breast cancer, clinical stage I–IV, irrespective of histologic subtype. All consecutive, newly diagnosed patients presenting to participating centers between January 2016 and March 2018 were invited to enroll. At baseline, participants completed a structured sociodemographic and clinicopathological questionnaire, underwent physical examination, and had medical records reviewed by trained study investigators. Longitudinal follow-up included annual chart review to document treatment patterns, recurrence, disease progression, and survival outcomes. Insurance status was categorized as public (Brazilian Unified Health System – SUS) or private (private health insurance or self-funded care). The AMAZONA III cohort is registered on ClinicalTrials.gov (identifier NCT02663973). The present study constitutes a subanalysis of this multicenter prospective registry. This study included patients diagnosed with breast cancer, aged over 18 years, without metastatic disease, who underwent systemic neoadjuvant treatment, surgery, and PORT as part of the LACOG 0115 AMAZONA III study. All patients received RT to the breast or chest wall, with or without regional nodal irradiation.

Several articles have already been published using data from the LACOG 0115 AMAZONA III study, each addressing different scientific questions and methodological aspects of the cohort [9–14].

Patients who underwent neoadjuvant chemotherapy followed by surgery and PORT were categorized into two groups according to the time between surgery and the initiation of PORT: ≤ 8 weeks (without delay) and > 8 weeks (delay group). The 8-week cutoff was based on a previous study conducted in the Brazilian population, which demonstrated that a delay of >8 weeks in initiating PORT was associated with a

negative impact on overall survival [8].

Medical record abstraction was performed locally at each participating hospital by trained investigators using a standardized case report form (CRF) developed within the REDCap (Research Electronic Data Capture) platform. Clinical, pathological, and treatment variables were extracted from electronic or paper charts and entered directly into the REDCap-based CRF. The database, hosted on a secure server managed by the LACOG/GBECAM coordinating center, incorporated automated validation rules and routine quality-control procedures, including remote monitoring and periodic audits. Access to the system was restricted to authorized study personnel, and all procedures adhered to institutional and national data-protection requirements. The extracted variables included age, race, parity, employment status, marital status, education level, type of medical insurance (private or public), clinical stage (according to the TNM classification by the American Joint Committee on Cancer, Seventh Edition), and type of surgical procedure. We also assessed the monthly household income based on the minimum wage in Brazil. The minimum wage in Brazil, known as "salário mínimo," is the legally established minimum amount that employers must pay employees for their work. It serves as a baseline wage to ensure that workers receive a minimum income to cover basic living expenses. The minimum wage is periodically adjusted by the Brazilian government to account for inflation and economic factors. As of the latest update (which may vary due to exchange rates and adjustments), the Brazilian minimum wage is approximately R$1320 per month. Converting this to U.S. dollars can fluctuate based on the current exchange rate; for example, at an exchange rate of 1 USD = 5.0 BRL, this would be roughly $264 USD per month.

Statistical methods

Descriptive statistics were used to summarize demographic and baseline characteristics of the study population. Univariable and multivariable Poisson regression analyses were used to assess the impact of delayed PORT (categorized as ≤ 8 weeks and >8 weeks) based on demographic, socioeconomic, and clinicopathological features. Relative risks (RRs) with corresponding 95 % confidence intervals (95 % CIs) were calculated to quantify associations.

All tests were two-sided, and a p-value of 0.05 was considered statistically significant. SAS version 9.4 (SAS Institute, Cary, NC) was used for statistical analyses.

Results

A total of 582 patients were included in this study, with a mean age of 49 years (range: 25–87 years). The patient population consisted of diverse racial backgrounds: 41.9 % (n = 240) were white and 58.1 % (n = 333) were non-white. Educational attainment varied, with 48.8 % (n = 269) having an elementary/incomplete education and 51.2 % (n = 282) having completed secondary or higher education; information was unavailable for 5.3 % (n = 31) of patients. Most patients (74.1 %, n = 431) were treated within the Brazilian public health system (Table 1).

Regarding socioeconomic status, 51.7 % (n = 247) of patients reported no income or earnings up to two Brazilian minimum wages, 36.8 % (n = 176) had an income between two and five minimum wages, and 11.5 % (n = 55) earned more than five minimum wages, with 17.9 % (n = 104) not disclosing their income. More than half (56.2 %) were unemployed and financially dependent on family support. Additionally, 58.8 % (n = 342) were married or in a stable relationship, and 79.5 % (n = 463) had one or more children. (Table 1)

Clinical staging at initial diagnosis revealed that 58.9 % (n = 343) of cases were stage III, 38.8 % (n = 226) were stage II, and 2.2 % (n = 13) were stage I. Molecular subtypes included luminal B HER2-positive, luminal A/luminal B HER2-negative, and triple-negative, representing 31.5 % (n = 161), 45.4 % (n = 232), and 23.1 % (n = 118) of tumors, respectively. Mastectomy was the most common surgical procedure

Table 1
Clinical pathologic, treatment and socioeconomic characteristics of breast cancer patients.

Characteristics	Total N = 582 (%)	Missing N = 27 (%)	< 8 weeks N = 448 (%)	≥ 8 weeks N = 107 (%)
Age (years)				
≤ 50	320 (56.0)	14 (56.0)	254 (57.9)	52 (48.6)
> 50	251 (44.0)	11 (44.0)	185 (42.1)	55 (51.4)
Unknown*	11 (1.9)	2 (7.4)	9 (2.0)	0 (0.0)
Brazilian region				
Southeast	134 (23.1)	3 (11.5)	82 (18.3)	49 (45.8)
South	97 (16.7)	7 (26.9)	78 (17.4)	12 (11.2)
Northeast	223 (38.4)	15 (57.7)	178 (39.8)	30 (28.0)
North	3 (0.5)	0 (0.0)	3 (0.7)	0 (0.0)
Center-west	123 (21.2)	1 (3.7)	106 (23.7)	16 (15.0)
Unknown	2 (0.3)	1 (3.7)	1 (0.2)	0 (0.0)
Health coverage				
Public	431 (74.8)	21 (77.8)	313 (70.8)	97 (90.7)
Private	145 (25.2)	6 (22.2)	129 (29.2)	10 (9.3)
Race				
White	240 (41.9)	9 (33.3)	189 (42.9)	42 (40.0)
Non-white	333 (58.1)	18 (66.7)	252 (57.1)	63 (60.0)
Occupation status**				
Yes	249 (43.8)	10 (38.5)	197 (45.1)	42 (39.6)
No	320 (56.2)	16 (61.5)	240 (54.9)	64 (60.4)
Unknown	13 (2.2)	1 (3.7)	11 (2.5)	1 (0.9)
Marital status				
Married	342 (58.8)	15 (55.6)	268 (59.8)	59 (55.1)
Single	235 (40.4)	12 (44.4)	176 (39.3)	47 (43.9)
Unknown	5 (0.9)	0 (0.0)	4 (0.9)	1 (0.9)
Educational level				
Elementary/incomplete education	269 (48.8)	17 (65.4)	194 (45.6)	58 (58.0)
Complete secondary/higher education	282 (51.2)	9 (34.6)	231 (54.4)	42 (42.0)
Unknown	31 (5.3)	1 (3.7)	23 (5.1)	7 (6.5)
Family income				
No income up to 2 minimum salaries	247 (51.7)	15 (62.5)	181 (50.0)	51 (55.4)
From 2 to 5 minimum salaries	176 (36.8)	6 (25.0)	139 (38.4)	31 (33.7)
>5 minimum salaries	55 (11.5)	3 (12.5)	42 (11.6)	10 (10.9)
Unknown	104 (17.9)	3 (11.1)	86 (19.2)	15 (14.0)
Clinical stage				
I	13 (2.2)	1 (3.7)	10 (2.2)	2 (1.9)
II	226 (38.8)	7 (25.9)	173 (38.6)	46 (43.0)
III	343 (58.9)	19 (70.4)	265 (59.2)	59 (55.1)
Tumor grade				
1	53 (9.1)	1 (3.7)	39 (8.7)	13 (12.1)
2	182 (31.3)	5 (18.5)	139 (31.0)	38 (35.5)
3	145 (24.9)	6 (22.2)	111 (24.8)	28 (26.2)
Unknown	202 (34.7)	15 (55,5)	159 (35,4)	28 (26,2)
Estrogen receptor status				

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Total *N* = 582 (%)	Missing *N* = 27 (%)	< 8 weeks *N* = 448 (%)	≥ 8 weeks *N* = 107 (%)
Positive	180 (31.0)	5 (18.5)	146 (32.6)	29 (27.4)
Negative	89 (15.3)	2 (7.4)	76 (17.0)	11 (10.4)
Unknown	312 (53.7)	20 (74,1)	226 (50,5)	66 (62,2)
Progesterone receptor status				
Positive	149 (25.6)	3 (11.1)	116 (25.9)	30 (28.3)
Negative	120 (20.7)	4 (14.8)	105 (23.4)	11 (10.4)
Unknown	312 (53,7)	20 (74,1)	227 (50,7)	65 (61,3)
HER-2 status				
Positive	73 (12.6)	3 (11.1)	63 (14.1)	7 (6.6)
Negative	188 (32.4)	3 (11.1)	155 (34.6)	30 (28.3)
Unknown	314 (54,1)	21 (77,8)	227 (50,6)	66 (62,3
Molecular subtype classification				
Luminal A/ B with HER2 negative	232 (45.4)	6 (27.3)	169 (43.1)	57 (58.8)
Her 2 positive/ Luminal B with Her2 positive	161 (31.5)	12 (54.5)	124 (31.6)	25 (25.8)
Triple-negative	118 (23.1)	4 (18.2)	99 (25.3)	15 (15.5)
Unknown	71 (12.2)	5 (18.5)	56 (12.5)	10 (9.3)
Neoadjuvant chemotherapy				
Anthracycline-taxane	484 (83.2)	21 (77.8)	368 (82.1)	95 (88.8)
Others	98 (16.8)	6 (22.2)	80 (17.9)	12 (11.2)
Only Trastuzumab in Her-2 positive ($n = 161$)				
Yes	109 (67.7)	7 (58.3)	82 (66.1)	20 (80.0)
No	52 (32.3)	5 (41.7)	42 (33.9)	5 (20.0)
Trastuzumab + Pertuzumab in Her-2 positive ($n = 161$)				
Yes	8 (5.0)	1 (8.3)	6 (4.8)	1 (4.0)
No	153 (95.0)	11 (91.7)	118 (95.2)	24 (96.0
Hormone therapy in HR-positive Adjuvant ($n = 161$)				
Yes	104 (64.6)	6 (50.0)	80 (64.5)	18 (72.0)
No	54 (33.5)	6 (50.0)	42 (33.9)	6 (24.0)
Unknown	3 (1.9)	0 (0.0)	2 (1.6)	1 (4.0)
Surgery				
Mastectomy	331 (56.9)	21 (77.8)	243 (54.2)	67 (62.6)
Breast conserving surgery	224 (38.5)	4 (14.8)	184 (41.1)	36 (33.6)
Unknown	10 (1.7)	2 (7.4)	6 (1.3)	2 (1.9)

Note:.

[*] All participants fulfilled the eligibility criterion of age ≥ 18 years. 'Unknown' indicates cases in which only categorical age information (≥ 18 years) was available, and exact age in years could not be retrieved for this analysis.

[**] Occupation status: indicates whether the patient was employed at the time of diagnosis.

(56.9 %, $n = 331$), while 38.4 % ($n = 224$) underwent breast-conserving surgery. Adjuvant endocrine therapy was administered to 68.3 % ($n = 110$) of patients with estrogen receptor-positive tumors. A comprehensive overview of clinicopathological, treatment, and socioeconomic characteristics of patients with and without delayed RT is detailed in Table 1.

A total of 107 patients (18.4 %) experienced delayed initiation of PORT. The univariate and multivariate analyses assessing factors associated with PORT delays are summarized in Table 2. In the univariate analysis, factors associated with a higher risk of delayed PORT included low educational attainment (RR: 1.50; 95 % CI: 1.05–2.14; $p = 0.0276$), reliance on public health insurance (RR: 3.29; 95 % CI: 1.76–6.12; $p = 0.0002$), and the Luminal A/Luminal B HER2-negative tumor subtype (RR: 1.92; 95 % CI: 1.14–3.23; $p = 0.0153$) compared with the Triple Negative subtype. In contrast, patients who did not receive adjuvant endocrine therapy were at a reduced risk of delay (RR: 0.67; 95 % CI: 0.46–0.99; $p = 0.0338$). In the multivariate analysis, reliance on public health insurance emerged as the only independent predictor of PORT delay (RR: 2.98; 95 % CI: 1.60–5.55; $p = 0.0006$).

Discussion

Despite breast cancer being considered a malignancy with a relatively favorable prognosis when identified and treated promptly, mortality rates in Brazil remain high, primarily due to the frequent diagnosis of advanced-stage disease. A multidisciplinary approach is essential to ensure optimal treatment outcomes, with clinical practice commonly involving neoadjuvant systemic therapies before surgery, followed by adjuvant treatments, including RT. These treatment strategies have demonstrated efficacy in reducing recurrence and mortality rates [15–17].

Brazil's healthcare landscape is characterized by a dichotomy between private and public (*Sistema Único de Saúde* – SUS) sectors, with the SUS providing universal, cost-free healthcare to those without private insurance [18,19]. Approximately 75 % of RT treatments are administered through the public healthcare system. Despite this, Brazil faces a critical shortage of linear accelerators, with an estimated deficit of 300 machines. In 2018, around 100,000 patients were unable to access RT, emphasizing the pressing need to expand RT infrastructure. Addressing these deficiencies could potentially prevent over 5000 cancer-related deaths annually, especially from prevalent cancer types (including breast cancer) [20].

Delays in the diagnosis and treatment of breast cancer may result in a more advanced stage of the disease, necessitating a more aggressive therapeutic approach that leads to an unfavorable prognosis and increased mortality rates [15].

In this study, we evaluated the factors associated with delayed initiation of RT in breast cancer patients who underwent neoadjuvant chemotherapy and breast surgery. Approximately 18 % of these patients experienced delays of >8 weeks in starting RT. Socioeconomic factors associated with this delay include health insurance coverage and educational status. Patients with lower levels of education, such as incomplete primary education ($n = 58$; 23.02 %), experienced longer delays in initiating RT than those with completed secondary or higher education ($n = 42$; 15.38 %) ($p = 0.0276$). Furthermore, individuals without private health insurance and who depended on the Brazilian public health system had a longer delay in starting RT than those with private health insurance ($p = 0.0002$). This factor appears to be the most relevant, as the multivariate analysis consistently highlighted the significant association between the public health system and longer delays in initiating RT. In interpreting our findings, it is important to consider how the demographic and clinical characteristics of this cohort compare with the broader population of Brazilian patients with breast cancer. National epidemiological reports consistently show a high proportion of diagnoses at advanced stages and substantial regional disparities in access to timely diagnosis and treatment—patterns that are also reflected in our dataset. The distribution of socioeconomic indicators, and treatment modalities in this cohort aligns with previously published Brazilian studies, particularly those derived from large public-health registries, where patients more frequently present with lower educational levels, reduced income, and limited access to private health insurance. These similarities suggest that our findings are broadly representative of the

Table 2
Univariate and multivariate analysis for risk factors for delay in starting radiation therapy in patients with breast cancer.

			Univariate analysis			Multivariate analysis[d]		
Covariates		Delay of RT n %	Relative Risk[b]	95 % CI[c]	p value	Relative Risk[b]	95 % CI[c]	p value
Age (years)					0,0841			0,0646
	≤ 50[a]	52 (17,0)	1,35	0,96 – 1,89		1,37	0,98 – 1,92	
	> 50	55 (22,9)						
Race					0,5952			
	White[a]	42 (18,2)	1,10	0,77 – 1,56				
	Non-white	63 (20,0)						
Number of children					0,4995			
	≥1[a]	17 (17.0)	1,18	0,73 – 1,88				
	0	88 (20,0)						
Occupation status*					0.,3123			
	Yes[a]	42 (17,6)	1,20	0,84 – 1,70				
	No	64 (21,1)						
Marital status					0,3750			
	Married[a]	59 (18,0)	1,17	0,83 – 1,65				
	Single	47 (21,1)						
Educational level					0,0276			
	Elementary/incomplete education	58 (23,0)	1,50	1,05 – 2,14				
	Complete secondary/higher education[a]	42 (15,4)						
Health coverage					0,0002			0,0006
	Private[a]	10 (7,2)	3,29	1,76 – 6,12		2,98	1,60 – 5,55	
	Public	97 (23,7)						
Family income					0,6380			
	No income up or < 2 minimum salaries	51 (22,00)	1,14	0,62 – 2,10				
	From 2 to 5 minimum salaries	31 (18,2)	0,95	0,50 – 1,80				
	>5 minimum salaries[a]	10 (19,2)						
Clinical stage*					0,7056			
	I	2 (16,7)	0,79	0,22 – 2,88				
	II[a]	46 (21,0)	0,87	0,61 – 3,95				
	III	59 (18,2)						
Molecular Subtype					0,0153			
	Luminal A/ B with HER2 negative	57 (25,2)	1,92	1,14 – 3,23				
	Her 2 positive/ Luminal B with Her 2 positive	25 (16,8)	1,27	0,70 – 2,30				
	Triple negative[a]	15 (13,2)						
Surgical modality								
	Mastectomy	69 (21,1)	1,29	0,89 – 1,85	0,1622			
	Conservative surgery[a]	36 (16,4)						
Endocrine Therapy					0,0338			0,0560
	Yes[a]	74 (21,6)	0,67	0,46 – 0,99		0,69	0,47 – 1,01	
	No	30 (14,5)						

* Occupation status: indicates whether the patient was employed at the time of diagnosis.
[a] Reference level.
[b] Risk of delaying radiation therapy.
[c] Confidence Interval.

national context, especially within the public healthcare system, which treats the majority of breast cancer cases in the country. Nonetheless, regional heterogeneity in healthcare infrastructure and the predominance of public-system patients in our cohort must be considered when extrapolating results to populations with different resource availability or sociodemographic compositions [21,22].

In Brazil, there are reports of delays in starting treatment for women with breast cancer in public hospitals [9]. Furthermore, a correlation has been established between the increased incidence of breast cancer and geographical areas characterized by a lower socioeconomic status. Individuals with lower socioeconomic status encounter challenges in accessing and utilizing public healthcare services, leading to diagnostic delays and delays in receiving appropriate therapeutic interventions [23].

A study conducted by Albrecht et al. in 2013 [24] demonstrated that breast cancer prevention was significantly influenced by socioeconomic status. According to their findings, there is a positive correlation between good socioeconomic status and involvement in preventive procedures. Additionally, females with limited educational backgrounds were strongly linked to advanced disease staging and an elevated risk of metastasis development, making them more susceptible to a late diagnosis than women from higher social classes and with a higher level of education.

Similarly, Rodrigues et al. (2010) [25] observed higher survival rates in patients with a more affluent economic status as women from lower socioeconomic classes face limitations in accessing healthcare services. This results in delays in early detection, hindering timely and effective treatment. Guerra et al. (2015) [26] also identified a correlation between receiving care from public healthcare and poorer patient outcomes, likely due to late-stage disease diagnosis. These research outcomes highlight the presence of disparities in accessing preventive measures, leading to delayed diagnoses and, subsequently, a worse prognosis for women of lower socioeconomic status.

The international literature has further correlated the absence of private health insurance with delayed RT. Shammas et al. (2019) [27] identified a group of American women diagnosed with breast cancer who lacked private health insurance and experienced longer delays in receiving adjuvant RT compared to those with private health insurance ($p < 0.001$). Additional factors linked to delayed RT included race, particularly being black, and undergoing breast reconstruction. Within our cohort, we were unable to establish a relationship between patient ethnicity and delayed RT.

Currently, data on the consequences of delayed PORT are scarce, and prospective randomized trials are unlikely to be conducted due to ethical concerns. However, specifically regarding delay in receiving timely RT, the implications for patients may be directly related to worse

clinical outcomes. As reported by Marta et al. [28] RT initiated up to 8 weeks after surgery was related to better locoregional recurrence-free survival in patients with luminal breast cancer who underwent preoperative systemic therapy, suggesting that the early start of RT is important for these patients. This situation becomes even more relevant when Silva et al. [8] evaluated patients treated exclusively at a public center in Brazil and demonstrated that PORT started up to 8 weeks after surgery and was associated with better disease-free survival and overall survival in patients with locally advanced breast cancer who received neoadjuvant chemotherapy. Although understanding the impact of delayed PORT on oncologic outcomes is clinically relevant, survival analyses were not included in the present study, which was designed primarily to investigate determinants of delayed treatment initiation. Our group is currently developing a dedicated follow-up study to evaluate whether PORT timing is associated with differences in recurrence or survival outcomes within this national cohort.

Therefore, identifying factors contributing to delays in initiating RT is essential, as these delays are frequently multifactorial, as evidenced by our analysis. Social determinants, constrained service availability, medical decision-making processes, and patient comprehension, particularly in relation to educational level, are all influential. This study underscores the complex, multidimensional nature of these delays, highlighting the need for further research to enhance care delivery—particularly for patients in vulnerable circumstances. This understanding can assist in implementing organizational measures within both the public and private healthcare sectors to ensure optimal patient care and minimize the risk of compromising clinical outcomes. Furthermore, as cancer incidence and prevalence continue to rise, the Brazilian healthcare system must address structural and financial barriers to adequate treatment [29]. Without strategic interventions, the increasing demand for cancer care will further strain the system, exacerbating existing disparities. Financial toxicity and indirect barriers to care are also significant concerns that must be addressed to ensure equitable treatment access [18].

Although mastectomy was more frequently performed in the group experiencing delayed PORT initiation, this variable did not demonstrate a statistically significant association with delay in our multivariable analysis. This suggests that, within our cohort, surgical modality alone was not an independent determinant of treatment timing. Nonetheless, it is plausible that mastectomy may contribute indirectly to longer intervals between surgery and adjuvant therapy in some settings, given its potentially longer postoperative recovery and higher likelihood of requiring wound management. However, these factors did not appear to significantly influence PORT initiation in our population. Future studies with more granular postoperative data—including complication rates, healing time, and reconstructive details—may help clarify whether surgical modality meaningfully affects RT timing in different healthcare contexts.

Our study has certain limitations that should be acknowledged. The evaluated population may not fully represent the entire Brazilian population, given the variability in healthcare access and quality across different regions and municipalities. Additionally, we identified clinicopathological factors that influenced delays in initiating RT, such as molecular subtype and the use of endocrine therapy. Understanding the underlying reasons for these observed disparities is difficult, as these factors are not typically considered direct contributors to RT delays. Moreover, AMAZONA III cohort strengthens the reliability of data collection, unmeasured confounding variables—such as institutional workflow constraints, local radiotherapy infrastructure capacity, geographic distance to treatment centers, and postoperative complications—may also have influenced PORT timing but were not captured within the registry. Additionally, certain treatment-related variables that could contribute to a more granular understanding of delays—such as the interval between neoadjuvant chemotherapy completion and surgery, institution-level scheduling capacity, and the availability of RT equipment—were not available in the dataset. Incorporating these variables in future analyses may improve the characterization of multifactorial contributors to delayed PORT.

Nevertheless, our research was based on a comprehensive, prospective, population-based database that includes 22 centers from all regions of the country, offering a detailed overview of the national situation. Our findings highlight the urgent need for strategic health policy reforms aimed at minimizing delays in RT initiation in the public healthcare system. Such reforms should focus on expanding RT capacity, ensuring the equitable distribution of advanced technologies, and fostering collaboration among healthcare providers, policymakers, and community organizations to develop targeted interventions. Addressing these systemic inequities is essential to improving outcomes for vulnerable populations and potentially reducing cancer-related mortality.

In conclusion, in this Brazilian cohort, reliance on public health insurance emerged as the primary independent predictor of delayed initiation of PORT in breast cancer patients who received neoadjuvant chemotherapy. Socioeconomic factors, particularly lower educational levels and household income, also contributed to delays, highlighting disparities within the healthcare system. Addressing these barriers is essential to improve timely access to PORT and to potentially enhance clinical outcomes in this population.

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Author contributions

All authors contributed substantially to the project, as defined by the International Committee of Medical Journal Editors (ICMJE). Material preparation, data collection and analysis were performed by JP and GNM. The first draft of the manuscript was written by JP and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request. These data can be requested by any qualified researchers who engage in rigorous, independent, scientific research and will be provided following review and approval of a research proposal, statistical analysis plan, and execution of a data sharing agreement. Data requests can be submitted to the corresponding author at any time after acceptance of this manuscript for publication.

Ethics approval

This study was approved by the Institutional Review Boards of all participating institutions and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All study participants provided written informed consent prior to enrolment.

CRediT authorship contribution statement

Júlio César Prestes: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Gustavo Viani:** Investigation. **Andre Guimaraes Gouveia:** Investigation. **Maurício Fraga da Silva:** Investigation. **Fabio Ynoe. Moraes:** Investigation. **Daniela Dornelles Rosa:** Investigation. **Carlos Henrique Escosteguy Barrios:** Investigation. **Gustavo Werutsky:** Investigation.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Same authors, Carlos Barrios, Gustavo Werutsky, Tomás Reinert and Eduardo Cronemberger declare conflicts of interests (see below), the other authors have no relevant financial or non-financial interests to disclose.

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