

Twenty years of breast cancer epidemiology and treatment patterns in São Paulo, Brazil—observed versus expected treatment utilization in a retrospective cohort



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Summary

Background Over half of new breast cancer cases occur in low- and middle-income countries, with disparities in survival outcomes due to late-stage diagnoses, healthcare access gaps, and biological differences. This retrospective cohort study examined trends in survival, stage distribution, and treatment utilization for breast cancer in Brazil, an upper middle-income country.

Methods Patients newly diagnosed with invasive breast cancer between 2000 and 2019 were identified from São Paulo's Oncocenter Foundation registry. Data on demographics, diagnosis stage, diagnosis-to-treatment intervals, and treatments received were analyzed in 5-year blocks. Median overall survival was estimated using the Kaplan–Meier method. Actual treatment utilization was compared to model-based estimates of optimal utilization derived from the National Comprehensive Cancer Network Guidelines' Enhanced and Maximal Resource Modules.

Findings We included 125,005 patients, with a median age at diagnosis of 55 years (interquartile range 46–75); 99.4% (n = 124,218) were female. The proportion with early disease remained stable over time (61.7% in 2000–2004, 62.4% 2015–2019). Median overall survival increased from 10.7 years (2000–2004) to 11.7 years (2010–2014); median survival for 2015–2019 was not reached. Median overall survival was 20.8, 15.1, 6.8, and 2.0 years for stages I–IV, respectively. Median diagnosis-to-treatment interval more than doubled over time. From 2000 to 2004 to 2015–2019, chemotherapy use decreased from 71.5% to 68.9%; radiotherapy use decreased from 64.0% to 56.5%, and surgery utilization decreased from 80.3% to 74.8%; endocrine therapy use varied between 54% and 62%. Gaps between observed and model-based estimates of treatment utilization were seen across all stages.

Interpretation Overall survival in patients with breast cancer in São Paulo has improved over time. However, significant treatment gaps and increasing diagnosis-to-treatment intervals suggest systemic barriers to optimal care delivery.

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Research in context

Evidence before this study

We searched the PubMed database from study inception to February 28, 2025, for published studies pertaining to breast cancer survival outcomes in Brazil using the search terms: “breast cancer”, “Brazil”, “survival”, “mortality”, “epidemiology”, and “trend”. Prior work using data from six Brazilian registries has shown an improvement in 5-year net survival in patients with breast cancer between 2000 and 2009, which has stabilized between 2010 and 2014. However, information regarding longitudinal trends in treatment patterns and adherence to evidence-based care is scarce, particularly when considering evolving screening and treatment recommendations over the past two decades.

Added value of this study

Improvements in survival for patients with breast cancer in São Paulo between 2000 and 2019 may be related to the achievement of key performance indicators for early detection

as recommended by the Global Breast Cancer Initiative. The integration of local epidemiological data into existing modelling frameworks allowed comparisons between observed and expected treatment rates. Lower than expected treatment utilization across all treatment modalities and all stages at diagnosis suggest that focusing future efforts on improving the provision of guideline-concordant care to completion could further improve outcomes.

Implications of all the available evidence

Our findings underscore the need for targeted interventions to improve timely access to evidence-based care for patients with breast cancer in the state of São Paulo. Identifying overall differences between expected and observed treatment utilization will allow policy makers and governments to critically evaluate cancer care delivery and investment needs within their healthcare system.

Introduction

Breast cancer is the second most common cancer globally, with 2.2 million incident cases annually.¹ Over half of diagnoses occur in low- and middle-income countries (LMIC), where case-fatality rates exceed those of high-income countries (HIC). This discrepancy is attributable to various factors such as late-stage diagnosis and disparities in access to health care.²

Breast cancer is the second most common cancer in Brazil, and the leading cause for cancer-related death in women.¹ Prior work using data from six Brazilian registries, including over 49,000 patients with breast cancer revealed an increase in 5-year net survival from 2000 to 2009, followed by stabilization through 2014.³ A nationwide cohort study in over 59,000 women with breast cancer found significant differences in survival outcomes according to race.⁴ Similar to other LMIC in Latin America, the proportion of late-stage diagnosis (i.e., stages III–IV) in Brazil is approximately 40%, with significant regional variations.⁵ Despite multimodal treatment being recommended for most patients with breast cancer, population-based registries in Brazil have shown that only 58% of patients receive more than one treatment modality.⁶ Further examination is warranted to assess longitudinal trends in treatment patterns and adherence to evidence-based care to better characterize potential gaps in care delivery. The State of São Paulo, Brazil, has maintained a high-quality cancer registry since 2000, providing an opportunity for detailed analysis of treatment patterns and stage at presentation from an upper middle-income country with a dual public and private healthcare system.

In this study, our objectives are to: (i) characterize the stage distribution and temporal trends for patients diagnosed with breast cancer in São Paulo in 2000–2019, (ii)

examine survival outcomes by stage at diagnosis, (iii) characterize treatment utilization by stage; and (iv) compare observed treatment utilization to published model estimates, adapted to local stage distribution.

Methods

This retrospective cohort study includes all incident cases of invasive breast cancer diagnosed in the State of São Paulo, Brazil, between 2000 and 2019 identified from São Paulo's Oncocenter Foundation (FOSP) registry (available at <http://fosp.saude.sp.gov.br>). The FOSP registry is a publicly accessible dataset that has gathered information on cancer cases diagnosed in the state of São Paulo since January 1, 2000. It includes comprehensive details on cancer staging, demographic characteristics, treatment modalities, and patient outcomes. It is made up of 81 hospital-based cancer registries covering over 40 municipalities across all regional departments of health in the state of São Paulo and it is an important tool for monitoring and improving the quality of oncological care. The database undergoes a validation process on a quarterly basis. Information for patient follow-up is obtained through review of medical records and updated yearly. Quality control indicators for completeness follow national and international recommendations, aiming for $\geq 95\%$ of cases with histologic confirmation, $\leq 10\%$ of cases with missing staging information, and $\leq 20\%$ of cases lost to follow up.⁷

Cohort identification

Patients aged ≥ 18 years diagnosed with invasive breast carcinoma between January 1, 2000, and December 31, 2019, were included. Patients were identified using the International Classification of Diseases for Oncology

(ICD-O) codes C50.0–C50.9. The second edition of ICD-O was used until 2005, and starting in 2006, patients were coded following the third edition. A complete list of included and excluded histological subtypes is available in [Supplementary Fig. S1](#). To address potential sources of bias due to incomplete information, patients with unknown stage were excluded. Patients with ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) were also excluded to avoid biased estimations of survival.

The following information was extracted for analysis: patient age, level of schooling, sex, clinical stage, year and date of diagnosis (grouped into 5-year blocks), date of first appointment, date of treatment initiation, type of treatment received (including radiation, surgery, chemotherapy, endocrine therapy), date of last follow-up, and vital status. Within the FOSP registry, sex is coded as male/female. Clinical stage was coded according to the AJCC (American Joint Committee on Cancer)/UICC (Union for International Cancer Control) TNM (tumor-node-metastasis) staging system's 5th edition until 2005, the 6th edition from 2006 to 2013, and the 7th edition starting in 2014. Treatment information for all modalities is coded as treatment received/not received without information on treatment completion. Causes of death are coded as cancer-related or due to other causes. We determined age subgroups by eligibility for mammographic screening according to national and international guidelines (<40 years, 40–49 years, 50–69 years, ≥70 years), and we grouped educational level according to compulsory education in Brazil (illiterate; incomplete/complete compulsory education grouped as 'some schooling'; higher education). Diagnosis-to-treatment intervals were calculated from the date of diagnosis to the date of treatment initiation, and dichotomized using a cutoff of 60 days in accordance to Brazilian Law 12.732/2012, mandating that all patients with cancer initiate treatment within 60 days of pathological confirmation in the public health system (*Sistema Único de Saúde*).⁸ Patients were followed until death or November 30, 2023, whichever occurred first.

Estimates of guideline concordance

Estimates of the expected treatment demands presented throughout this manuscript were drawn from existing modelling tools for systemic treatment, surgery, and radiation.^{9–11} The methods to adapt these tools to local contexts have been previously described.⁹ Given Brazil's status as an upper middle-income country, we used the National Comprehensive Cancer Network (NCCN) Enhanced resource module to estimate stage-specific chemotherapy and endocrine therapy demands. However, NCCN guidelines likely overestimate chemotherapy demands for LMICs.⁹ Therefore, we performed a secondary comparison to Maximal level resource estimates, which incorporate genomic assays for

chemotherapy selection. Stage specific estimates of optimal utilization were available for endocrine therapy, surgery and chemotherapy, but not for radiotherapy. We estimated the optimal radiotherapy demands would be 87% in the total population based on published models,¹¹ regardless of stage distribution, acknowledging that the estimated proportion for radiation may be higher than expected in an LMIC due to a higher proportion of mastectomy and later disease stage presentation. For radiation and surgery, due to the absence of resource stratified estimates, identical estimates were used for both the enhanced and maximal setting.

We explored guideline concordance amongst the subgroup of patients with stage IIIA disease. This population was chosen as guidelines recommend chemotherapy, surgery and radiation for almost all patients, regardless of histological subtype. We did not include endocrine therapy in our estimates of guideline concordance due to lack of histological data in our dataset. Patients were categorized into 3 groups: patients receiving all guideline concordant care (All Group), patients receiving some guideline concordant care (Some Group—receiving at least one of radiation, chemotherapy, surgery), and patients receiving no guideline concordant care (None Group). Survival was compared between these three groups.

Analysis

Patient, disease and treatment characteristics are reported as median with interquartile range (IQR). Temporal trends, grouped into 5-year blocks, are evaluated for demographic features, treatment, and diagnosis-to-treatment intervals. For comparisons across groups, the chi-square test was used for proportions, and the Kruskal–Wallis test for non-parametric data. Survival was estimated using the Kaplan–Meier method and compared using the log-rank test. Overall survival was defined as the time from the date of diagnosis to death from any cause. Cancer-specific survival was defined as the time from date of diagnosis to death due to cancer, with patients who died from other causes censored at the time of death. Patients were censored if they were still alive at time of last follow-up. Patients without updated follow-up information for over two consecutive years were considered lost to follow-up, as per FOSP registry guidelines, and censored at the date of last contact. We performed Cox proportional hazards regression analyses, adjusting for key covariates including patient age, treatment modalities (chemotherapy, surgery, radiation therapy, and hormone therapy), cancer stage, diagnostic periods, and diagnosis-to-treatment intervals. A second stage-stratified analysis was also performed. Survival estimates and hazard ratios (HR) are reported with 95% confidence intervals (95% CI). The threshold for statistical significance was set at $p < 0.05$; however, given the dataset's large size and resulting statistical power, we focus on numerical and clinically significant differences

over time and between patient groups, rather than statistical significance. All analyses were performed using STATA versions 17 and 18.¹² Analyses were conducted using complete case data; patients with missing values for any variables of interest were excluded. This report was organized following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines¹³ for cohort studies.

This study was exempt from research ethics board review in accordance with Resolution 674 of the Brazilian National Health Council and the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans—TCPS 2 (Chapter 2), as it relied exclusively on publicly available information that is legally accessible and appropriately protected by law.

Results

Description of cohort and baseline demographics

Our cohort included 125,005 patients diagnosed with invasive breast cancer in São Paulo between 2000 and 2019 ([Supplementary Fig. S1](#)). Baseline characteristics for patients excluded due to unknown stage (N = 2890) can be found in [Supplementary Table S1](#). Among the cohort of 125,005 patients, the median follow-up was 7.4 years (95% CI 7.38–7.47). Among 22.1% patients considered as lost to follow-up in the FOSP registry (n = 27,674), median follow-up was 7.1 years (95% CI 7.03–7.14). The median age at diagnosis was 55 years (IQR 46–75); 0.6% of the population (n = 787) was male. The number of patients included in the FOSP registry increased over each 5-year block: 21,481 (17.2%) of patients were diagnosed in 2000–2004, while 39,778 (31.8%) were diagnosed in 2015–2019. Most patients were diagnosed with early-stage disease, with 23.7% (n = 29,683) diagnosed with stage I disease and 38.6% (n = 48,217) with stage II; 27.4% (n = 34,333) were diagnosed with locally advanced disease, and 10.2% (n = 12,772) with de novo metastatic disease. Regarding receipt of treatment, 69.6% (n = 87,023) of patients received chemotherapy, 57.6% (n = 72,042) radiotherapy, 78.5% (n = 98,153) surgery, and 57.4% (n = 71,741) endocrine therapy, while 2.3% (n = 2931) received no treatment. Half of the cohort (52.5%; n = 65,603) arrived at a FOSP institution without a prior histologic diagnosis of breast cancer, while 47.5% (n = 59,402) had a histological diagnosis before their first appointment. Median time from diagnosis to first treatment was 57 days (IQR 27–99), with 47.9% (n = 58,553) starting treatment ≥60 days after confirmed diagnosis ([Table 1](#)).

Treatment and outcomes stratified by stage

Patient characteristics, treatments and outcomes differed by stage at diagnosis ([Table 1](#)). Median time from diagnosis to first treatment differed across stages, being longest for stages II (60 days; IQR 23–104) and III (60 days; IQR 28–103) and shortest in stage IV (50 days;

IQR 24–90) (p < 0.0001). Median overall survival in the full cohort was 11.6 years (95% CI 11.4–11.7). Median overall survival by stage at diagnosis was 20.8 (95% CI 20.1–21.5), 15.1 (95% CI 14.8–15.4), 6.8 (95% CI 6.7–7.0), and 2.0 (95% CI 2.0–2.1) years for stages I, II, III, and IV, respectively (p < 0.0001) ([Fig. 1](#)). Of 47,231 deaths observed during the study period, 65.6% were cancer related. In the full cohort, the median cancer-specific survival was not reached. According to stage, the median cancer-specific survival was not reached for stages I and II. Median cancer-specific survival for stages III and IV was 11.0 years (95% CI 10.6–11.4) and 2.2 years (95% CI 2.2–2.3), respectively ([Supplementary Fig. S2](#)).

On multivariate analysis, the variables with the largest impacts on overall survival were stage and treatment modalities ([Supplementary Table S2](#)). Compared to patients with stage I disease, hazards of death were progressively higher for patients with stage II (HR 1.8, 95% CI: 1.7–1.8), stage III (HR 4.1, 95% CI: 3.9–4.2), and stage IV disease (HR 11.1, 95% CI: 10.7–11.5), respectively. All treatment modalities were associated with a significant reduction in the hazard of death. A diagnosis-to-treatment interval over 60 days showed a hazard ratio of 0.877 (95% CI: 0.861–0.895). Age at diagnosis showed an increase in hazard with each additional year (HR = 1.021, 95% CI: 1.021–1.022). Diagnostic periods showed improved outcomes over time, with the periods 2010–2014 and 2015–2019 demonstrating hazard ratios of 0.835 (95% CI: 0.813–0.858) and 0.766 (95% CI: 0.743–0.790), respectively, compared to the baseline period of 2000–2004.

Treatment and outcomes stratified by time-period

We also observed differences in patient characteristics, treatments and outcomes over time ([Table 2](#)). The proportion of patients diagnosed with early-stage (I/II) disease remained relatively constant over time: 61.7% (n = 13,245) in 2000–2004, 62.7% (n = 16,445) in 2005–2009, 62.4% (n = 23,399) in 2010–2014, and 62.4% (n = 24,811) 2015–2019. However, modest stage migration was seen from stage III to IV ([Fig. 2](#)). The proportion of chemotherapy usage decreased slightly from 71.5% (n = 15,349) to 68.9% (n = 27,394) between 2000–2004 and 2015–2019. Similarly, the proportion of radiation and surgery utilization decreased between 2000–2004 and 2015–2019 from 64.0% (n = 13,738) to 56.5% (n = 22,494), and from 80.3% (n = 17,246) to 74.8% (n = 29,735), respectively. Endocrine treatment utilization fluctuated over time, with the highest proportion observed in 2005–2009 (62.5%, n = 16,404), and the lowest in 2015–2019 (54.4%, n = 21,649). Median overall survival increased from 10.7 years (95% CI 10.4–10.9) in 2000–2004 to 11.7 years (95% CI 11.5–12.0) in 2010–2014; median overall survival has not been reached in the 2015–19 period (p < 0.0001) ([Fig. 3](#)). In patients with stage III disease, median

Characteristic	Full cohort (N = 125,005)	Stage I (n = 29,683)	Stage II (n = 48,217)	Stage III (n = 34,333)	Stage IV (n = 12,772)	p-value
Gender						<0.0001
Female	124,218 (99.4%)	29,526 (99.5%)	47,955 (99.5%)	34,078 (99.3%)	12,659 (99.1%)	
Male	787 (0.6%)	157 (0.5%)	262 (0.5%)	255 (0.7%)	113 (0.9%)	
Median age in years (IQR)	55 (46–75)	58 (49–67)	55 (46–65)	54 (45–65)	56 (46–67)	<0.0001
Age subgroup						<0.0001
<40	13,224 (10.6%)	1842 (6.2%)	5174 (10.7%)	4606 (13.4%)	1602 (12.5%)	
40–49	29,154 (23.3%)	6204 (20.9%)	11,688 (24.2%)	8635 (25.2%)	2627 (20.6%)	
50–69	60,155 (48.1%)	16,116 (54.3%)	22,906 (47.5%)	15,201 (44.3%)	5932 (46.4%)	
≥70	22,472 (18.0%)	5521 (18.6%)	8449 (17.5%)	5891 (17.2%)	2611 (20.4%)	
Year of diagnosis						<0.0001
2000–2004	21,481 (17.2%)	3941 (13.3%)	9304 (19.3%)	6222 (18.1%)	2014 (15.8%)	
2005–2009	26,230 (21.0%)	6055 (20.4%)	10,390 (21.5%)	7531 (21.9%)	2254 (17.6%)	
2010–2014	37,516 (30.0%)	9372 (31.6%)	14,027 (29.1%)	10,239 (29.8%)	3878 (30.4%)	
2015–2019	39,778 (31.8%)	10,315 (34.8%)	14,496 (30.1%)	10,341 (30.1%)	4626 (36.2%)	
Level of education						<0.0001
No schooling	4926 (3.9%)	726 (2.4%)	1801 (3.7%)	1691 (4.9%)	708 (5.5%)	
Some schooling	72,313 (57.8%)	16,526 (55.7%)	27,796 (57.6%)	20,943 (59.2%)	7673 (60.1%)	
University schooling	13,074 (10.5%)	4254 (14.3%)	5098 (10.6%)	2766 (8.1%)	956 (7.5%)	
Missing data	34,692 (27.8%)	8177 (27.5%)	13,522 (28.0%)	9558 (27.8%)	3435 (26.9%)	
Treatments received						
Any surgery	98,153 (78.5%)	25,688 (86.5%)	41,598 (86.3%)	26,770 (78.0%)	4097 (32.1%)	<0.0001
Any radiation	72,042 (57.6%)	17,833 (60.1%)	28,140 (58.4%)	21,290 (62.0%)	41,779 (37.4%)	<0.0001
Any chemotherapy	87,023 (69.6%)	12,502 (42.1%)	35,637 (73.9%)	29,201 (85.1%)	9,683 (75.8%)	<0.0001
Any endocrine therapy	71,741 (57.4%)	19,545 (65.8%)	28,921 (60.0%)	17,571 (51.2%)	5704 (44.7%)	<0.0001
No treatment	2931 (2.3%)	619 (2.1%)	649 (1.3%)	614 (1.8%)	1049 (8.2%)	<0.0001
Median time from diagnosis to date of first treatment (IQR) ^a	57 days (27–99)	60 days (23–104)	60 days (28–103)	55 days (28–94)	50 days (24–90)	<0.0001
Time to treatment >60 days ^a	58,553 (47.9%)	14,498 (49.9%)	23,767 (49.9%)	15,367 (45.6%)	4921 (41.9%)	<0.0001
Median overall survival in years (95% CI)	11.6 (11.4–11.7)	20.8 (20.1–21.5)	15.1 (14.8–15.4)	6.8 (6.7–7.0)	2.0 (2.0–2.1)	<0.0001

IQR, interquartile range. ^aAmong the 122,074 patients who received treatment only. Date of treatment initiation was missing in 38 patients.

Table 1: Patient characteristics in the full cohort and by stage at breast cancer diagnosis.

overall survival increased from 5.3 years (95% CI 5.1–5.6) in 2000–2004 to 7.3 years (95% CI 7.0–7.6) in 2015–2019 ($p < 0.0001$). There has been little numerical change in median overall survival over time for stages I, II, and IV. Cancer-specific survival showed an increase over time ([Supplementary Fig. S3](#)), and stage-by-stage 5-year cancer-specific survival estimates over time are reported in [Supplementary Table S3](#).

The median time from diagnosis to first treatment increased from 32 days (IQR 0–63) in 2000–2004 to 76 days (IQR 44–120) in 2015–2019 ($p < 0.0001$). Diagnosis-to-treatment intervals were longer in patients diagnosed at facilities outside of FOSP (47.5% of the cohort) (median 79 days, IQR 47–128) compared to those diagnosed at FOSP institutions (median 41 days, IQR 0–72). The proportion of patients treated ≥ 60 days after first diagnosis rose from 26.8% ($n = 5630$) in 2000–2004 to 61.8% ($n = 23,942$) in 2015–2019. Overall survival was longer for those treated ≥ 60 days after diagnosis for patients with stage II, III and IV in the overall population ([Fig. 4](#)). Across all stages of disease, endocrine therapy utilization was higher among patients treated ≥ 60 days after

diagnosis in comparison to those that initiated treatment < 60 days after diagnosis. For stage I, 69.4% ($n = 10,133$) received endocrine therapy in the ≥ 60 -day group versus 63.6% ($n = 9408$) in the < 60 -day group; for stage II 62.3% ($n = 14,839$) versus 58.9% ($n = 14,071$); for stage III 54.2% ($n = 8344$) versus 50.1% ($n = 9225$); and for stage IV, 52.4% ($n = 2592$) versus 45.2% ($n = 3111$).

A comparison of actual and expected treatments by stage

A comparison of actual and expected treatment use proportions for surgery, radiation, chemotherapy and endocrine therapy are shown in [Fig. 5](#) and [Table 3](#). Potential causes for treatment gaps are explored in [Supplementary Table S3](#).

Among patients with stage I disease, only 60.1% ($n = 17,833$) received radiation. The proportion of surgical resection rates was 86.5% ($n = 25,688$), though the type of surgery (mastectomy versus lumpectomy) could not be determined. By comparison, the model estimate for surgical resection in stage I disease is 99%. Chemotherapy utilization was 42.1% ($n = 12,502$) in

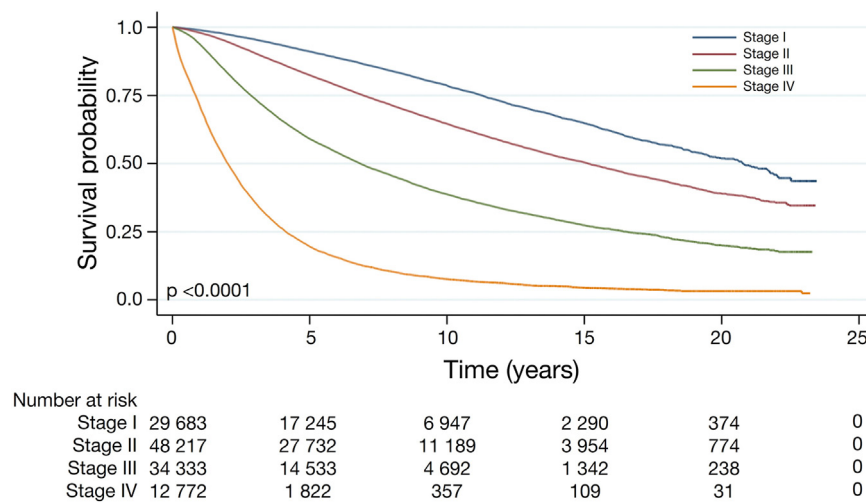


Fig. 1: Overall survival stratified by cancer stage at diagnosis.

patients with stage I disease, compared to a model estimate of 37.8% (n = 11,220) using NCCN Maximal resources, which assumes use of genomic assays for

chemotherapy selection. Endocrine therapy usage was 65.8% (n = 19,545), compared to model estimates of 80.6% (n = 23,924).

Characteristic	2000–2004 (n = 21,481)	2005–2009 (n = 26,230)	2010–2014 (n = 37,516)	2015–2019 (n = 39,778)	p-value
Gender					0.010
Female	21,361 (99.4%)	26,076 (99.4%)	37,297 (99.4%)	39,484 (99.3%)	
Male	120 (0.6%)	154 (0.6%)	219 (0.6%)	294 (0.7%)	
Median age in years (IQR)	55 (46–66)	55 (46–66)	56 (47–66)	56 (46–66)	<0.0001
Age subgroup					<0.0001
<40 years	2283 (10.6%)	2651 (10.1%)	3926 (10.5%)	4364 (11.0%)	
40–49 years	5412 (25.2%)	6310 (24.1%)	8611 (23.0%)	8821 (22.2%)	
50–69 years	9757 (45.4%)	12,516 (47.7%)	18,217 (48.6%)	19,665 (49.4%)	
≥70 years	4029 (18.8%)	4753 (18.1%)	6762 (18.0%)	6928 (17.4%)	
Stage at diagnosis					<0.0001
I	3941 (18.3%)	6055 (23.1%)	9372 (25.0%)	10,315 (25.9%)	
II	9304 (43.3%)	10,390 (39.6%)	14,027 (37.4%)	14,496 (36.4%)	
III	6222 (28.9%)	7531 (28.7%)	10,239 (27.3%)	10,341 (26.0%)	
IV	2014 (9.4%)	2254 (8.6%)	3878 (10.3%)	4626 (11.6%)	
Level of education					<0.0001
No schooling	1423 (6.6%)	1076 (4.1%)	1284 (3.4%)	1143 (2.9%)	
Some schooling	11,402 (53.1%)	13,393 (51.1%)	21,754 (58.0%)	25,764 (64.8%)	
University schooling	1667 (7.8%)	1965 (7.5%)	4048 (10.8%)	5394 (13.6%)	
Missing data	6989 (32.5%)	9796 (37.3%)	10,430 (27.8%)	7477 (18.8%)	
Treatments received					
Any chemotherapy	15,349 (71.5%)	18,827 (71.8%)	25,453 (67.8%)	27,394 (68.9%)	<0.0001
Any radiation	13,738 (64.0%)	14,959 (57.0%)	20,851 (55.6%)	22,494 (56.5%)	<0.0001
Any surgery	17,246 (80.3%)	21,405 (81.6%)	29,767 (79.3%)	29,735 (74.8%)	<0.0001
Any endocrine therapy	12,386 (57.7%)	16,404 (62.5%)	21,302 (56.8%)	21,649 (54.4%)	<0.0001
No treatment	446 (2.1%)	461 (1.8%)	988 (2.6%)	1036 (2.6%)	<0.0001
Median time from diagnosis to date of first treatment (IQR) ^a	32 days (IQR 0–63)	45 days (IQR 17–78)	64 days (IQR 33–106)	76 days (IQR 44–120)	<0.0001
Time to treatment >60 days ^a	5630 (26.8%)	9526 (37.0%)	19,455 (53.3%)	23,942 (61.5%)	<0.0001
Median overall survival in years (95% CI)	10.7 (10.4–10.9)	11.4 (11.2–11.7)	11.7 (11.5–12.0)	NR (NR)	<0.0001

IQR: interquartile range. ^aAmong the 122,074 patients who received treatment only. Date of treatment initiation was missing in 38 patients.

Table 2: Patient characteristics by year of breast cancer diagnosis.

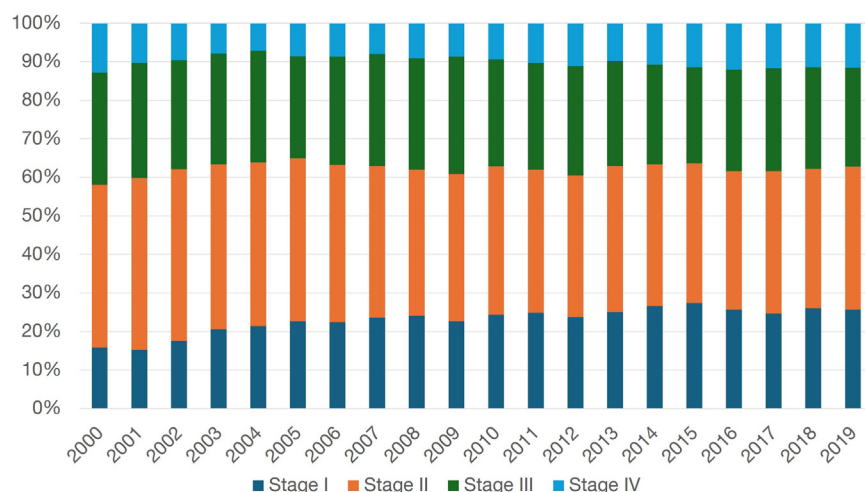


Fig. 2: Changes in breast cancer stage at diagnosis over time.

Among patients with stage II disease, 86.3% ($n = 41,598$) underwent surgical resection compared to a model estimate of 99% ($n = 47,735$). Only 58.4% ($n = 28,140$) received radiation, with inferior overall survival for those untreated ($p < 0.0001$) (Supplementary Fig. S4). Chemotherapy was given to 73.9% ($n = 35,637$), compared to a model estimate of between 37.8% ($n = 18,226$) and 85.3% ($n = 41,129$), depending on resource level. Only 60% ($n = 28,921$) were prescribed endocrine therapy, compared to our model estimate of 80.6% ($n = 23,924$).

Among patients with stage III disease, 85.1% ($n = 29,201$) received chemotherapy versus a model estimate of 95% ($n = 32,616$). Only 51.2% of patients ($n = 17,571$) received endocrine therapy, against a model

estimate of 72% ($n = 24,720$). Radiation was administered to 62% ($n = 21,290$), and 6.4% ($n = 2,214$) received radiation without surgical resection, possibly reflecting unresectable disease. In patients with stage IIIA disease, 64.4% ($n = 10,442$) received radiation, 81.5% ($n = 13,202$) underwent surgery, and 87.4% ($n = 14,172$) had chemotherapy; 54.8% ($n = 8,885$) received All recommended care (radiation, surgery and chemotherapy), 42.8% ($n = 6,933$) received Some, and 2.4% ($n = 388$) received None. Among those who received only partial guideline concordant care, the most frequently omitted treatment was radiation (77.5%, $n = 5,376$), followed by surgery (37.7%, $n = 2,616$) and chemotherapy (23.7%, $n = 1,646$). Significant differences in median overall survival were seen across these 3 groups (All 10.9 years

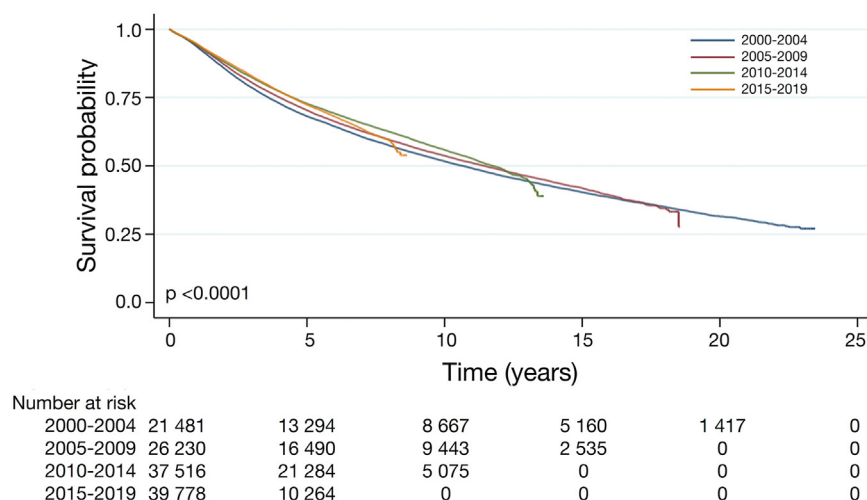


Fig. 3: Overall survival stratified by year of diagnosis.

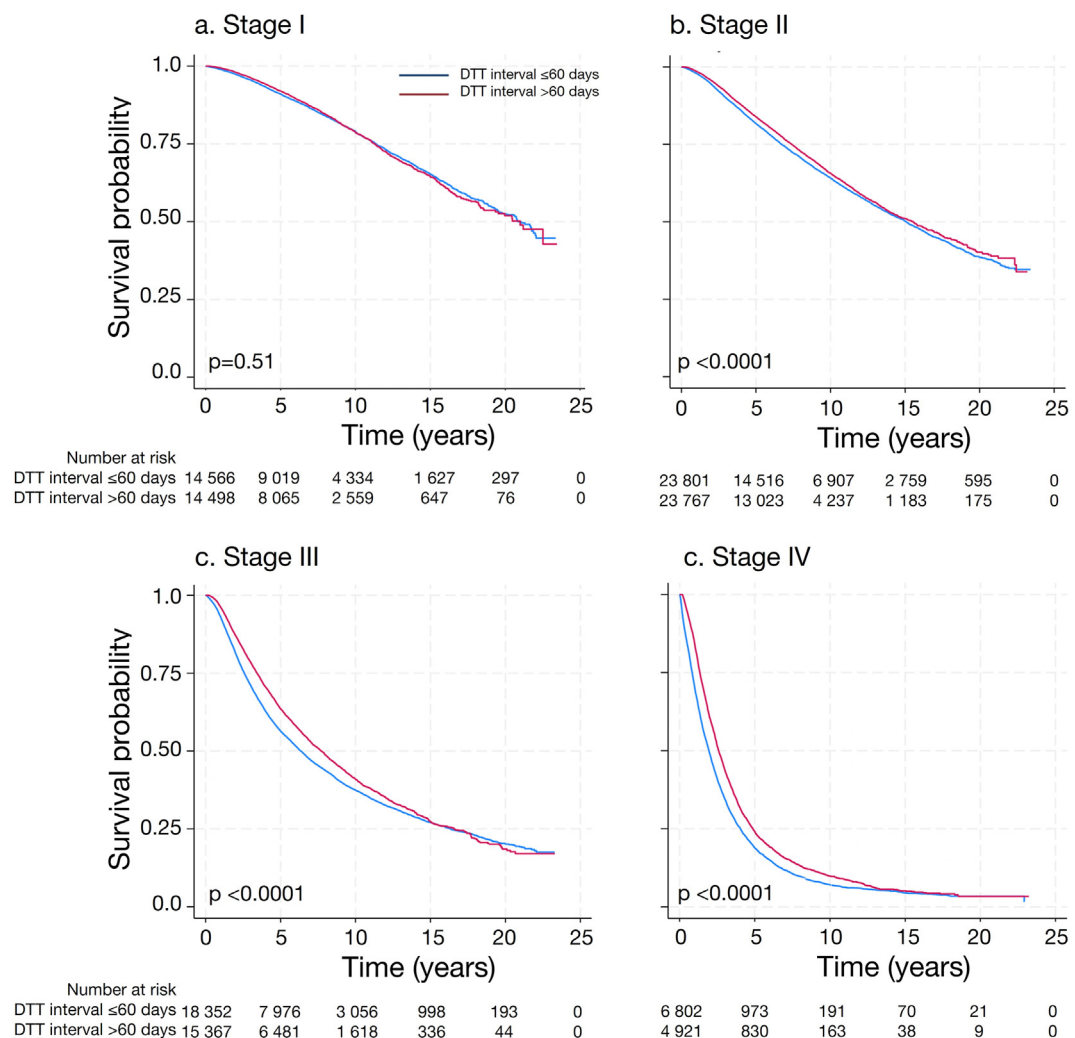


Fig. 4: Overall survival according to interval from diagnosis to treatment stratified by stage. DTT interval: diagnosis-to-treatment interval, measured from the date of diagnosis to the date of treatment initiation. Overall survival according to DTT interval was analyzed in patients who received treatment (n = 122,074).

(95% CI 10.4–11.3), Some 7.3 years (95% CI 6.9–7.7), None 3.7 years (95% CI 3.2–4.35) (Fig. 6).

Among patients with stage IV disease, 75.8% (n = 9683) received chemotherapy compared to the model estimate of 95% (n = 12,133). Only 44.7% (n = 5704) received endocrine therapy, below the model estimate of 72% (n = 9196). Radiation was administered to 37.4% (n = 4779) Surgery was performed in 32.1% (n = 4097), though the types of surgery could not be ascertained.

Discussion

Our study shows an increase over time in survival for patients with breast cancer in São Paulo, in line with global improvements in survival outcomes from breast

cancer.¹⁴ Median overall survival increased by around 8.5% between 2000–2004 and 2010–2014. We also observed an increase in cancer-specific survival over time. These important improvements may reflect a higher proportion of early detection and advancements in breast cancer care, as well as reduced competing mortality risks. However, we also found lengthening diagnosis-to-treatment intervals over time, which could impact patient care. Through the integration of local epidemiological data into existing modelling frameworks, we found lower than expected utilization of surgery, radiation and endocrine therapy across most subgroups, with the largest observed gaps for radiation. Chemotherapy prescription was higher than expected, particularly in patients with stage II disease. We discuss these findings within the context of the World Health

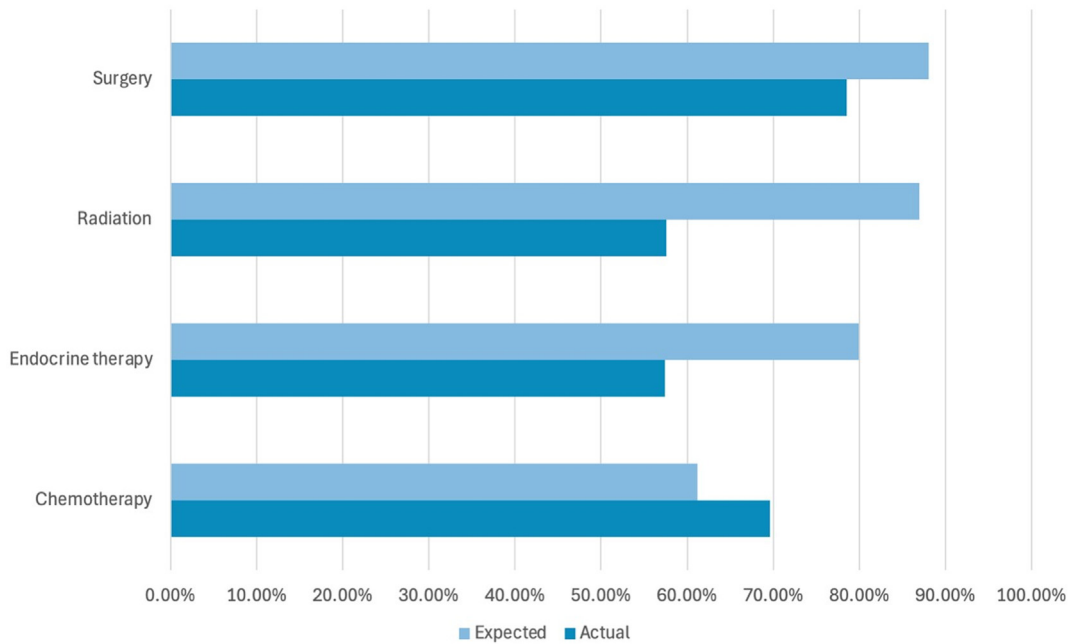


Fig. 5: Comparison of expected and actual treatment proportions for breast cancer across various treatment modalities.

	Actual Treatment Utilization (n; %)	Model Estimate –Enhanced resources (n; %)	Model Estimate –Maximal resources (n; %)	Reference
Chemotherapy				
Overall	87,023 (69.6%)	110,379 (88.3%)	76,503 (61.2%)	9
Stage I	12,502 (42.1%)	25,319 (85.3%)	11,220 (37.8%)	
Stage II	35,637 (73.9%)	41,129 (85.3%)	18,226 (37.8%)	
Stage III	29,201 (85.1%)	32,616 (95%)	32,616 (95%)	
Stage IV	9683 (75.8%)	12,133 (95%)	12,133 (95%)	
Endocrine therapy				
Overall	71,741 (57.4%)	99,879 (79.9%)	99,879 (79.9%)	9
Stage I	19,545 (65.8%)	23,924 (80.6%)	23,924 (80.6%)	
Stage II	28,921 (60.0%)	38,863 (80.6%)	38,863 (80.6%)	
Stage III	17,571 (51.2%)	24,720 (72%)	24,720 (72%)	
Stage IV	5704 (44.7%)	9196 (72%)	9196 (72%)	
Radiation therapy				
Overall	72,042 (57.6%)	108,754 (87%)	108,754 (87%)	11
Stage I	17,833 (60.1%)	N/A	N/A	
Stage II	28,140 (58.4%)	N/A	N/A	
Stage III	21,290 (62.0%)	N/A	N/A	
Stage IV	4779 (37.4%)	N/A	N/A	
Surgery				
Overall	98,153 (78.5%)	110,004 (88%)	110,004 (88%)	10
Stage I	25,688 (86.5%)	29,386 (99%)	29,386 (99%)	
Stage II	41,598 (86.3%)	47,735 (99%)	47,735 (99%)	
Stage IIIA	13,202 (78.0%)	16,044 (99%)	16,044 (99%)	
Stage IIIB/C	13,568 (74.8%)	N/A	N/A	
Stage IV	4097 (32.1%)	N/A	N/A	
Stage IIIB/C and IV combined	17,665 (57%)	17,303 (56%)	17,303 (56%)	

Table 3: Estimated demands and actual utilization of chemotherapy, endocrine therapy, radiation and surgery for breast cancer in São Paulo 2000–2019 (N = 125,005).

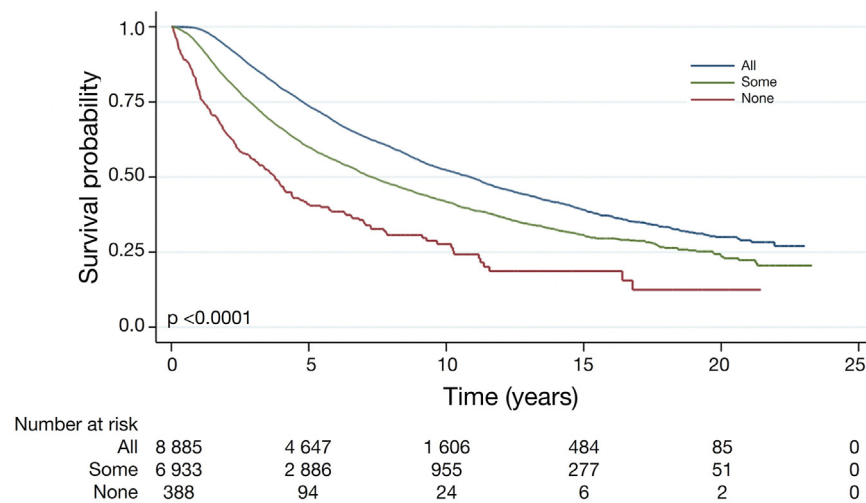


Fig. 6: Survival outcomes based on guideline concordant care for the subset of patients with stage IIIA breast cancer. All = patients received chemotherapy, surgery and radiation in keeping with guideline recommendations. Some = patients received some of the recommended treatments (i.e., at least one of chemotherapy, surgery and radiation), but did not receive all three recommended treatment modalities. None = patients did not receive any of the recommended treatment modalities.

Organization Global Breast Cancer Initiative (GBCI) Implementation Framework's three pillars (early detection, prompt diagnosis, and treatment to completion), and the corresponding key performance indicators.¹⁵ Identifying achieved and unmet key performance indicators can allow policy makers and governments to critically evaluate cancer care delivery and investment needs within their healthcare system.

The proportion of patients diagnosed with stage I–II disease was 63%, comparable to proportions observed at a national level in Brazil in 2011–2015,¹⁶ but lower than the 80–90% seen in HIC.¹⁷ Throughout all observed periods, the proportion of patients diagnosed with stage I or II remained over 60%, meeting the key performance indicator for the first pillar in the GBCI framework on early detection and the pre-diagnostic interval.¹⁵ We observed a modest downward stage migration within early breast cancer, with a 7% increase in stage I and a proportional decrease in stage II following the introduction of mammographic screening in Brazil's national guidelines in 2004.¹⁸ This downward stage migration, as well as the sustained proportion of cases diagnosed at earlier stages may partially explain the observed improvement in survival over the study period. Current national guidelines recommend biennial mammography for women aged 50–69,¹⁹ although screening remains opportunistic without formally organized screening programs. Between 2010 and 2019, mammogram coverage in the state of São Paulo was estimated at 52%, the highest across all states in Brazil.²⁰ Unfortunately, our dataset did not include information on whether diagnosis was made following mammographic screening or clinical symptoms. For screening

programs to be effective, an expansion in diagnostic and treatment infrastructure and workforce will be required to ensure timely access to care.²¹

The second pillar of the GBCI framework is timely diagnosis to ensure timely treatment initiation. Treatment delays can lead to inferior survival outcomes,²² and more advanced stage at diagnosis.²³ Each four-week delay in breast cancer surgery is associated with an 8% increase in risk of death,²² and delays in initiating adjuvant chemotherapy can also negatively affect outcomes.²⁴ Delays in diagnosis and treatment initiation can also cause patient anxiety and reduce satisfaction with care,²⁵ particularly in symptomatic or advanced-stage disease.²⁶ The corresponding key performance indicator benchmark within the GBCI framework is that >80% of patients receive a diagnosis within two months of their initial diagnostic evaluation, with the aim of starting treatment less than three months after initial presentation. Since 2012, legislation mandating that all patients with cancer in the Brazilian public health system initiate treatment within 60 days of pathological diagnosis.⁸ Yet, 49% of this cohort started treatment ≥ 60 days after diagnosis, with this proportion more than doubling over the study period. Similar increases in the diagnosis to treatment interval have been reported for other cancers in São Paulo.²⁷ Somewhat paradoxically, after matching by age, stage, treatment utilization, and time period, we found that patients initiating treatment ≥ 60 days from diagnosis had improved survival overall. Patients treated ≥ 60 days after diagnoses were more likely to receive endocrine therapy, which raises the hypothesis that the health system may be effectively triaging patients with more aggressive disease, such as

those with hormone receptor-negative breast cancer, to receive treatment more rapidly. Confirming this hypothesis would require additional data, including histological grade, hormone receptor and Human Epidermal Growth Factor Receptor 2 (HER2) status, as well as detailed information on the timing and sequence of individual treatment modalities. Nonetheless, outcomes may be further improved by reducing diagnosis-to-treatment intervals. Unfortunately, since our dataset lacked information on the pre-diagnostic interval, we could not directly evaluate the GBCI key performance indicator, and further research is needed. Treatment delays, starting from the pre-diagnostic interval, may be due to patient factors and/or provider and system factors.²⁸ While we could not examine patient delay factors, we compared system factors by examining patients referred to the FOSP system with and without a prior histologic diagnosis. Diagnosis-to-treatment intervals were almost twice as long in the 47% of patients diagnosed outside FOSP, which could reflect additional administrative and logistical barriers, or differences in these patient populations.

We identified gaps between guideline-based model estimates of expected demands and observed treatment utilization across all treatment modalities. A surgical utilization proportion of 86% for stages I–II represents a substantial shortfall compared to the model prediction for expected surgical utilization.¹⁰ The absolute number of breast cancer surgeries performed within the *Sistema Único de Saúde* between 2008 and 2014 remained stable despite a rising number of breast cancer cases,²⁹ suggesting that capacity may not be matching epidemiological trends. This is in line with our observation that over time, a higher proportion of patients with stage I–II disease, for which surgery is the initial treatment modality for most patients, started treatment more than 60 days after diagnosis. Since many early-stage cancers are detected through mammographic screening, screening programs must be accompanied by a corresponding expansion of surgical capacity.

We identified a 30% treatment gap for radiation across the entire population. In Brazil, 51–54% of patients undergo breast conserving surgery (BCS)³⁰ compared to 60% in HIC,³¹ which would decrease expected radiotherapy utilization. However, even after accounting for this difference, a large radiation treatment gap persists pointing to the well described shortage and unequal distribution of radiotherapy services in São Paulo and throughout Brazil.³⁰ Palliative radiation use in stage IV disease was 37%, which is also lower than the expected proportion of 50%.³² This gap may be due to infrastructure limitations, inaccessibility, out of pocket costs, travel challenges, or societal factors.

Gene expression assays to predict adjuvant chemotherapy benefit in patients with early-stage hormone receptor-positive disease have become common in HIC since publication of the TAILORx³³ and RxPONDER³⁴

trials, but their use in the public system in Brazil is limited due to lack of cost-effectiveness.³⁵ The observed chemotherapy utilization proportion of 42.1% for stage I disease approached our model estimate of 38.7%, suggesting clinicians are risk-stratifying based on clinicopathological features in the absence of genomic assays. Gene expression assays may play a greater role in reducing population-level chemotherapy prescription for stage II disease, where the observed proportion was 73.9%. Chemotherapy utilization was also lower than expected for stage III (85.5% versus 95%) and stage IV disease (75.8% versus 95%). While our model assumes that 5% of patients are unfit for chemotherapy due to poor baseline functional status, it may underestimate the proportion of such patients in Brazil. Lack of timely access to high value drugs^{36,37} and other system factors including those listed in [Supplementary Table S4](#) should be evaluated.

Endocrine therapy is recommended in almost all women with hormone receptor-positive breast cancer. Data from HICs suggests 70–80% of patients with stage I–III breast cancer have hormone receptor-positive disease, and a study using FOSP's Immunohistochemistry Laboratory Database reported a hormone receptor-positive proportion of 74%, in keeping with our model estimate. In contrast, endocrine therapy utilization in our cohort was only 50–65%. An even larger discrepancy was seen in stage IV disease, with modeled estimates at 72% versus an observed proportion of 44.7%. Potential causes for these large treatment gaps include diagnostic barriers (lack of universal testing for HR and HER2 status), societal factors (including patient preferences), treatment delivery barriers (failure to offer therapy or loss to follow-up), or drug access barriers (including unstable drug supply chains and drug costs) ([Supplementary Table S3](#)).

The final pillar in the GBCI framework is the treatment interval, for which the key performance indicator benchmark is completion of recommended treatment in >80% of patients.¹⁵ Our analysis of patients with stage IIIA disease, who would be recommended to receive surgery, chemotherapy, and radiotherapy regardless of histologic subtype, showed that only 54.8% of patients received all three recommended modalities. While our database lacked information on treatment completion rates, the proportion of patients even initiating all recommended therapy falls well short of the 80% target. We found that those receiving all recommended treatments had significantly improved survival compared to those who received some or none of the recommended treatments, in line with prior literature suggesting that patients who receive guideline concordant care have improved outcomes.³¹ Due to the lack of histological details in our dataset, we were not able to determine whether endocrine therapy would be recommended in these patients. However, the observed utilization of endocrine therapy for patients with stage III disease was more than 20% lower than would be expected. Given

that significant gaps in expected and observed treatment utilization were observed across all stages, increasing system capacity to deliver care until completion of all recommended treatment modalities could improve survival outcomes even further.

This study has several limitations. First, comparing actual and expected treatment utilization requires model assumptions which could influence the reliability of the estimates. The implications of model assumptions have been previously published.⁹ For this work, a major limitation includes the lack of stage-specific radiotherapy utilization estimates. Second, there is a risk of misclassification within any administrative dataset. In this study, misclassification of stage or treatment utilization could affect the accuracy of our results. However, this database undergoes a validation process on a quarterly basis, and quality control indicators for completeness follow national and international recommendations, thereby minimizing the risk of misclassification. Third, lack of histological details including HR and HER2 receptors necessitated assumptions based on published data regarding the prevalence of these variables. Fourth, the dataset lacks granular information on types of surgical procedures, radiotherapy intent, specific chemotherapy and hormone treatments, treatment discontinuations and interruptions, and germline mutation status. This lack of detail prevents a deeper analysis of treatment outcomes, adherence, and costs. Our dataset did not include important sociodemographic characteristics such as race and ethnicity, which have been associated with disparities in access to treatment in Brazil,⁴ and incorporating these variables into future research would be important. Furthermore, differences in stage distribution have also been reported across regions in Brazil, with the proportion of diagnosis at stages III–IV in the northern region being around 10% higher than in the southeast, where São Paulo is located.⁵ This suggests that our findings may not be representative of the current status of breast cancer care in Brazil as a whole, and that not all regions are achieving early detection benchmarks. Future research comparing diagnostic intervals and receipt of guideline concordant care across regions would provide more information at a national level. Additionally, a minority of patients may seek treatments at external institutions outside of the FOSP system which would not be captured in the dataset. Over time, the number of institutions included within the FOSP database has expanded, and some of the temporal changes seen could reflect institutional differences. Finally, as our data was obtained from a hospital-based registry, no inferences on breast cancer incidence could be made.

Despite these limitations, comparing model-based and actual treatment utilization can still offer important insights for health systems. First, we can begin to identify key elements that registries and administrative databases should capture to accurately populate model

estimates and improve predictions. This work can therefore inform data collection plans for future registries at local and national levels. Second, sensitivity analyses can be performed for any model input parameter (e.g., stage distribution, hormone receptor status) to explore how different epidemiological variables might affect treatment demands. Third, comparing estimated and observed treatment demands may help policy makers and governments prioritize investment and capacity building within the cancer system to target significant treatment gaps, or perform quality assessments to better understand clinical decision-making and system processes in areas where observed treatment exceeds expected.

Conclusion

This study reveals substantial treatment gaps across all breast cancer stages in São Paulo, Brazil, over the past two decades. Despite significant improvements in overall survival over time and advancements in treatment and early detection, many patients still lack guideline-concordant care, especially in radiation therapy. Lengthening diagnosis-to-treatment intervals and underutilized treatment modalities indicate systemic barriers to optimal care. These findings highlight the need for targeted interventions to close treatment gaps and improve access to evidence-based care, which is essential for enhancing breast cancer outcomes in São Paulo and similar resource-limited regions across Latin America.

Contributors

Haydee Verduzco-Aguirre, MD—Formal analysis; Methodology; Project administration; Validation; Visualization; Writing—original draft; Writing—review & editing.

Fernanda Mallucelli Favorito—Conceptualization; Data curation; Resources; Writing—review & editing.

Fabio Ynoe de Moraes, MD PhD MBA—Conceptualization; Data curation; Resources; Data interpretation; Writing—review & editing.

Gustavo Marta, MD PhD—Data interpretation; Writing—review & editing.

Camila Tagle, MD—Data interpretation; Writing—review & editing.

Carlos Henrique dos Anjos, MD—Data interpretation; Writing—review & editing.

Andre Mattar, MD—Data interpretation; Writing—review & editing.

Brooke Wilson, MBBS MSc—Conceptualization; Formal analysis; Data interpretation; Methodology; Resources; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing.

All authors had full access to all the data in the study and accept responsibility to submit for publication.

Data sharing statement

Individual participant data and the data dictionary used for this study are publicly available at the FOSP website (in Portuguese) at <http://fosp.saude.sp.gov.br>.

Declaration of interests

Haydee Verduzco-Aguirre reports travel support and honoraria from Asofarma, outside of the submitted work.

Brooke E Wilson reports consulting fees or honoraria from Astra-Zeneca, Gilead and Novartis and an institutional grant from BMS, outside of the submitted work.

No other conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.lana.2025.101115>.

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